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Is serum zinc status related to gestational diabetes mellitus? A meta-analysis

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Abstract

Gestational diabetes mellitus (GDM) is a common medical disorder that begins during pregnancy. The present work aimed to investigate the relationship of maternal or foetal circulatory zinc levels with GDM. Related studies were retrieved against the PubMed/Medline, Web of Science, Scopus databases till July 2020. The overall effects were expressed as standard mean difference (SMD). Furthermore, the random effects model was used to assess the summarised risk ratios (SRRs) to determine the relationship between zinc and the risk of GDM. A total of 15 articles involving were retrieved for meta-analysis; in the meantime, 4955 subjects including 1549 GDM cases were enrolled for quantitative analysis. Compared with normal control, GDM cases had decreased circulating zinc level on the whole, but the difference was not statistically significant (SMD = −0.40, 95%CI: −0.80 to −0.00, P = 0.05). Interestingly, upon subgroup analysis stratified by serum zinc content but not plasma zinc concentration, there was significant difference in zinc content between GDM cases and normal controls (SMD = −0.56; 95%CI: −1.07 to −0.04, P = 0.03). Meanwhile, subgroup analysis also revealed similar tendency among the Asians and during the 2nd trimester, but not among the Caucasians or during the 1st or 3rd trimester. Data extracted from four studies that compared pregnant women with GDM in the high level of zinc and GDM in the low level of zinc yielded an SRR of 0.929 (95%CI: 0.905–0.954). According to existing evidence, the serum zinc content decreases among GDM cases compared with subjects with no abnormality in glucose tolerance, in particular among the Asians and during the second trimester. Nonetheless, more well designed prospective study should be carried out for understanding the dynamic relationship of zinc level with the incidence of GDM.

KEYWORDS
diabetes mellitus, meta-analysis, pregnancy, risk ratio, zinc

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is an abnormal pathophysiological change of glucose metabolism in pregnant women (McIntyre et al., 2019). Hyperglycaemia during pregnancy can induce oxidative stress (OS) in the mother and foetus, playing a role in pregnancy and normal childbirth (Al-Saleh et al., 2004; Farrar et al., 2016), which may be related to poor foetal prognosis, such as foetal distress, giant infants or other congenital developmental abnormalities (Anderson et al., 2005; Bo et al., 2005). The GDM incidence shows an increasing trend, especially among the developing countries such as Africa, China, and India, which has attracted more attention (Gao et al., 2019; Muche et al., 2019).

The nutritional reserves and diet of pregnant women provide all the micronutrients for supporting optimal foetal development, which plays an essential role for a safe pregnancy (Zgliczynska & Kosinska-Kaczynska, 2021). Recently, it has been suggested that autoimmune antibodies of zinc transporter-8 takes part in the pathogenesis of GDM (Dereke et al., 2016). Zinc deficiency during pregnancy can lead to related complications (Uriu-Adams & Keen, 2010), from the beginning of infertility to pregnancy hypertension, gestational diabetes, foetal growth retained, etc. in the gestation process, as well as the adverse pregnancy outcomes such as miscarriage and premature delivery (Oh et al., 2020; Uriu-Adams & Keen, 2010).

Zinc may be related to the maintenance of physiological glucose absorption, regulation of glucose utilisation in cells, and reduction of insulin resistance degree (Cooper-Capetini et al., 2017; Cruz et al., 2017). Some scholars believe that GDM is closely related to the imbalance of maternal serum zinc (Wang et al., 2002). Therefore, some reports suggest that pregnant women need to supplement the trace element zinc during pregnancy (Karamali et al., 2016; Li & Zhao, 2019). The zinc concentration within umbilical cord blood increases relative to the maternal circulation level, as well as zinc actively transported in the placenta, suggesting the importance of zinc for foetal growth (Al-Saleh et al., 2004; Wibell et al., 1985).

Zinc, once of the vital trace elements, exerts a vital part in cell metabolism to regulate cell growth and cell differentiation (Hambidge, 2000; MacDonald, 2000). It is an important component of more than 1000 proteins, such as the zinc transporters, zinc binding factors, metalloenzymes, as well as antioxidant enzymes. These zinc binding proteins participate in various biologically necessary events, such as metabolism of proteins and carbohydrates, biosynthesis of RNA and DNA, cell differentiation and duplication, together with hormone regulation (Maret, 2009; Prasad, 2008). Zinc plays a critical role in the antioxidant system in body. Antioxidant properties resist free radicals in the islet cells along with pancreatic cells (Sun et al., 2009), by enhancing tyrosine kinase phosphorylation and regulating the insulin tyrosine kinase receptors, not only insulin synthesis, storage and secretion are effective (Wiernsperger & Rapin, 2010), but also effective for insulin function (Konukoglu et al., 2004). Catalase and superoxide dismutase, will delay the oxidation process, especially the oxidation process associated with diabetes (Caulfield et al., 1998).

