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RESEARCH ARTICLE

Cadmium exposure and the risk of GDM: evidence emerging from the systematic review and meta-analysis

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Abstract

Gestational diabetes mellitus (GDM) has become a global concern for its severe adverse effects on both mother and fetus. Recent epidemiological studies reported inconsistent results of the association between cadmium (Cd) exposure and GDM. Therefore, a systematic review and meta- analysis were performed. PubMed, Web of Science, Scopus, Embase, and SpringerLink were searched up to July 2021. Observational studies containing the adjusted relative risks between Cd exposure and GDM were included in the quantitative synthesis. The retrieval comprised 218 articles out of which 11 met our criteria and 9 were included in the meta-analysis, representing a total of 32,392 subjects (2881 GDM). In total, Cd exposure might increase the risk of GDM in some extent ($OR = 1.21$, 95% CI [0.89, 1.64]), even without statistical significance in high heterogeneity ($Q = 28.45$, $p < 0.05$, $I^2 = 71.9\%$). Filtering two outliers indicated by Galbraith plot yielded a similar risk ($OR = 1.19$, 95% CI [1.02, 1.39]) with statistical significance. However, the heterogeneity among studies was obviously reduced ($Q = 11.75$, $p = 0.068$, $I^2 = 48.9\%$). Additionally, biological specimen, study design, and diagnostic criteria contributed to the high heterogeneity according to the subgroup analysis. Since some important results do not deny that Cd exposure increases the risk of GDM, high-quality multi-centered large cohort studies are required in the future.

Keywords Gestational diabetes mellitus · Cadmium · Heavy metal · Risk factor · Pregnancy

Abbreviations

GDM	Gestational diabetes mellitus
BMI	Body mass index
Cd	Cadmium
EDC	Endocrine Disrupting Chemicals
PRISMA	Preferred Reporting Item for Systematic Reviews and Meta- analysis
PECOS	Population Exposure Comparison Outcome Study design
MeSH	Medical Subject Headings
RR	Risk ratio
OR	Odds ratio
HR	Hazard ratio
PR	Prevalence ratio
CI	Confidence interval
NOS	Newcastle–Ottawa scale
AHRQ	Agency for Healthcare Research and Quality
DCT-1	Divalent Cation Transporter-1
B-Cd	Cadmium in blood
U-Cd	Cadmium in urine
Cas-3	Caspase 3
ROS	Reactive oxygen species
TBARS	2-Thiobarbituric acid reactive substances
Nrf2	Nuclear factor E2-related factor 2
JNK	C-Jun NH(2)-terminal kinases
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor alpha
FFA	Free fatty acid

Introduction

Gestational diabetes mellitus (GDM) is characterized as glucose intolerance that first diagnosed during the second or third trimester of pregnancy with varied severity of hyperglycemia (American Diabetes 2021). The development of GDM is attributed to pancreatic β-cell dysfunction and reduced tissue insulin sensitivity existed before

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pregnancy, causing progressive effects on both pancreas and other organs comprising liver, skeleton muscles, and adipose tissues (Plows et al. 2018). According to the report of International Diabetes Federation (IDF), it is estimated that one in every six pregnant women suffers hyperglycemia globally, 83.6% of which is diagnosed as GDM, with a continuously elevated tendency due to the improvement of diagnostic criteria (International Diabetes Federation 2019). Concerns are aroused widely that GDM could trigger serious and adverse effects on both maternal and fetal health, including fetal malformation, preterm birth, macrosomia, and cardiovascular diseases (Archambault et al. 2014; Daly et al. 2018; Domanski et al. 2018; Kc et al. 2015; Vounzoulaki et al. 2020; Wu et al. 2020; Yu et al. 2019). Therefore, the risk factors of GDM are well analyzed and documented by the recent epidemiological studies, commonly consisting of maternal age, pre-pregnancy *BMI*, smoking status, history of diabetes, and changes of lifestyle (Bar-Zeev et al. 2020; Goldstein et al. 2017; Moosazadeh et al. 2017; Sheen et al. 2018). In addition, there is increasing epidemiological evidence that environmental factors participate in the etiology of GDM in line with the alternations of industrial activities and modes of life, somehow compensating the shortages in investigating environment-human health interaction.

Previous studies have proposed potential linkages between heavy metals and disturbance of glucose metabolism (Gonzalez-Villalva et al. 2016), in which arsenic (As), mercury (Hg), lead (Pb), cadmium (Cd), iron (Fe), and nickel (Ni) are described as hyperglycemic metals. Among those metals, Cd is an endocrine-disrupting heavy metal (Onat et al. 2021) that has been heated explored contributing to its wide distribution, numerous ways of exposure and severe toxic effects. Occupational exposures are industrial activities including metal mining, alloy, batteries, and phosphate fertilizers manufacturing. Dust inhalation, tobacco smoking, and consumption of contaminated food or water are more regular for non-occupational population to be chronically exposed (Domingo-Relloso et al. 2020; Faroon et al. 2012; Filippini et al. 2018). Prolonged exposure with large dose of Cd could be inspected due to the accumulation in the kidney and liver, posing severe impacts on human health (Cabral et al. 2021; Genchi et al. 2020). Cd has been categorized as cancerogenic to human by the International Agency for Research on Cancer (IARC) (International Agency for Research on Cancer 2012) for its potential linkage between kidney, pancreas, and breast cancers (Buha et al. 2017; Filippini et al. 2020; Il'yasova and Schwartz 2005). In addition, evidence has been accumulated that Cd exposure is associated with increased risk for metabolic diseases including obesity, diabetes mellitus, osteoporosis, and cardiovascular diseases (Filippini et al. 2021; Green et al. 2018; Jeong et al. 2020; Reyes-Hinojosa et al. 2019; Tellez-Plaza et al. 2013; Wang et al. 2018). Particularly, the diabetogenic effect of Cd has been well indicated (Edwards and Prozialeck 2009) for the capability of causing inflammation and insulin resistance, and inducing death of pancreatic β cell (Bimonte et al. 2021; Buha et al. 2020). In recent years, greater attention has been invested in the problem whether Cd exposure prior to or during pregnancy could impact glucose metabolism in gestational status, causing widely prevalent GDM (Jia et al. 2021; Liu et al. 2018; Oguri et al. 2019; Peng et al. 2015; Rezaei et al. 2021; Romano et al. 2019; Shapiro et al. 2015; Soomro et al. 2019; Wang et al. 2020; Wang et al. 2019; Xing et al. 2018). However, accounting for those conclusions were mostly evidenced by small scale and single-central studies with inconsistent design and biological specimens (i.e., blood, urine, meconium, and hair), and more importantly, some of which were discordant or even contradictory, there is still an urgent demand to further clarify the association.

Therefore, the aim of our work is to explore whether Cd exposure could be a potential risk factor for GDM based on the systematic review and meta-analysis of relevant studies and additionally, to provide evidence for future policies and research from a more accurate and object perspective.

Materials and methods

The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al. 2009), of which protocol was registered in PROSPERO prior to data extraction (CRD42021249057).

Literature search

Systematic retrieval was performed in five electronic databases including PubMed, Web of Science, Scopus, Embase, and SpringerLink consistent with the PECOS principles (Cooke et al. 2012). In total, two searches were conducted on separate dates, as the first attempt took place in March 2021 and a subsequent search was repeated later in July to update any relevant and eligible materials if available. Keywords represented for population of interest (pregnant, pregnancy, pregnant women, gestational women, gestation, and maternal) were input in combination with objective exposure (cadmium) and outcome (gestational diabetes mellitus and gestational diabetes) with restriction to English language. Detailed strategies can be achieved in Supplementary Table 1. Distinct strategies were utilized in accordance with each database to optimize output, for example, applying MeSH terms in conjunction with free text words in PubMed. In addition, relevant citations were manually retrieved after investigation of reference lists and consensus was achieved after the discussion of two authors.

Titles and abstracts were first reviewed by two researchers (M.Q.Z and L.Q.P) independently to exclude any irrelevant studies. Subsequently, full-text manuscripts were further scrutinized, and a final agreement was attained according to the predefined inclusion/exclusion criteria.

Inclusion criteria

The inclusion criteria were as follows: (1) pregnant women confirmed as GDM based on credible criteria (e.g., CDA-SOGC Diagnostic Criteria, the Carpenter and Coustan Criteria, JSOG and JAOG Criteria, ADA Diagnostic Criteria, IADPSG's criteria, American College of Obstetricians and Gynecologists guidelines, and WHO Diagnostic Criteria et al.). (2) Appropriate Cd exposure indicators to assess body burden (e.g., Cd in blood, urine, meconium, and hair). (3) Risk estimates (e.g., OR, RR, HR) with 95% confidence interval (CI) appraising risk of GDM after metal exposure were reported or information was provided enough to calculate the relative risk. (4) Study type constricted to observational experiment (e.g., cross-sectional study, case-control study, and cohort study).

Studies that did not report workable data, for example, reviews, abstracts, case reports or series, book chapters, animal experiments, conference proceedings, and editorials were further excluded. In addition, citations with low credibility in design and data, such as lack of control group and baseline information, were also abandoned. Of note, if a cohort was reported in more than one trial, the latest publication would be included. Indistinct information relevant to qualitative or quantitative synthesis was inquired responsible authors through e-mails.

Data extraction

Information collected by two independent reviewers (M.Q.Z and L.Q.P) was as follows. (a) Author's first name; (b) publication year; (c) study region; (d) study design;(e) study period or follow-up years for cohort study; (f) sample sizes for cases and controls; (g) age of enrolled participants; (h) diagnostic criteria of the disease; (i) exposure markers; (j) exposure conditions of population; (k) when exposure was measured; (l) risk estimates with 95%CI; (m) confounding factors in statistical analysis.

Quality appraisal

Cohort study and case-control study were appraised through the Newcastle-Ottawa scale (NOS) (Stang 2010), while cross-sectional study was evaluated with the guideline suggested by Agency for Healthcare Research and Quality (AHRQ) (https://www.ncbi.nlm.nih.gov/books/NBK33514/), independently by two reviewers (M.Q.Z and L.Q.P). Discriminations were consulted with a third author (Y.W.F). The NOS assessed quality in terms of three dimensions, including cohort selection (max four points), comparability (max two points), and outcome (max four points) for cohort design and selection of case/control (max four points), comparability (max four points), and exposure measurements (max four points) for case-control study respectively. We categorized the citation as good, if more than two points was gained in selection and outcome/exposure aspects and more than one score in comparability part; rational level was appraised if the citation obtained two scores in both selection and outcome/exposure section with more than one point in comparability; research was considered to be in poor quality when either one or zero point was achieved in selection and outcome/exposure area or none score in comparability domain. Additionally, in total, eleven items were evaluated in AHRQ scale. Still, three levels, poor, rational, and good, occurred in accordance with 0–5, 6–8, and 9–11 points respectively (Supplementary Table 2).

Data analysis

The OR data was adopted to measure the overall association between Cd exposure and GDM. Risk estimates (e.g. OR and RR) were extracted from original studies and RR was considered OR if the incidence of GDM is low (less than 10%) in the study population (Zhang and Yu 1998). We only included risk estimates adjusted by confounding factors and calculated by the single metal model, and when studies reported risk estimates in stratified values (e.g., tertiles or quartiles), we utilized the data in the highest exposure level.

Risk estimates with its 95% CI were transformed into ln form and combined with inverse-variance method by both fixed and random model according to the reported heterogeneity among studies, subsequently demonstrated by visible forest plots. Cochran's Q test and I^2 test were employed to investigate heterogeneity. p-value less than 0.1 was considered having heterogeneity in Cochran's Q test (Higgins et al. 2019). Insignificant, low, moderate, and high heterogeneity were allocated respectively to I^2 value of 0–25%, 25%–50%, 50%–75%, and $\geq 75\%$ (Higgins et al. 2003). We adopted random effect model (DerSimonian and Laird approach) (DerSimonian 1986) to pool the data if I^2 was more than 50%; otherwise, fixed effect model (Mantel– Haenszel approach) was applied (Higgins et al. 2003; Mantel 1959). p-value < 0.05 was considered statistically significant.

We further constructed Galbraith plot to identify the heterogeneity caused by a single study (Galbraith 1988). Studies outside the two regression lines were accounted for outliers presenting high heterogeneity with others (Galbraith 1988). Subgroup analysis was later conducted to reduce the heterogeneity. Predefined subgroups comprising sample form (e.g., maternal blood, urine, and meconium), study design (cohort study, case-control

study, and cross-sectional study), dignostic criteria, study region (Asia and North America), and sample sizes (< 100 cases or ≥ 100 cases) were analyzed through both fixed and random effect model due to their heterogeneity. Sensitivity analysis was performed by removing one study at a time to identify the heterogeneity sources and robustness of results. Publication bias was evaluated through funnel plot and its asymmetry was testified by Egger's test (Egger et al. 1997). The whole analytical process was conducted in StataSE 16 (StataCorp, College Station, TX, USA).

Results

Literature characteristics

The literature search ascertained a total of 218 citations, of which 11 remained in the systematic review in accordance with inclusion criteria and 9 were included in meta-analysis (Fig. 1). Among those studies in systematic review were six cohort studies (Liu et al. 2018; Romano et al. 2019; Shapiro et al. 2015; Soomro et al. 2019; Wang et al. 2020; Xing

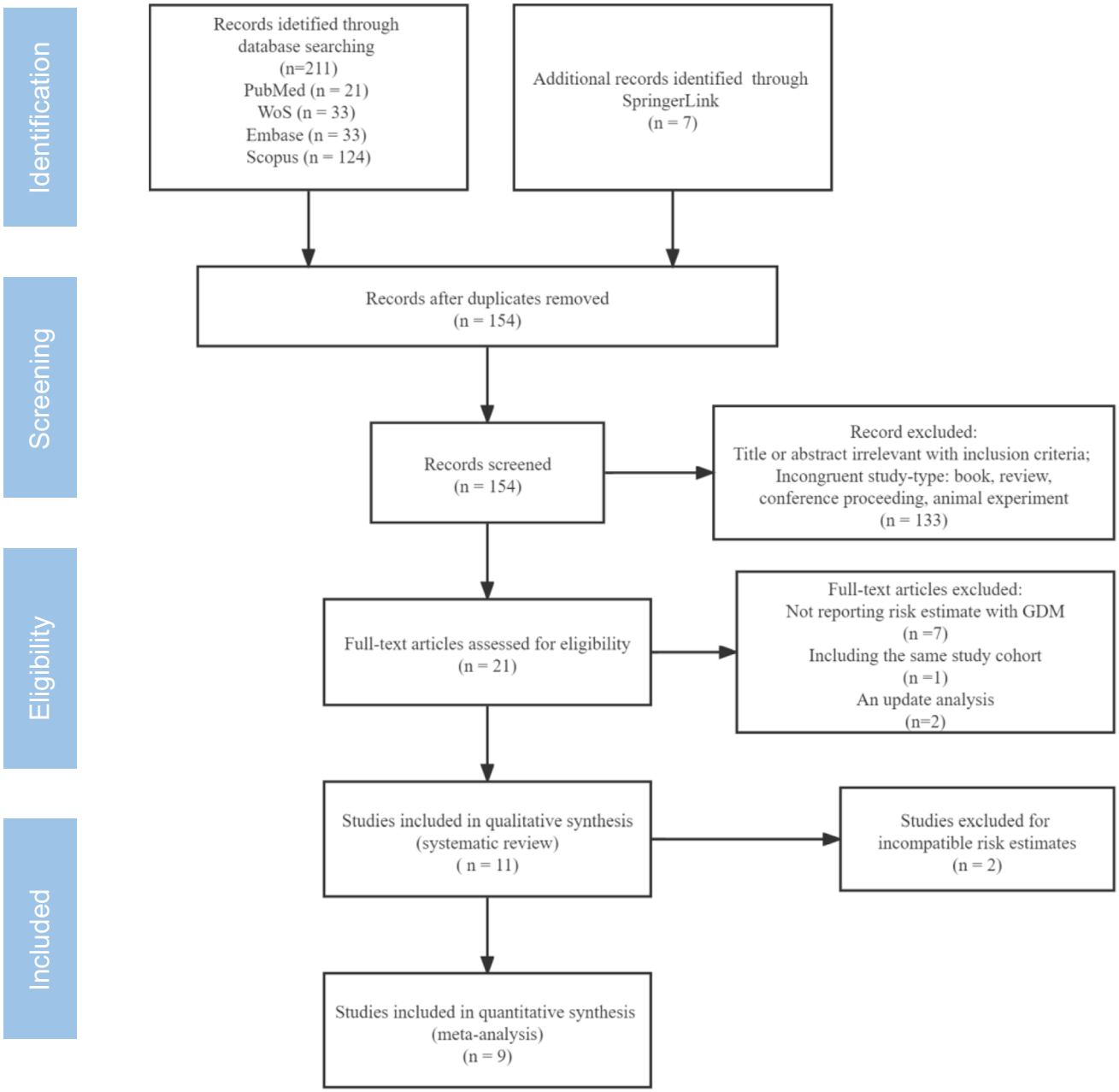

Fig. 1 PRISMA flow diagram of identification, screening, eligibility and inclusion. Abbreviation: GDM, gestational diabetes mellitus