Key messages

- The measurement of serum zinc concentration during the second trimester of gestation period helps to distinguish high risk cases for gestational diabetes mellitus (GDM), so that these cases can receive more care.
- Simultaneously, it is simple and feasible to measure the serum zinc level. Besides, measuring zinc elements potentially indicates that it is necessary to alter the diet and change the health promotion behaviours (e.g., Asian pregnant women).
- Some modifications in the lifestyle are important for the pregnant females not just according to the decreased zinc element contents.

Several scientific studies have shown that the concentration of maternal serum zinc during pregnancy is associated with GDM incidence (Hamdan et al., 2014; Mishu et al., 2019). Both epidemiological and experimental articles indicate that, zinc uptake can prevent type II diabetes mellitus (T2DM)(Taylor, 2005). The double-blind, prospective randomised, placebo-controlled, study supports the finding that higher zinc uptake relates to the reduced T2DM incidence (Marreiro et al., 2006). In another randomised control trial, compared with women who did not receive zinc supplements, pregnant women with GDM supplemented with zinc can improve metabolic conditions, such as reducing plasma glucose and serum insulin levels (Karamali et al., 2015). But the study of the correlation between serum zinc and GDM pathogenesis remains a source of controversy. For instance, certain articles report that GDM cases have decreased serum zinc levels relative to the normal pregnant women (Mishu et al., 2019), but others suggest no difference in serum zinc concentrations between GDM women and healthy pregnant women (Behboudi-Gandevani et al., 2013; Luo et al., 2020).

In order to comprehensively evaluate the association of zinc status during pregnancy with GDM incidence, the present meta-analysis and systemic review was carried out on related articles, it is necessary to draw conclusions for determining whether the gestational dietary or circulating zinc was the key factor related to gestational diabetes.

2 | METHOD AND MATERIALS

2.1 | Search strategy

The protocol of this meta-analysis and systematic review was retrospectively registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO) as CRD42021240599 on 19 April 2021. The

present systemic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines (McInnes et al., 2018; Shamseer et al., 2015) (http://www.prisma-statement.org/) and the statements in the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria (Stroup et al., 2000). Databases, including Medline, Web of science, and Scopus, were searched to identify articles reporting the association of zinc level with GDM incidence from inception till 8 July 2020.

Studies concerning serum or plasma zinc and the GDM were reviewed by MEDLINE database (through PubMed; 1966 till July 2020), Scopus database (using Scopus; 1974 till July 2020), and Web of Science Core Collection database (via Web of Science [v.5.35]; 1926 till July 2020) according to the MEDLINE database via two reviewers independently (J.F. and B.Z.).

The Medical Subject Headings (MeSH) search words below were adopted to search the MEDLINE database, including GDM or diabetes, diabetes or gestational, pregnancy-induced or pregnancy induced diabetes or diabetes mellitus or gestational diabetes, gestational; and zinc or plasma zinc or serum zinc (Supporting Information S1). Other related articles were manually retrieved from the reference lists or citations in the initial search or using the "Similar Articles" PubMed option.

For Scopus database, the following search term was used in this work, including "zinc", "zinc-binding proteins," "zinc compounds," "gestational diabetes mellitus," "diabetes pregnancy," "GDM," and "insulin gestation". In this meta-analysis, only human studies written in English were enrolled. All the relevant studies identified in the present meta-analysis were comprehensively examined according to the reference lists. Each literature was registered at the ISI WEB OF KNOWLEDGE: WEB OF SCIENCE database (1991 to 2020), which can be applied in searching the cited studies.

2.2 | Eligibility criteria and study selection

The eligibility criteria were conducted in accordance with the PICOS (Population, Intervention/Exposure, Control, Outcomes, and Study design) framework:

a. Population: participants were free of pre-pregnancy diabetes (type 1 or 2 diabetes) and/or infectious diseases.
b. Intervention/Exposure: The exposure of interests were serum or plasma zinc level.
c. Control: The controls were healthy pregnant women.
d. The outcome of interest was GDM, and diagnosis of GDM patients was in accordance with the criteria of the glucose tolerance test or oral glucose tolerance test.
e. Study design: they contained original data from observational studies (cohort, case–control, and cross-sectional).

The following exclusion criteria were also used:

a. Reviews;
b. studies whose units of measurement were not given;
c. experimentation on animals or in vitro;
d. no available full text or eligible information;
e. no control group;

(e) For different articles reported by one institution, the most rigorously published one was adopted for avoiding data duplication.

In addition, two researchers (J.F. and T.Z.) independently evaluated the topics and abstracts of those enrolled studies. Any disagreement between these two researchers was settled by the opinion of the third researcher (B. Z.).

2.3 | Data collection and quality evaluation

In this meta-analysis, the information below was collected based on every article: author; country; publication year; population; study design; age; sample size; trimester at which the zinc level was measured; the diagnosis standards for GDM; zinc analysis method; together with outcomes obtained based on every article. Apart from the collection of the above-mentioned information, the study quality was also assessed. This work applied the Newcastle-Ottawa Scale (NOS) guidelines (McInnes et al., 2018) in evaluating study quality. Studies modified by NOS guidelines achieving at least 6 stars were considered as the high-quality studies.