et al. 2018), three case-control studies nested in a cohort (Jia et al. 2021; Peng et al. 2015; Wang et al. 2019), and two cross-sectional studies (Oguri et al. 2019; Rezaei et al. 2021) published recently ranging from 2015 to 2021, as a representative of totally 32392 pregnant subjects and 8.9% of which were diagnosed as GDM. Characteristics of citations were depicted in Table 1. Regression models were constructed after adjusting multiple confounding variates to obtain the final associations (i.e., OR, RR, PR, RD) between Cd exposure and risk of GDM. Cd exposure was represented by either categorical variables based on tertiles/quartiles of metal concentrations or continuous data normalized by log-transformation. Three studies further explored how relative risk altered in subjects with different pre-pregnant body weight (Liu et al. 2018; Wang et al. 2019; Xing et al. 2018). Five studies collected maternal blood samples in mostly the first or second trimester of gestation (Oguri et al. 2019; Rezaei et al. 2021; Shapiro et al. 2015; Soomro et al. 2019), only one of which extracted samples at delivery (Wang et al. 2019). Urine samples were utilized in four studies (Liu et al. 2018; Romano et al. 2019; Wang et al. 2020; Xing et al. 2018) and unconventional samples (i.e., hair, meconium) were measured in two articles (Jia et al. 2021; Peng et al. 2015).

There were six citations assessed as good quality including five cohort (Liu et al. 2018; Shapiro et al. 2015; Soomro et al. 2019; Wang et al. 2020; Xing et al. 2018) and two case-control studies (Jia et al. 2021; Wang et al. 2019). A cohort (Romano et al. 2019) and a cross-sectional study (Oguri et al. 2019) were evaluated as rational status and two studies (a case-control study and a cross-sectional) were as poor correspondingly (Peng et al. 2015; Rezaei et al. 2021) (Supplement table 2).

Meta-analysis

Risk estimate of maternal Cd exposure and GDM

Summarizing results from nine studies, the pooled OR suggested a statistically non-significant association between maternal cadmium exposure and GDM (OR = 1.21, 95% CI [0.89, 1.64]) (Fig. 2a). However, remarkable heterogeneity (Q = 28.45, p<0.05, I^2 = 71.9%) was observed among studies. Galbraith plot was further introduced to detect the source of heterogeneity depicting two outliers outside the parallel regression lines of 95% CI (Peng et al. 2015; Wang et al. 2019) (Fig. 3a). Notably, the association became significant after the removal of those two citations (OR = 1.19, 95% CI [1.02, 1.39]) (Fig. 2b) with reduced heterogeneity demonstrating by both I^2 test and Galbraith plot (Q = 11.75, p = 0.068, I^2 = 48.9%) (Fig. 3b). However, changing into random effect model did not observe the statistically significant association (OR = 1.16, 95% CI [0.89, 1.53]). Considering pre-pregnancy *BMI* is related to incidence of GDM, we pooled OR data stratified by body weight. Interestingly, there was a significant risk of women with normal weight (*BMI*= 18–23.9 kg/m^2) to develop GDM after Cd exposure revealed by the positive association (OR=1.46 95% CI [1.14, 1.86]) with trivial heterogeneity (Q = 0.32, p = 0.574, I^2 <0.1%) (Supplementary fig. 1a), whereas the same result was not observed in overweight pregnant females (OR = 1.80, 95% CI [0.77, 4.21]) (Supplementary fig. 1b). Slight asymmetry was inspected in the funnel plot. However, no evidence of publication bias was found according to Egger's test (t=0.95, p=0.374) (Fig. 4).

Subgroups analysis

Subgroup analyses identifying robustness and heterogeneity of results were conducted in terms of design, sample form, diagnostic criteria, region, and sample sizes exhibiting in the following summary Table 2. Detailed forest graph could be inspected in Supplementary fig. 2 Stratified studies by cohort design reduced the original heterogeneity (I^2 = 51.1%), whereas by nested case-control design yielded extremely higher heterogeneity (I^2 = 92.7%) suggesting study protocol may be one of the sources of heterogeneity. Interestingly, the combined OR data in cohort group indicating a nearly significant association (OR = 1.27, 95% CI [0.96, 1.68]). There was a significant difference of heterogeneity detected in studies utilizing urine samples (I^2 = 28%) and blood samples (I^2 = 69.9%), determining the variation exerted by distinct biological samples. Notably, urine group manifested a nearly statistically positive risk estimate with reasonable low heterogeneity (OR = 1.17, 95% CI [0.99, 1.38]). Removing the study conducted by Wang et al. (2019) lifted the risk estimate from blood group, though trivial improvement of heterogeneity was detected. Heterogeneity among studies was reduced when pooling studies that applied the one-step approaches (I^2 = 55.9%) though still non-significant association was observed. Combining studies according to region did not significantly impact the heterogeneity, and when stratified by sample size, the heterogeneity was lower in studies with patient samples of ≥100 cases (I^2= 69.8%) but higher in studies with patient samples of <100 cases (I^2=75.8%).

Sensitive analysis

We performed sensitive analysis by removing one study each time and calculating the overall effect estimate of the remaining scientific literatures before and after the adjustment of Galbraith plot. No significant alteration of risk estimate with its corresponding CI was detected in overall studies ranging from 1.09 (95% CI [0.84, 1.40]) to 1.31 (95% CI [0.92, 1.87]) (Fig. 5a). However, after introduction

Table 1 Characteristics of including citations

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
Maternal blood (5 studies)													
1	Shapiro et al. 2015	Canada	Cohort study	2008–2011	44/1088	≤29 yo (24.2%) 30–34yo (35.1%) ≥35yo (40.4%)	CDA-SOGC Diagnostic Criteria [f] (Berger et al. 2002)	Maternal blood samples	1st trimester	LOD: 0.04 ug/L Categorical variables based on quartiles Reference(Q1): 0.0–0.1 Q2: 0.1–0.2 Q3: 0.2–0.3 Q4: 0.3–5.1	maternal age, race, pre-pregnancy BMI, and education	aOR (95% CI) Q2: 2.1 (0.8–5.4) Q3: 1.4 (0.5–3.9) Q4: 2.5 (1.0–6.4)	Good
2	Soomro et al. 2019	France	Cohort study	02/2003–01/2006	44/579	29.02 ± 4.9 yo	the Carpenter and Coustan Criteria [g]	Maternal blood samples	2nd trimester	LOD: 0.05 ug/L Ln-Cd exposed: ≥0.315 Categorical variables based on quartiles Reference(Q1): 0.1–0.5 Q2: 0.5–0.8 Q3: 0.8–1.2 Q4: 1.2–9.6	maternal smoking, maternal age, maternal BMI, maternal education level, pregnancy induced hypertension, number of siblings and recruitment center	aOR (95% CI) Ln-Cd: 1.81 (0.93–3.50) Quartiles: Q2: 0.62 (0.18–2.09) Q3: 1.44 (0.38–3.47) Q4: 2.01 (0.73–5.53)	Good

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
3	Oguri et al. 2019	Japan	Cross-sectional study	01/2011–03/2014	Parous: 224/11106 Nulliparous: 102/4970	cases: 33.2 ± 5.0 yo controls: 31.1 ± 5.0 yo	JSOG and JAOG Criteria [g] (Minakami et al. 2011)	Maternal blood samples	22–28 gestational week	LOD: 0.0234 ng/g Categorical variables based on quartiles Reference(Q1): ≤ 0.50 Q2: 0.51–1.00 Q3: 1.01–1.50 Q4: ≥ 1.51	maternal age at birth, pre-pregnancy BMI, history of GDM pregnancy-induced hypertension, and smoking pack-years	Parous aOR (95% CI) Q2: 1.26 (0.88–1.81) Q3: 1.37 (0.87–2.16) Q4: 0.60 (0.27–1.34) Nulliparous aOR (95% CI) Q2: 0.86 (0.53–1.38) Q3: 0.87 (0.45–1.66) Q4: 0.81 (0.30–2.20)	Rational