2.4 | Heterogeneity evaluation

The fixed effects model was used in the present work, unless there was obvious heterogeneity. I^2 test was used to evaluate the heterogeneity degree; to be specific, the I^2-value $= 25$ indicated low inconsistency, that of 25–50 represented moderate inconsistency, and that of >50% represented great inconsistency (Higgins & Thompson, 2002). We also did sub-group analysis for exploring the possible heterogeneity source in the presence of significant heterogeneity among different articles. Subgroup analysis was conducted based on serum or plasma level, the trimester period, geographic site, study design, and cord blood.

2.5 | Statistical analysis

The conversion factors were utilised for converting zinc measures into µg/L; for instance, results presented as µg/dL were multiplied by 10; if blood zinc level were shown as µM or µmol/L were divided by 0.0153, if results presented as mg/L, multiply 1000; and serum zinc was measured by µg/ml, then multiply 1000, respectively.

Standard mean difference (SMD), together with 95%CIs, was determined for assessing those differences between different groups with regard to circulating zinc status. Z test was carried out to determine the significance level. Effect sizes, along with the corresponding

95%CIs were demonstrated by forest plots. I^2 statistics and Cochran's Q statistics were utilised to assess the heterogeneities among the enrolled articles.

The funnel plot was used to detect the potential publication bias. In the absence of any publication bias, all data points showed symmetric distribution in an inverted V shape. Moreover, for evaluating the heterogeneities, Egger regression asymmetry plot was drawn based on those data points (Egger & Smith, 1995), whereas publication bias was assessed by Egger graphical exploration (Egger et al., 1997).

For dose–response meta-analysis, due to the low GDM incidence (about 10% among the pregnant women) (Lee et al., 2018), Odds Ratios (ORs) were used to be Risk Ratios (RRs) in a majority of articles. When related data were collected and sorted, RRs together with the corresponding 95% CIs were compared between the highest and the lowest zinc contents. For exploring the association of zinc exposure with GDM incidence, the random effects model was used to assess the summarised RRs (SRRs) with corresponding 95% CIs, for the sake of summarising the GDM risk among the enrolled articles (Nikolakopoulou et al., 2014). A linear dose–response trend was obtained for each study using Greenland and Longnecker's method (Greenland & Longnecker, 1992). In addition, the random effects model was also applied in detecting variations within and between studies. As a result, those study-specific RRs were summarised to compare pregnancies between the highest and lowest zinc levels.

The statistical analysis was performed using a spread sheet (Microsoft Excel 2010; Microsoft, Redmond, WA, USA), while the Review Manager (version 5.3, http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5) was employed to assess the risk of bias, synthesise data and draw the funnel plots. Because of the functionality and uniqueness of the statistical software, STATA meta.ado module (version 16.0; College Station, TX, USA) was utilised to perform Egger test/Egger plot and meta-regression. A difference of $P < 0.05$ indicated statistical significance.