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
4	Wang et al. 2019	China	Case–control study nested in a cohort	2012–2016	776/776	cases: 31.00 ± 4.53 yo controls: 30.97 ± 4.53 yo	ADA Diagnostic Criteria [g] (American Diabetes Association 2011)	Maternal blood samples	at delivery	LOD: Unavailable Categorical variables based on tertiles Reference (Low): < 0.69 μg/L Middle: 0.69–3.43 μg/L High: ≥ 3.43 μg/L	pre-pregnancy BMI, gestational weight gain, physical activity, parity, family history of diabetes, and month of conception, maternal age, residence, education, family monthly income, active and passive smoking during pregnancy, and fetal gender	aOR (95% CI) Middle: 1.01 (0.78, 1.31) High: 0.83 (0.64, 1.08)	Good
5	Rezaei et al., 2021	Iran	Cross-sectional study	09/2018–02/2019	60/42	cases: 31.10 ± 5.67 yo controls: 28.05 ± 5.91 yo	IADPSG's criteria [g] (American Diabetes Association 2011)	Maternal blood samples	unavailable	LOD: unavailable	age and previous GDM history	aRD (95% CI) 0.656 (0.478, 0.835)	Poor

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
Urine (4 studies)													
6	Liu et al. 2018	China	cohort study	10/2013–04/2016	198/1828	<25yo (7.50%) 25-29yo (60.52%) 30-34yo (25.96%) ≥35yo 122 (6.02%)	IADPSG's criteria	Urine samples	13 gestational week	LOD: 0.001ug/l SG Categorical variables based on tertiles Reference: <0:51 Medium: 0.51–0.86 High: ≥0:86	maternal age, education, maternal pre-pregnancy BMI, parity, passive smoking, total arsenic level, and hypertensive disorder in pregnancy, fetal sex	18.5 < BMI ≤ 23.9 Medium: 1.21 (0.77, 1.91) High: 1.62 (1.04, 2.53) BMI ≥ 24.0 Medium: 0.70 (0.39, 1.25) High: 1.14 (0.64, 2.04)	Good
7	Xing et al. 2018	China	Retrospective cohort study	9/2012–10/2014	656/6181	cases: 30.02 ± 4.04 yo controls: 28.27 ± 3.59 yo all samples: 28.44 ± 3.67 yo	IADPSG's criteria	Urine samples	within 3 days before delivery	LOD: 0.003 μg/L Categorical variables based on quartiles Q1: <0.40 μg/g creatinine Q2: 0.40–0.58 μg/g creatinine Q3: 0.58–0.85 μg/g creatinine Q4: ≥0.85 μg/g creatinine	age, pre-pregnancy BMI, parity, education, passive smoking,	aRR (95% CI) Ln-Cd: 1.16 (1.03, 1.33) Categorical variables: Q2: 1.21 (0.97, 1.50) Q3: 1.24 (1.00, 1.53) Q4: 1.30 (1.05, 1.61)	Good

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
8	Romano et al., 2019	USA	Cohort study	01/2009–12/2017	64/559	all samples: 31.4 ± 4.7 yo	American College of Obstetricians and Gynecologists [g] (Committee on Practice Bulletins-Obstetrics 2013)	Urine samples	24–28 gestational week	LOD:0.001–0.02 µg/g	enrollment age, prepregnancy BMI, pregnancy weight gain, smoking (ever/never), creatinine (mg/dL), and gestational age at glucose testing	aOR (95% CI) Log2-Cd: 0.86 (0.51–1.44)	Rational

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
9	Wang et al. 2020	China	Cohort study	07/2014–07/2016	241/1849	all subjects: 28.40 ± 3.47 yo cases: 29.54 ± 4.13 yo controls: 28.25 ± 3.34 yo	ADA Diagnostic Criteria	Urine samples	< 20 gestational week	LOD: 0.009 μg/L Categorical variables based on tertiles Reference(Low): < 0.65 Middle: 0.65–1.10 High: ≥ 1.10	maternal age, prepregnancy BMI, gravidity, occupational status, smoking exposure, average personal monthly income, family history of diabetes, physical activity, fetal sex	aRR (95% CI) Ln-Cd: 0.98 (0.81, 1.18) Categorical variables: Middle: 1.04 (0.78, 1.39) High: 1.05 (0.77, 1.41)	Good
Meconium (1 study)													
10	Peng et al., 2015	China	Case–control study nested in a cohort	06/2012–07/2012	137/190	cases: 27.85 ± 3.87 yo controls: 26.34 ± 2.64 yo	WHO Diagnostic Criteria [h] (Alberti and Zimmet 1998)	Newborn meconium samples	the first 2 postnatal days	LOD: 0.03 ng/mL Categorical variables based on quartiles of the control group	maternal age, prepregnancy BMI, gravidity, parity, HBV infection, newborn sex	aOR (95% CI) Q2 3.07 (0.69–13.74) Q3 16.87 (4.19–67.86) Q4 11.95 (2.97–48.04)	Poor
Hair (1study)													

Table 1 (continued)

Study ID	Author, year	Study country	Study design	Study period	Sample size (cases/controls)	Age description[a]	Definition of cases	Exposure measurement			Confounding factors[d]	Risk estimate[e]	Quality
								Samples	Collection period[b]	Levels[c] (cut-offs or LOD)			
11	Jia et al., 2021	China	Case–control study nested in a cohort	10/2017–10/2018	335/343	< 35 yo (82.9%) ≥ 35 yo (17.1%)	ADA Diagnostic Criteria [g]	maternal hair	1st trimester	LOD: < 0.001 ug/g Categorical variables based on tertiles	maternal age, occupation, pre-pregnancy BMI, parity, passive smoking, light activity time, hair dye, and hypertension during pregnancy	aPR (95% CI) Middle: 1.09 (0.91–1.32); 1.10 (0.91–1.33) High: 1.03 (0.85–1.24); 1.03 (0.85–1.24)	Good

Abbreviations: *yo*, years old; *CDA-SOGC*, Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada; *LOD*, limit of detection; *BMI*, body mass index; *aOR*, adjusted odds ratio; *Ln*, logarithm; *JSOG and JAOG Criteria*, Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists criteria; *ADA*, American Diabetes Association; *IADPSG's criteria*, International Association of Diabetes and Pregnancy Study Group; *aRD*, adjusted risk difference; *SG*, specific gravity; *aRR*, adjusted risk ratio; *WHO*, World Health Organization; *HBV*, Hepatitis B virus; *aPR*, adjusted prevalence ratio; *OGTT*, Oral Glucose Tolerance Test

[a]The range of age (percentage in total subjects) or mean ± SD was reported. [b]The time period when samples of subjects were collected. [c]Exposure level was reflected by categorical variables (quartiles/tertiles) or log-transformed continuous variable. [d]Confounding factors adjusted in the final statistical analysis. [e]Adjusted risk estimates of categorical or continuous handle of exposure condition. [f]3h-100 g-OGTT positive (more than 2 blood glucose concentrations greater than the following cut points: fasting = 95 mg/dL; 1 h = 180 mg/dL; 2 h = 155 mg/dL; 3 h = 140 mg/dL) [g]2h-75 g-OGTT positive (more than 1 blood glucose concentrations greater than the following cut points: fasting = 92 mg/dL (5.1 mmol/L); 1 h = 180 mg/dL (10.0 mmol/L); 2 h = 153 mg/dL (8.5 mmol/L)).[h]2h-75 g-OGTT positive (fasting serum glucose ≥ 7.0 mmol/L and/or 2-h serum glucose ≥ 11.1 mmol/L)