3 | RESULTS

3.1 | Study retrieval

The present systemic review and meta-analysis flow path was demonstrated following the PRISMA group (Figure 1). Figure 1 shows the flow chart for study inclusion and exclusion. According to study retrieval strategy, after removing the duplicates ($n = 265$), a total 77 citations were discovered based on those three databases. Among the 77 articles, 12 irrelevant articles, three Review, three not English articles, and four deficient maternal results, respectively, and were excluded. Simultaneously, two researchers independently selected the titles as well as abstracts for those possible eligible articles ($n = 55$). Another five papers contained multiple adverse gestational outcomes, 13 studies reported incomplete data, and 12 not meet the participates criteria of our study.
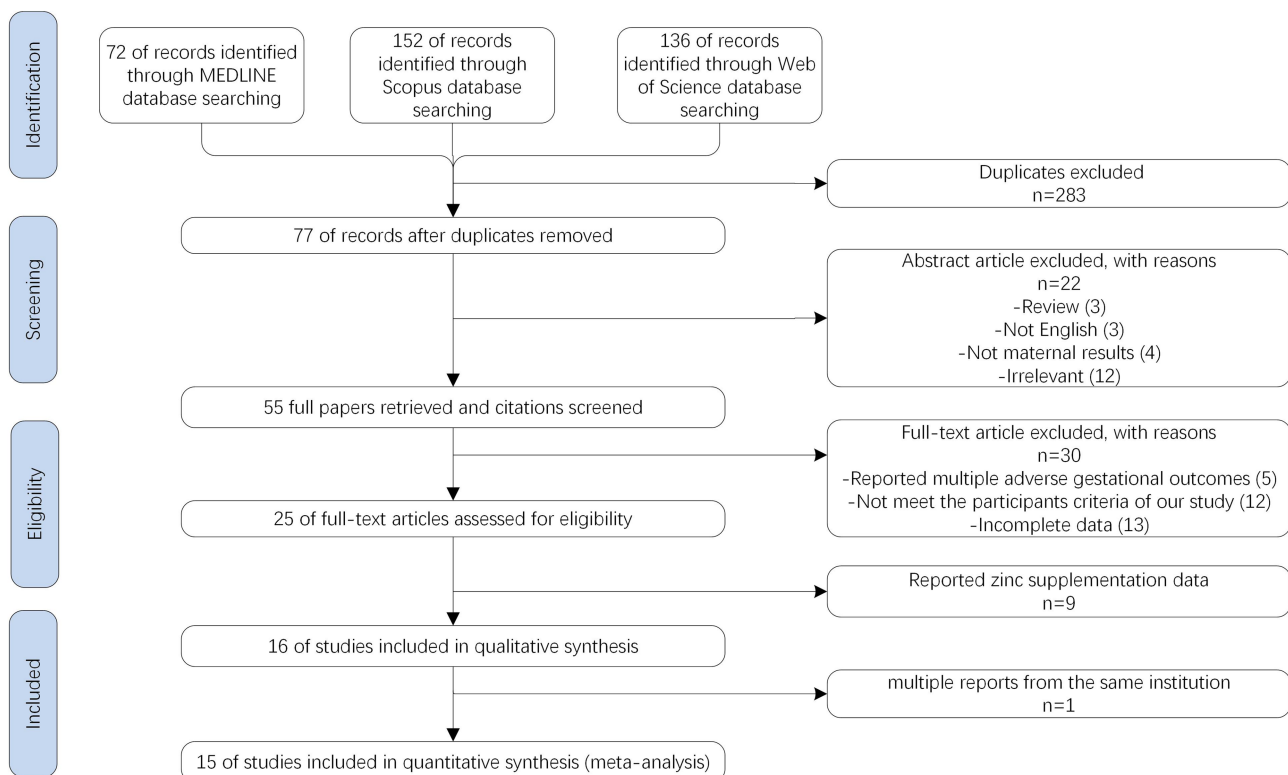

FIGURE 1 Flow diagram of study recruiting

There are nine studies includes the effect of zinc supplementation on women with GDM.

In addition, Al-Saleh (Al-Saleh et al., 2006) and Al-Saleh (Al-Saleh et al., 2007) were regarded as one study in analysis because they were conducted at the identical institution and population. For another two articles Al-Saleh (Al-Saleh et al., 2004) and Al-Saleh (Al-Saleh et al., 2005) reported by one institution, circulating zinc value are presented as mean and SEM but not SD, for the latter reports. Therefore, we selected the former published one was adopted for avoiding data duplication.

In addition, because two articles (Mishu et al., 2019; Wibell et al., 1985) included two different trimesters, data were collected in the form of two separate studies. As a result, 15 articles were eventually enrolled into the present meta-analysis (Al-Saleh et al., 2004, 2007; Behboudi-Gandevani et al., 2013; Bo et al., 2005; Borella et al., 1990; Hamdan et al., 2014; Lewandowska et al., 2020; Luo et al., 2020; Mahmoud et al., 2012; Mishu et al., 2019; Noureldeen et al., 2018; Roshanravan et al., 2018; Wang et al., 2002; Wibell et al., 1985; Wilson et al., 2018) including altogether 4955 females.

3.2 | Features of the enrolled studies

Table 1 shows baseline features of the enrolled articles. The enrolled articles were observational studies published between 2000 and 2019, which involved 1549 GDM cases (144 with glucose tolerance impairment) together with 3406 normal pregnant females. Among those 15 articles enrolled in this meta-analysis, three were completed in Kuwait (Al-Saleh et al., 2004, 2007; Mahmoud et al., 2012), two in China (Luo et al., 2020; Wang et al., 2002), two in Italy (Bo et al., 2005; Borella et al., 1990), two in Iran (Behboudi-Gandevani et al., 2013; Roshanravan et al., 2018), one in Poland (Lewandowska et al., 2020), one in Bangladesh (Mishu et al., 2019), one in Saudi Arabia (Noureldeen et al., 2018), one in Sweden (Wibell et al., 1985), one in Australia (Wilson et al., 2018) while one in Sudan (Hamdan et al., 2014).

The diagnosis of GDM is generally made between 24 and 28 weeks in the gestation period. Blood samples were collected in the second trimester (Behboudi-Gandevani et al., 2013; Bo et al., 2005; Luo et al., 2020; Mishu et al., 2019; Roshanravan et al., 2018; Wibell et al., 1985) and third trimester (Borella et al., 1990; Mahmoud et al., 2012; Mishu et al., 2019; Noureldeen et al., 2018; Wibell et al., 1985) of gestation to measure zinc level. For the enrolled articles, the sample size was 21–1496.