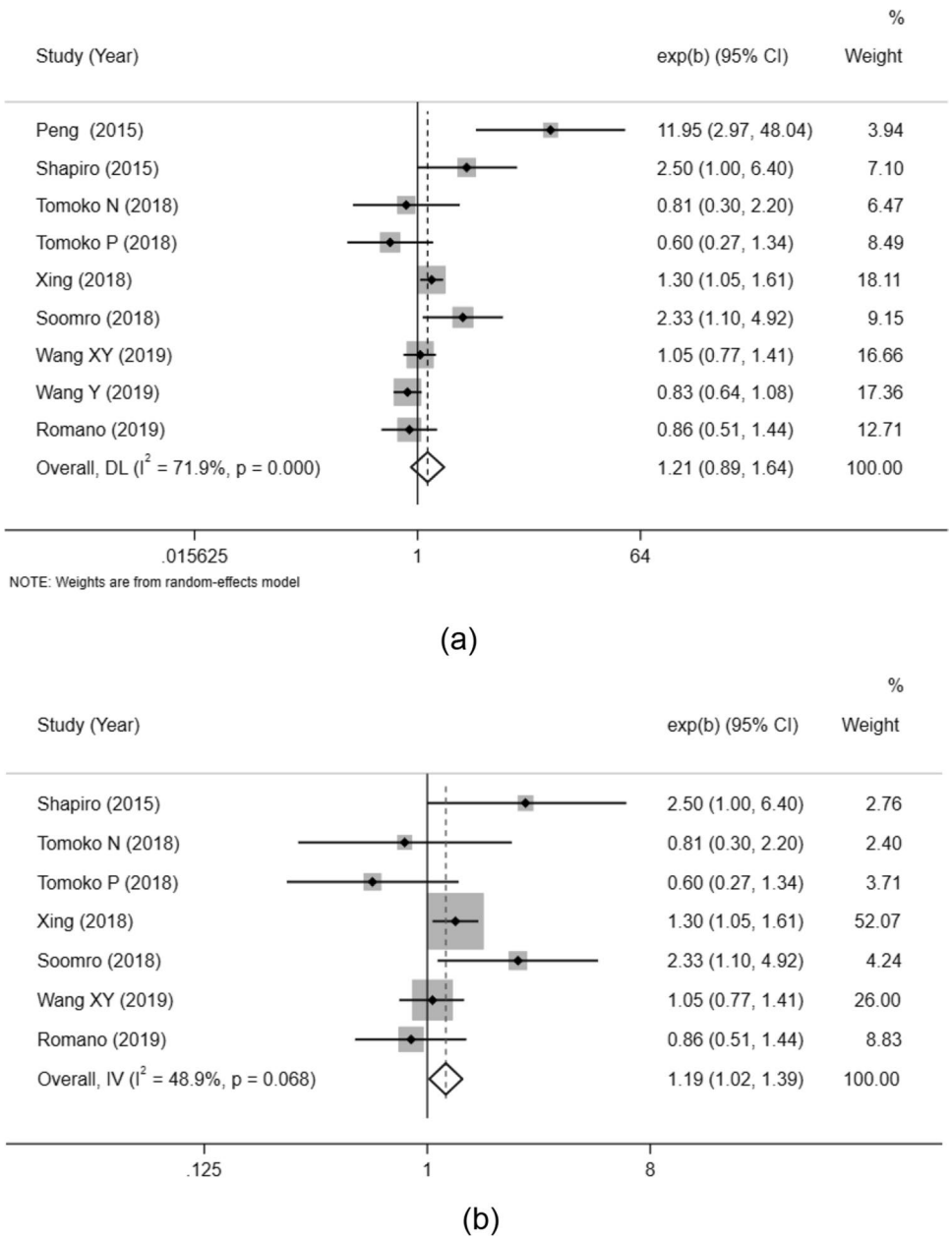

Fig. 2 **a** Forest graph illustrating the association between Cd exposure and risk for GDM. The overall estimate was obtained by adopting the random-effects model. The size of the gray square was proportional to the weight percentage of each study. The horizontal lines described 95% CI. The diamond sign indicated the pooled OR with its 95%CI. **b** Forest graph depicting the association after exclusion of two studies (Peng et al. 2015; Wang et al. 2019) Abbreviations: Cd, cadmium; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval

of Galbraith plot, results showed less stable, as eliminating study of Xing et al. (Xing et al. 2018) significantly shifted the result (Fig. 5b).

Discussion

Principal findings

Combined with the results of overall analysis and subgroup analysis, we could not surely reject that maternal exposure to Cd is not related to GDM; however, possibility is accounted that high dose of Cd exposure can increase the risk of GDM by 19% compared with low dose exposure. However, these results are required to interpret cautiously as the association might alter if future studies would enroll in the meta-analysis.

High heterogeneity among studies may be the primary reason of underestimating relative risk of the overall analysis. The Galbraith plot tool could be utilized to examine whether a particular study may affect the direction of heterogeneity (Ballarini et al. 2020). Exclusion of citations that indicated to be heterogeneous subsequently yielded a statistically significant association (Peng et al. 2015; Wang et al. 2019). We considered the filtration might reveal a more accurate and proper conclusion. Though Peng et al.

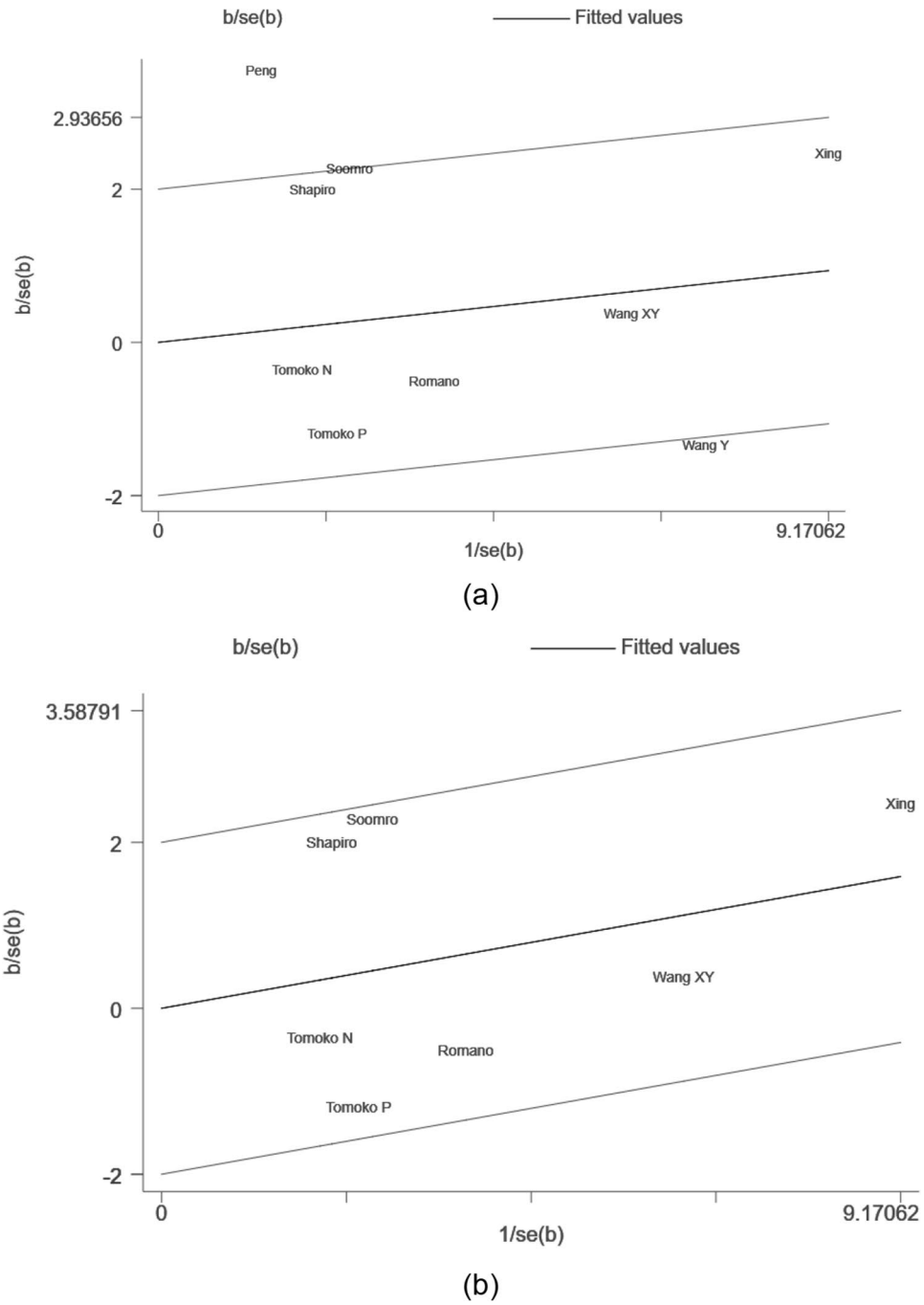

Fig. 3 **a** Galbraith plot illustrating the heterogeneity sources. Two citations (Peng et al. 2015; Wang et al. 2019) outside the parallel regression lines were identified as outliers. **b** Galbraith plot constructed by removing those two citations. All citations were within the regression lines

stringently followed recruitment criteria including conforming to universal GDM diagnostic approach and eliminating other clinical complications related to GDM, the sample size of whose study was still not large enough (Peng et al. 2015). Besides, critical factors consisting of maternal age, pre- pregnancy *BMI* and rate of cesarean were significantly different between cases and controls (Peng et al. 2015). Even though regression model was introduced to adjust those discrepancies, there is still an unavoidable bias existing in selection component. Another reason contributing to the high heterogeneity may be the unconventional application of meconium specimens. Though utilizing meconium matrices certainly offers advantages including convenience and non-invasiveness in sampling and mutual reflection of maternal and fetal exposure (Gil and Hernandez 2015), there are still remarkable disparities in sample preparation, instruments, statistical approaches, and metal concentrations among current biomonitoring studies (Michelsen-Correa et al. 2021). Notably, Cd could be actively transported to placental cells through channels (e.g., Divalent Cation Transporter-1,