Ten studies were case–control (Al-Saleh et al., 2004, 2007; Bo et al., 2005; Borella et al., 1990; Hamdan et al., 2014; Mahmoud et al., 2012; Noureldeen et al., 2018; Roshanravan et al., 2018; Wang et al., 2002; Wibell et al., 1985), and prospective cohorts (Behboudi-Gandevani et al., 2013; Lewandowska et al., 2020; Luo et al., 2020; Wilson et al., 2018) and a cross-sectional design (Mishu et al., 2019). Table 2 demonstrates the study quality evaluation for cohort study and Table 3 shows study quality evaluation for case–control study. As

suggested by quality evaluation, 15 articles had at least six stars according to the modified NOS (Tables 2 and 3).

3.3 | Pooled meta-analysis

According to Figure 2, the pooled serum zinc levels among GDM cases decreased compared with those among normal controls, but the difference was not significant (SMD = −0.40, 95%CI: −0.80 to −0.00, P = 0.05). The random-effects model was utilised to analyse SMDs of all articles because of the obvious heterogeneity (P < 0.00001, I^2 = 96%). There was no evidence of obvious publication bias in this meta-analysis (Figure 3a,b) (Begg's test: P = 0.274; Egger's test: P = 0.557).

3.4 | Subgroup analysis

For exploring the potential heterogeneity source and obtaining complete data to carry out the present meta-analysis, this study conducted sub-group analysis.

First of all, subgroup analysis stratified by trimester period was conducted, as shown in Figure 4. Pooled analysis was completed using the random effects model due to the obvious heterogeneity (First trimester: not applicable; Second trimester: P < 0.00001, I^2 = 97%; Third trimester: P < 0.00001, I^2 = 96%). According to Figure 4, there was significant difference in zinc content between GDM patients and normal controls through subgroup analysis stratified by second trimester (SMD = −0.78; 95%CI: −1.42 to −0.13, P = 0.02), and the difference did not exist at first trimester (SMD = 0.09; 95%CI: −0.12 to 0.30, P = 0.40) or third trimester (SMD = −0.62; 95%CI: −1.91 to 0.67, P = 0.35).

For subgroup analysis stratified by serum and plasma zinc measurement, two studies evaluated the zinc level in plasma (Borella et al., 1990; Luo et al., 2020). In subgroup analysis stratified by plasma or serum zinc for the measurement of zinc level among pregnant females, there was significant difference in zinc content between GDM patients and normal controls for serum zinc level (SMD = −0.56; 95%CI: −1.07 to −0.04, P = 0.03), but not for plasma zinc level (SMD = 0.46; 95%CI: −0.45 to 1.38, P = 0.32). The results were summarised in Figure 5.

In the subgroup analysis stratified based on geographical position, nine articles were categorised into Asian group (Al-Saleh et al., 2004, 2007; Behboudi-Gandevani et al., 2013; Luo et al., 2020; Mahmoud et al., 2012; Mishu et al., 2019; Noureldeen et al., 2018; Roshanravan et al., 2018; Wang et al., 2002), four were classified as European group (Bo et al., 2005; Borella et al., 1990; Lewandowska et al., 2020; Wibell et al., 1985), and one African group (Hamdan et al., 2014). The four articles conducted in Asia and Europe, separately, showed heterogeneities (for Asia: P < 0.00001, I^2 = 96%; for Europe: P < 0.00001, I^2 = 96%), so pooled analysis was conducted using the random effects model. As observed from Figure 6, circulating zinc contents among the Asia population declined among the

TABLE 1 Characteristics of studies included in this meta-analysis

Author	Years	Country	Population	Period	Design	N-all	n-control
Al-Saleh	2007	Safat, Kuwait	Obese GDM and obese control	October 2002 to March 2004	Case–control	21	11
Al-Saleh	2004	Safat, Kuwait	–	October 2002 to June 2003	Case–control	30	15
Behboudi-Gandevani	2013	Tehran, Iran	Singleton pregnant	September 2010 to October 2011	Longitudinal prospective cohort	1033	961
Bo	2005	Turin, Italy	–	April 1999 to November 2000	Case–control	420	294
Borella	1990	Italy	Hospitalised pregnant	Not reported	Case–control	53	35
Hamdan	2014	Medani, Sudan	Singleton pregnant	June 2009 to August 2009	Case–control	62	31
Lewandowska	2020	Warsaw, Poland	Polish Caucasian women	2017 to 2019.	Prospective cohort	563	453
Luo	2020	Taiyuan, China	Chinese women	2012 to 2016	Matched cohort study	1496	744
Mahmoud	2012	Kuwait	Gestational diabetes dieting	Not reported	Case–control	59	33
Mishu	2019	Mymensingh, Bangladesh	–	July 2013 to June 2014	Cross-sectional study	172	86
Noureldeen	2018	Kingdom of Saudi Arabia	–	Not reported	Case–control	89	47
Roshanravan	2018	Shabestar, north west of Iran	Singleton pregnant women, IGT	December 2013 to April 2014	Case–control	81	35
Wang	2002	Shanggai, China	IGT	Not reported	Case–control	98	–
			GDM			136	90
Wibell	1985	Uppsala, Sweden	–	Not reported	Case–control	33	13
Wilson	2018	Adelaide, Australia	SCOPE, nulliparous women singleton pregnancy	November 2004 to September 2008	Prospective cohort study	609	558

Note: GTT, glucose tolerance test; OGTT, oral glucose tolerance test; OGTT, oral glucose challenge test; IVGTT, intravenous glucose tolerance test; IGT, impaired glucose tolerance; SCOPE, Screening for Pregnancy Endpoints; IADPSG, International Associations of Diabetes and Pregnancy Study Groups criteria.