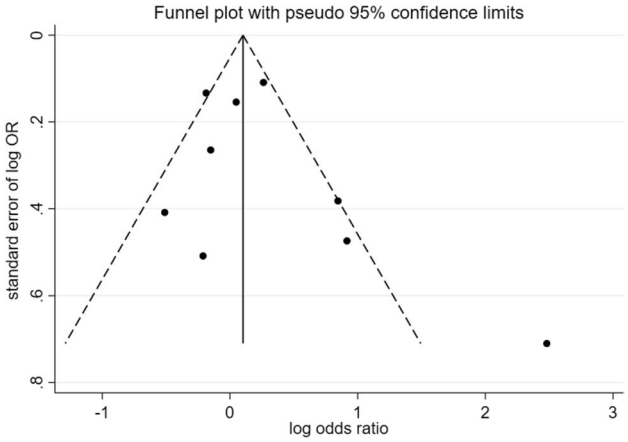

Fig. 4 Funnel plot describing the publication bias

DCT-1) involved in migration of essential divalent cations, contributing to the inequivalence between maternal and fetal circulation (Ballatori 2002). This might propose a doubt whether high level of metal deposition in meconium indicates high maternal intake (Michelsen-Correa et al. 2021), emphasizing the demand to ensure the appropriateness of choosing meconium as metal-exposure indicator. In addition, a low detection rate could be observed in the case–control samples, leading to some degree of assessment bias.

In addition, another study of Wang et al. could not explain causal relation between exposure and effect as they collected blood samples at delivery after the diagnosis of GDM (Wang et al. 2019), considered to be less proper for risk factor evaluation. Identification of causal relation of exposure and outcome is crucial for observational studies. It is noteworthy that varied biological samples have significant discrepancies in representing exposure window. Cd in blood (B-Cd) is valid for representing recent exposure, as it rapidly responds to the exposure doses, however, partially reflects long-term body burden attributable to its short half-life (3–4 months) (Järup et al. 1997). In this connection, extraction of maternal blood after the 28th gestational week when GDM is already diagnosed would be less persuasive in appraisal of the casual association. In contrast, Cd in urine indicates a strong temporal stability regardless of extraction time due to its long-lasting biological half-life (i.e., 10–30 years), making it appropriate to represent continuing body exposure (Järup and Akesson 2009; Mason et al. 1999; Vacchi-Suzzi et al. 2016). Similarly, meconium can assess long-term burden,

Table 2 Subgroup analyses

Total	No. of studies	Risk estimates			Heterogeneity		
		OR	LCI	UCI	*Q*	*P*	I^2
Study design							
Cohort studies	5	**1.27**	**0.96**	**1.68**	8.17	0.085	51.10%
Nested case–control studies	2	2.87	0.21	39.00	13.63	0.000	92.70%
Cross-sectional studies	2	0.68	0.36	1.26	0.21	0.645	0.00%
Sample form							
Maternal blood	5	0.94	0.76	1.18	12.07	0.017	66.90%
Maternal blood less Wang Y et al.[a]	4	1.31	0.63	2.72	8.67	0.034	65.40%
Urine	3	**1.17**	**0.99**	**1.38**	2.78	0.249	28.00%
Meconium	1	11.95	2.97	48.06	/	/	/
Diagnostic criteria							
Two-step[b]	4	2.406	0.943	6.138	15.37	0.002	80.50%
One-step[c]	5	0.991	0.771	1.273	9.07	0.059	55.9%
Study region							
Asia	6	1.09	0.76	1.56	20.66	0.001	75.80%
North America	2	1.36	0.48	3.84	3.87	0.049	74.10%
Europe	1	2.33	1.10	4.92	/	/	/
Sample size							
Small[d] (< 100 cases)	3	1.61	0.75	3.42	20.66	0.001	75.80%
Large[e] (≥ 100 cases)	6	1.03	0.76	1.56	6.63	0.036	69.80%

Subgroup analyses were performed to reduce heterogeneity. Studies were stratified by design, sample form, diagnostic criteria, study region, and sample size. [a]Because of the inconsistent methodology, citation of Wang Y was excluded in blood subgroup. [b]Two-step measuring means the diagnosis of GDM requires one positive value of Glucose Challenge Test (GCT) and two positive values of Oral Glucose Tolerance Test (OGTT). [c]One-step measuring means the diagnosis of GDM requires one positive value of OGTT. [d]Small sample size referred to study containing less than one hundred cases of patients. [e]Large sample size represented studies enrolling more than one hundred cases of patients

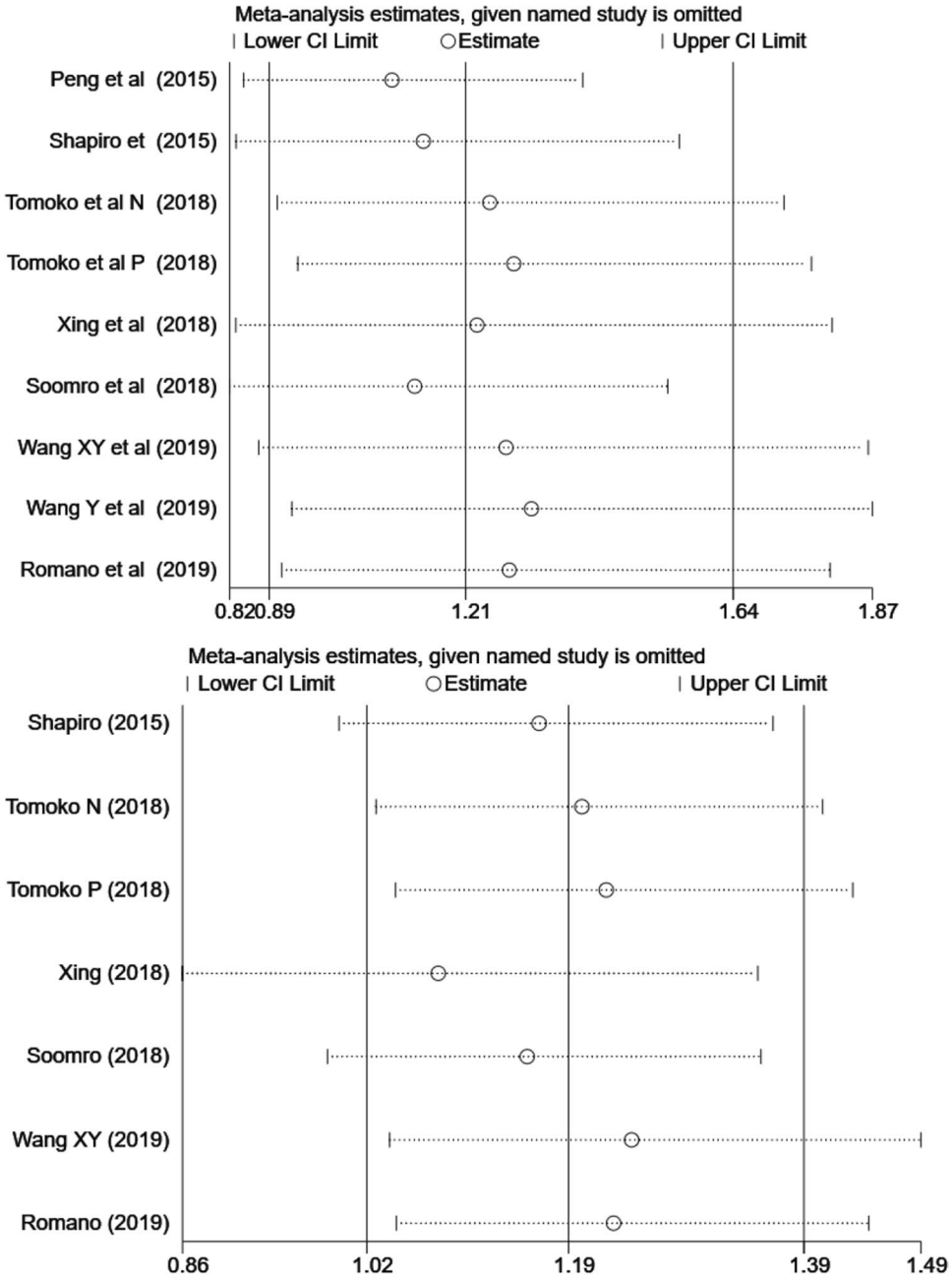

Fig. 5 **a** Sensitive analyses of the association between Cd exposure and risk for GDM were conducted by removing one study at a time. **b** Sensitive analyses after the filtration of two studies indicated by Galbraith plot (Peng et al. 2015; Wang et al. 2019). Abbreviations: Cd, cadmium; GDM, gestational diabetes mellitus

as whose secretion sustains from the 12th gestational week to the end of pregnancy (Gil and Hernandez 2015; Woźniak et al. 2018). Therefore, aggregating urine and meconium samples as exposure indicators after the diagnosis of GDM is plausible to explain the correlation. In our quantitative synthesis, all the studies except citation of Wang et al. (2019) could potentially elucidate the causation of risk factor and endpoint.

Notably, a significant association between Cd and GDM was yielded in women with normal weight; however, it did not occur in obese mothers. Meanwhile, Romano et al. observed slightly increased risks of hyperglycemia and higher urinary Cd concentrations in women with normal weight ($BMI \leq 25$ kg/m^2) comparing to overweight women ($BMI > 25$ kg/m^2). The reasons may be being overweight is an intensive risk factor for GDM which conceals the role of Cd exposure. Therefore, exposure to Cd may pose an additional risk for women who are not at risk for being obesity. However, the significant association in pregnant women with normal weight is needed to interpret with caution due to the small-scale sample sizes and potential variances between normal and overweight group, emphasizing the demands of future study to investigate whether pre-pregnant *BMI* could modify the Cd-GDM correlation.

Source of heterogeneity

Various biological samples in metal measurement may contribute to heterogeneity and underestimation of the correlation. The current subgroup analyses observed a lower heterogeneity in U-Cd group than B-Cd group due to its stability and longevity as mentioned before. In addition, a higher and nearly significant OR data could be found pooling studies assessing U-Cd than B-Cd, giving evidence of that the application of blood sample may underestimate risk estimates of chronic disease as it ignores the cumulative Cd exposure (Mason et al. 1999). This suggests analysis of the contaminant in urine may be more apposite to identify Cd exposure. Another factor that increases the heterogeneity among studies is study design. Pooling cohort studies reduced the heterogeneity and lifted OR estimate to approach the statistically significant value which indicates a more applicable and appropriate result explained by cohort study.

Variances in diagnostic criteria devote to heterogeneity. Four studies adopted two-step screening for GDM in which a 50 g Glucose Challenge Test (GCT) was performed initially and a 75 g or 100 g Oral Glucose Tolerance Test (OGTT) was conducted lately if the result of GCT exceeds clinical cut-off value. A diagnosis of GDM was ensured if two blood glucose levels exceed clinical cut-off values. However, one-step 75 g OGTT were utilized in remaining studies and GDM is diagnosed if one parameter exceeds clinical cut-off points of blood glucose concentration (i.e., fasting, 1 h, 2 h after glucose intake), which may promote the incidence of GDM. Thus, variance in diagnostic criteria may contribute to underestimation of relative risks as GDM cases might be unrecognized if two-step approach has been applied. Notably, impaired glucose tolerance (IGT) refers to a pre-diabetic stage, indicating existent glucose metabolic or insulin functional impairments, and likely transmits to diabetes in later life. Soomro et al. observed a significant association between Cd and IGT ($OR = 1.61$, 95% CI = [1.05, 2.48]); however, Shapiro et al. and Romano et al. did not announce the same positive results (Romano et al. 2019; Shapiro et al. 2015; Soomro et al. 2019). Therefore, there is a possibility that Cd could induce glucose metabolic impairments which do not approach the clinical criteria for GDM, which emphasizes future study to further investigate the association between Cd and pre-diabetes.

Elements such as study region may contribute to heterogeneity though subgroup analysis failed to explain it, as stratifying of the citations by study region did not reduce heterogeneity either for studies conducted in North America or in Asia (Supplementary table 3). For blood samples, general Cd concentrations in studies from China (Taiyuan) and France (Poitiers and Nancy) were higher than those from Japan and Canada due to the heavy industrial activities and dependence of coal for fueling in Taiyuan and high smoking rate among gestational population in Poitiers and Nancy. Meanwhile, the cohort exposure level in study from Canada was lower than national surveys monitoring women of the same age-period (Shapiro et al. 2015). As with urine specimens, Cd contents were higher in studies from China comparing to which from the USA. Romano et al. stated a lower degree of Cd levels in their cohort comparing to the national survey (Romano et al. 2019). Therefore, the low Cd concertation could elucidate some unsignificant associations as whose contribution to GDM was masked by other strong risk factors including obesity and maternal age. Additionally, sample size donates trivially to the heterogeneity, since only a slightly reduced heterogeneity could be detected in study with large patient population. Besides, inherent disparities including genetic factors, ethnicity, lifestyle, incomes, and educational levels might dedicate to the heterogeneity which cannot be avoided in observational study.

Linkages between Cd toxicity and GDM

In early stage of pregnancy, there is a promotion of glucose uptake and fat storge accompanied by increased insulin sensitivity to meet the energy demands for fetal growth and later pregnancy (Weir et al. 2001). However, increased insulin resistance could be viewed in late gestation, as insulin-antagonistic hormones (e.g., TNF, leptin, estrogen, progesterone, cortisol, placental lactogen, and placental growth hormone) significantly emerge, resulting in the elevation of maternal glucose level and free fatty acid concentrations (Parsons et al. 1992). During that process, insulin-producing cells (pancreatic β cells) undergo various compensatory behaviors including hypertrophy, hyperplasia, and increased glucose-stimulated insulin secretion to maintain glucose metabolism (Catalano et al. 1999; Parsons et al. 1992). Thus, minor defects in the β-cell function including inabilities to perceive blood glucose level or secret sufficient insulin in response may be exserted and exaggerated in times of pregnancy, a kind of metabolic stress (Plows et al. 2018), during which special condition Cd exposure may additionally disrupt gestational glucose metabolism leading to hyperglycemia or ultimately GDM..

Animal studies demonstrated that Cd could selectively accumulate in pancreatic islets and alter their insulin secretion followed by cytotoxicity and inflammation (Al Doghaither et al. 2021; El Muayed et al. 2012; Fitzgerald et al. 2020). Intracellular oxidative stress is a crucial factor constituting metal-induced cytotoxicity. Oxidative biomarkers (e.g., ROS, TBARS, Nrf2) significantly elevated in Cd-treated pancreatic β cells (10uM $CdCl_2$/d) (Al Doghaither et al. 2021). Though Cd is not a natural redox agent, it is a high thiol-affinity agent that can bind thiol-contained antioxidant enzymes (GSH) and replace other free redox-active metal in multiple proteins, indirectly promoting the

generation of ROS (Cuypers et al. 2010). Intracellular ROS could further activate multiple downstream signaling pathways and damage mitochondria function donating to later cell dysfunction, apoptosis, and death events (Bhatti et al. 2017). Multiple studies have observed a phenomenon of Cd-induced apoptosis in pancreatic cells via complex mechanisms (Al Doghaither et al. 2021; Chang et al. 2013; Huang et al. 2019; Wu et al. 2021). Al Doghaither et al. inspected up-regulation of pro-apoptosis gene expression (Bax), and apoptosis intermediate effector casepase-3 (cas-3) protein yet down-regulation of anti-apoptosis gene expression (Bcl-2) in Cd-treated pancreatic beta cells (Al Doghaither et al. 2021). Chang et al. first reported the activation of JNK (c-Jun NH(2)-terminal kinases), caused by Cd-induced intracellular oxidative stress, was a pivotal signaling component in Cd-induced pancreatic β cell apoptosis. (Chang et al. 2013). In line, Huang et al. indicated Cd-induced intracellular Ca^{2+} generation was another trigger of downstream activation of JNK apoptotic pathway (Huang et al. 2019). In addition, Wu et al. suggested a novel mechanism of Cd-induced apoptosis via the activation of the endoplasmic reticulum stress pathway in Cd-administrated pig pancreatic β cells correlated with the disturbance of immune cells (Th1/Th2) equilibrium and increase of Th1 cytokine secretion (Wu et al. 2021). Inflammation occurs as a defense reaction in response to numerous stimuluses including stress, pathogens, and toxicants. Inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) were elevated in Cd-treated pancreatic β cells. (Al Doghaither et al. 2021). Additionally, pro-inflammatory lipid contents were promoted in one lipidomic analysis of Cd-treated pancreatic β-cells, marking the interference of Cd to lipid metabolism (Hong et al. 2021). Therefore, oxidative stress, apoptosis, and inflammatory response may independently, or mutually contribute to Cd-induced pancreatic β cell injury.