TABLE 1 Continued

Author	n-GDM	Age	Time at which gestation	GDM diagnosis	Trimester	Serum zinc	Zinc examination
Al-Saleh	10	31	Not reported	GTT	Not reported	Serum	Atomic absorption spectrophotometry
Al-Saleh	15	23.1	Not reported	Not reported	Not reported	Serum	Atomic absorption spectrophotometry
Behboudi-Gandevani	72	27.57	14 to 20 weeks	GCT + OGTT	Second trimester	Serum	Flame atomic absorption spectrometry
Bo	126	32	24 to 28 weeks	OGTT	Second trimester	Serum	Flame atomic absorption spectrometry
Borella	18	Not reported	29 to 40 weeks	Self	Third trimester	Plasma	Flame atomic absorption spectrophotometry
Hamdan	31	31	Not report	OGTT	Not reported	Serum	Atomic absorption spectrophotometry
Lewandowska	110	31.0	10–14th gestational week	OGTT	First trimester	Serum	Inductively coupled plasma mass spectrometer:
Luo	752	31	Gestational age of 20 weeks or more	OGTT	Second trimester	Plasma	Inductively coupled plasma-mass
Mahmoud	26	Not reported	Not reported	GTT	Third trimester	Serum	Atomic absorption spectrophotometry
Mishu	86	28	Second and third trimester of pregnancy	OGTT, WHO	Second $n = 43$ Third trimester $n = 43$	Serum	Colorimetric method with 2-(5-Brom-2-pyridylazo)-5-[N-propyl-N-(3-sulfopropyl) amino]-phenol
Noureldeen	42	29.57 ± 0.78 for control33.48 ± 0.83 for GDM	13–38 weeks26.98 ± 0.95 for control28.45 ± 1.03 for GDM	OGTT, WHO	Not calculated	Serum	Flam atomic absorption
Roshanravan	46	31.24 ± 4.81 for IGT29.31 ± 4.99 for control	24–28 weeks	OGCT	Second trimester	Serum	Photometric technique
Wang	98 46	Not reported	Not specified	OGTT	Not calculated	Serum	Inductively coupled plasma atomic emission spectroscopy
Wibell	20	31 for GDM18–32 for control	14–18 weeks n = 16 32–36 weeks n = 25	IVGTT	Second n = 16 Third trimester n = 26	Serum	Atomic absorption spectrophotometry
Wilson	51	23.71 ± 5	15 ± 1 weeks	IADPSG	Not calculated	Plasma	Inductively-coupled plasma mass spectrometry(ICP-MS)

Note: GTT, glucose tolerance test; OGTT, oral glucose tolerance test; OGTT, oral glucose challenge test; IVGTT, intravenous glucose tolerance test; IGT, impaired glucose tolerance; SCOPE, Screening for Pregnancy Endpoints; IADPSG, International Associations of Diabetes and Pregnancy Study Groups criteria.

TABLE 2 Newcastle–Ottawa scale of cohort studies

Study	Years	SELECTION				COMPARABILITY	OUTCOME		
		Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present	Comparability of exposure and non-exposure	Ascertainment of outcome	Follow up enough for outcome	Adequacy of follow up
Behboudi-Gandevani	2013	★	★	★	★	★★	★		
Lewandowska	2020	★	★	★	★	★★	★		★
Luo	2020	★	★	★	★	★★	★		
Mishu	2019	★	★	★	★	★	★		
Wilson	2018	★	★	★	★	★	★		

TABLE 3 Newcastle–Ottawa scale of case–control studies

Study	Years	Selection				Comparability	Exposure		
		Case definition adequate	Representativeness of the cases	Selection of controls	Definition of control	Comparability of cases and controls	Ascertainment of exposure	Same method of cases and controls	Non-response rate
Al-Saleh	2007	★	★	★	★	★★		★	
Al-Saleh	2004	★	★	★	★	★★	★	★	
Bo	2005	★	★	★	★	★★		★	★
Borella	1990	★			★	★★		★	★
Hamdan	2014	★	★	★	★	★★		★	★
Mahmoud	2012	★			★	★★		★	★
Noureldeen	2018	★			★	★★		★	★
Roshanravan	2018	★	★	★	★	★		★	
Wang	2002	★	★		★	★★		★	★
Wibell	1985	★		★	★	★★		★	★