Apart from the direct toxicity to pancreatic β-cells, exposure to Cd induces tissue insulin resistance in several organs and tissues consisting of skeletal muscles, liver, and adipose tissues, which further deteriorates the imbalance of glucose homeostasis (Buha et al. 2020). Accumulation of Cd in varied types of cells could inhibit the downstream signaling pathway of insulin receptor caused by the generation of ROS (Sarmiento-Ortega et al. 2021). In adipose tissues, suppression of insulin pathway may enhance lipogenic process and secondarily promote lipolysis (Petersen and Shulman 2018). Sarmiento et al. observed hypertrophy of adipose tissues accompanied by increased triglycerides synthesis and accumulation in Wistar rats orally exposed to Cd agent (Sarmiento-Ortega et al. 2021). In the liver, lipogenesis and glycogen synthesis are inhibited yet gluconeogenic process is activated (Petersen and Shulman 2018). Similarly, glucose utilization and storage are constricted in skeletal muscles as total glucose transport and glycogen synthesis are reduced. (Buha et al. 2020). Insulin resistance results in a lifted level of blood glucose that further deteriorate pancreatic β cell function via glucose overload, forming a vicious circle in the etiology of GDM (Plows et al. 2018).

The placenta is an essential organ involved in the maternal–fetal nutrients transportation but also the secretion network of hormones and cytokines. Recent study pointed out Cd was associated with downregulation of glucose transporter (GLUT3) mediated by site-specific DNA methylation (Xu et al. 2016). In addition, studies indicated the disruption of Cd on the biological synthesis and secretion of placental-derived hormones including progesterone and placental lactogen associated with regulation of gestational glucose metabolism (Kawai et al. 2002; Lee et al. 2009; Xiong et al. 2020). However, concrete relationships and mechanisms of Cd exposure, placental dysfunction, and GDM are still not clear, warranted to be determined and investigated in future study. Therefore, the potential consistency indicates a concern about the linkage between Cd exposure and risk for GDM (Fig. 6), though it still needs to be verified in gestational animal models.

Strengths and limitations

The major strength of our meta-analysis is, to our knowledge, the first quantitative overview features a new glance of the potential positive association between Cd exposure and diabetes occurring in the gestational phase based on the available published studies. To thoroughly interpret the result, we persistently retrieved five databases proven to be authoritative and representative in evidence-based medicine to find and update eligible citations in the whole period of our meta-analysis. We continued to ensure the efficiency by detecting causal relationship of heavy metal exposure and GDM outcome and investigate heterogeneity through various methods, verifying the completeness and credibility of our work.

However, some limitations that existed in our work are also demanded to interpret with caution. There is an undeniable fact that the number of studies included in this quantitative synthesis was not ideally abundant due to the lack of epidemiological studies focusing on our study object. Another drawback may attribute to **t**he insufficient statistical power, since our analytical strategy is to combine OR data from the highest exposure level versus reference level, which is commonly applied in most meta-analysis evaluating risk factor with stratified values. However, the risk estimates obtained by this method could only imply population with highest exposure level in the original study, giving rise to ignorance of OR data from low and middle exposure levels. A dose–response curve could be introduced to solve the issue; however, we failed to perform it on account of the constricted available data.

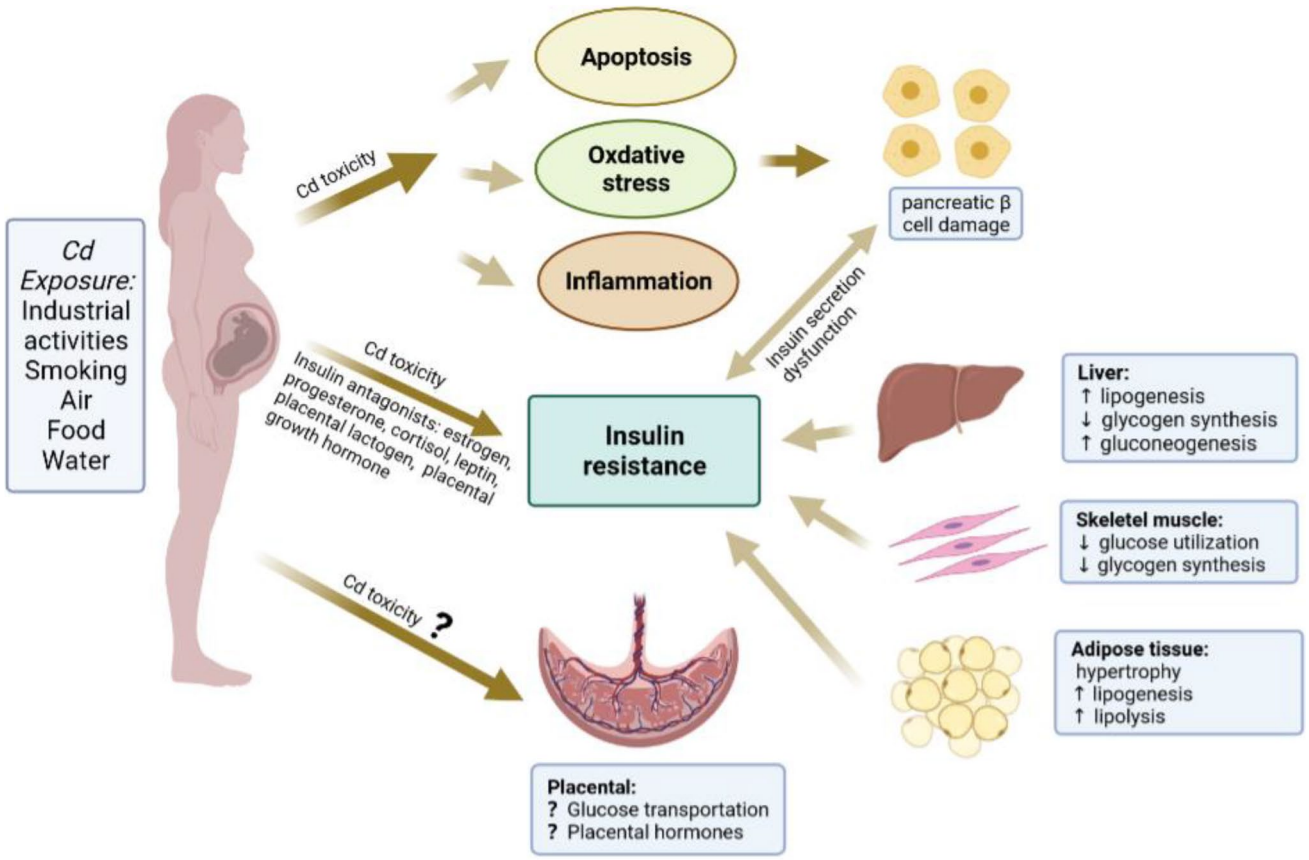

Fig. 6 The possible linkages between Cd exposure and GDM. Cd could induce pancreatic β cell damage and disturb insulin secretion via oxidative stress, apoptosis, and inflammatory reaction. Cd toxicity causes wide tissue insulin resistance via suppression of insulin pathways. The role of disturbances of Cd on placental glucose metabolism and hormones secretion in the etiology of GDM is still unclear

Inspiration for future

The prevalence for GDM is continuously elevated, ascribing to the standardization of clinical criteria and more frequent occurrences of high-risk factors including advanced maternal age, history of diabetes or GDM, obesity, smoking behavior, unhealthy dietary habits, and less physical activities (Zhang and Ning 2011; Zhang et al. 2016). Our meta-analysis proposes another important sight to investigate the etiology of metabolic gestational disease in terms of the alterations after heavy metal exposure. In this sense, future exploration based on large-scale, precise designed and standardized executed research focusing on the association between hyperglycemic metals exposure as well as their interactional effects and risk for GDM would be taken as priorities.

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Author contribution M.Q.Z put forward the study design. M.Q.Z and L.Q.P conducted literature search, quality appraisal and data extraction. M.Q.Z performed the procedure of data analyses. M.Q.Z and L.Q.P contributed to work of writing the draft of the manuscript. J.M.W, R.C, and Z.X.O helped to answer crucial questions and provided significant suggestions for language correction. Y.W.F guaranteed the whole procedure and gave guides when confuses arose. All authors agree with the last version of manuscript.

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Data availability All concerned data are posted on the manuscript and its supporting information files. Moreover, registration form of this meta-analysis (CRD42021249057) can be viewed on PROSPERO database: https://www.crd.york.ac.uk/PROSPERO.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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