Study or Subgroup	GDM Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Al-Saleh 2004	610	27	10	666	34	11	5.2%	-1.74 [-2.78, -0.70]
Al-Saleh 2007	610.3	60.1	15	656.2	241.2	15	6.4%	-0.25 [-0.97, 0.46]
Behboudi-Gandevani 2013	848	440	72	835	444	961	7.8%	0.03 [-0.21, 0.27]
Bo 2005	856.2	189.5	126	1,026.14	163.4	294	7.8%	-0.99 [-1.21, -0.77]
Borella 1990	766.6	117.6	18	627.5	150	35	6.8%	0.98 [0.38, 1.58]
Hamdan 2014	498.9	77	31	486.4	65.75	31	7.1%	0.17 [-0.33, 0.67]
Lewandowska 2020	629.2	104.66	110	615.9	158.54	453	7.9%	0.09 [-0.12, 0.30]
Luo 2020	661	197	752	653	200	744	8.0%	0.04 [-0.06, 0.14]
Mahmoud 2012	645.9	23.9	26	671.6	37.8	33	7.0%	-0.78 [-1.32, -0.25]
Mishu 2019	454	47.76	86	673	78.1	86	7.2%	-3.37 [-3.84, -2.90]
Noureldeen 2018	690	194.4	42	590	205.8	47	7.4%	0.49 [0.07, 0.92]
Roshanravan 2018	610	203.9	46	719.7	300.5	35	7.3%	-0.43 [-0.88, 0.01]
Wang 2002	1,080	270	46	1,130	330	90	7.5%	-0.16 [-0.52, 0.20]
Wibell 1985	700	100	20	700	80	13	6.5%	0.00 [-0.70, 0.70]
Total (95% CI)			**1400**			**2848**	**100.0%**	**-0.40 [-0.80, 0.00]**

Heterogeneity: Tau² = 0.53; Chi² = 298.85, df = 13 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.94 (P = 0.05)

FIGURE 2 Forest plot of the circulating zinc level in gestational diabetes mellitus (GDM) and healthy pregnant women. The random effect model (inverse variance method) was applied
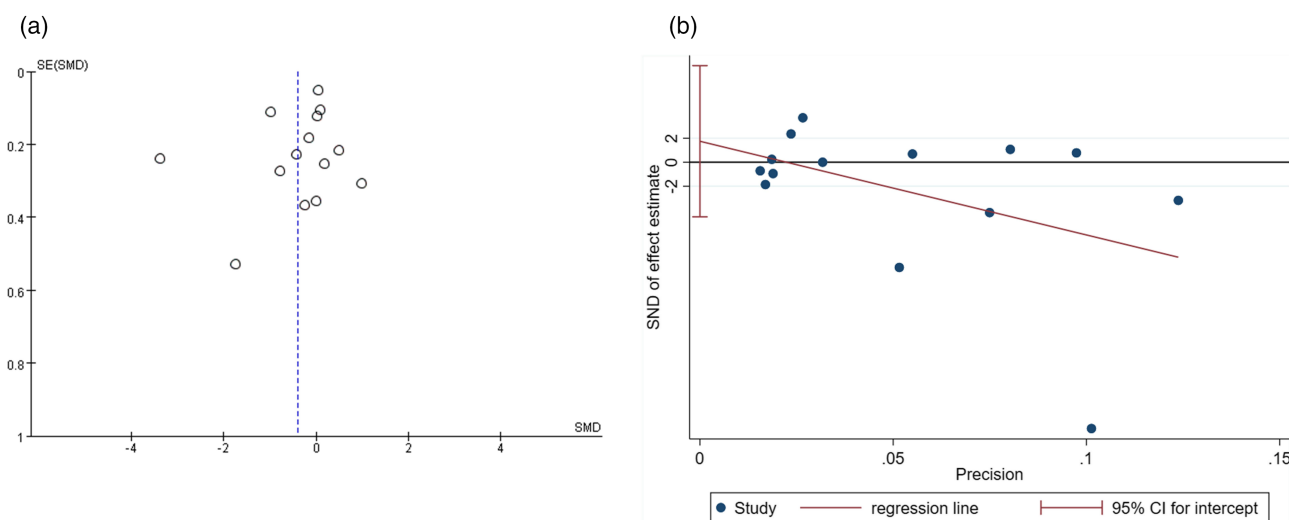
FIGURE 3 Funnel plot (a) and Egger's graphical test (b) of included studies for potential publication bias between gestational diabetes mellitus patients and healthy pregnant women. SMD, standard mean difference; SE, standard error; SND, standard normal deviation

GDM cases (for Asia: SMD = −0.65; 95%CI: −1.24 to −0.06, P = 0.03). But the circulating zinc contents among the Caucasians and Africans was not significant (for Europe: SMD = −0.01; 95%CI: −1.81–0.79, P = 0.98 and for African: SMD = 0.17; 95%CI: −0.33 to 0.67).

Based on those findings, subgroup analysis stratified based on study design helped to categorise studies into case–control, prospective cohort or cross-sectional studies. There was obvious heterogeneity, so pooled analysis was completed by the random effects model (prospective cohort study: P = 0.91, I² = 0%; case–control: P < 0.00001, I² = 89%; cross-sectional: not applicable). The SMD was 0.05 (95%CI: −0.04 to 0.13, P = 0.28) among the prospective cohort studies, and −0.24 (95%CI: −0.69 to 0.21. P = 0.29) for the case–control studies, whereas SMD was −3.37 (95%CI: −3.84 to −2.90, P < 0.00001) for cross-sectional study (Figure 7).

In addition, when stratifying by cord blood or umbilical vein blood of zinc measurement, the cord blood zinc levels among GDM cases decreased relative to those among normal controls, however, the difference was not significant (for SMD = −1.28, 95%CI: −2.71 to 0.15, P = 0.08, Figure 8).

3.5 | Zinc in association with gestational diabetes mellitus

Data extracted from four studies that compared pregnant women with GDM in the highest level of circulating zinc and GDM in the lowest level of zinc yielded an SRR of 0.929 (95%CI: 0.905 to 0.954, P < 0.001 Figure 9). No significant publication bias existed in the meta-analysis by Begg's test (P = 0.272), Egger's test (P = 0.081).

Study or Subgroup	GDM Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 First trimester								
Lewandowska 2020	629.2	104.66	110	615.9	158.54	453	9.3%	0.09 [-0.12, 0.30]
Subtotal (95% CI)			110			453	9.3%	0.09 [-0.12, 0.30]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								
1.2.2 Second trimester								
Behboudi-Gandevani 2013	848	440	72	835	444	961	9.2%	0.03 [-0.21, 0.27]
Bo 2005	856.2	189.5	126	1,026.14	163.4	294	9.3%	-0.99 [-1.21, -0.77]
Luo 2020	661	197	752	653	200	744	9.4%	0.04 [-0.06, 0.14]
Mishu 2019	439.3	54.8	43	673	78.1	43	7.8%	-3.43 [-4.11, -2.76]
Roshanravan 2018	610	203.9	46	719.7	300.5	35	8.7%	-0.43 [-0.88, 0.01]
Wibell 1985	900	130	4	900	150	12	5.9%	0.00 [-1.13, 1.13]
Subtotal (95% CI)			1043			2089	50.3%	-0.78 [-1.42, -0.13]
Heterogeneity: Tau² = 0.57; Chi² = 164.10, df = 5 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 2.37 (P = 0.02)								
1.2.3 Three trimester								
Borella 1990	766.6	117.6	18	627.5	150	35	8.1%	0.98 [0.38, 1.58]
Mahmoud 2012	645.9	23.9	26	671.6	37.8	33	8.4%	-0.78 [-1.32, -0.25]
Mishu 2019	486.6	31.2	43	675.8	91.2	43	8.1%	-2.75 [-3.35, -2.15]
Noureldeen 2018	690	194.4	42	590	205.8	47	8.7%	0.49 [0.07, 0.92]
Wibell 1985	700	90	13	800	90	12	7.1%	-1.07 [-1.92, -0.23]
Subtotal (95% CI)			142			170	40.4%	-0.62 [-1.91, 0.67]
Heterogeneity: Tau² = 2.07; Chi² = 101.50, df = 4 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.94 (P = 0.35)								
Total (95% CI)			1295			2712	100.0%	-0.62 [-1.07, -0.17]
Heterogeneity: Tau² = 0.56; Chi² = 274.93, df = 11 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.72 (P = 0.007)								
Test for subgroup differences: Chi² = 7.20. df = 2 (P = 0.03). I² = 72.2%								

FIGURE 4 Subgroup analysis of circulating zinc level in GDM or healthy pregnant women based on different trimester. The random effect model (inverse variance method) was applied

Study or Subgroup	GDM Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Serum								
Al-Saleh 2004	610	27	10	666	34	11	5.2%	-1.74 [-2.78, -0.70]
Al-Saleh 2007	610.3	60.1	15	656.2	241.2	15	6.4%	-0.25 [-0.97, 0.46]
Behboudi-Gandevani 2013	848	440	72	835	444	961	7.8%	0.03 [-0.21, 0.27]
Bo 2005	856.2	189.5	126	1,026.14	163.4	294	7.8%	-0.99 [-1.21, -0.77]
Hamdan 2014	498.9	77	31	486.4	65.75	31	7.1%	0.17 [-0.33, 0.67]
Lewandowska 2020	629.2	104.66	110	615.9	158.54	453	7.9%	0.09 [-0.12, 0.30]
Mahmoud 2012	645.9	23.9	26	671.6	37.8	33	7.0%	-0.78 [-1.32, -0.25]
Mishu 2019	454	47.76	86	673	78.1	86	7.2%	-3.37 [-3.84, -2.90]
Noureldeen 2018	690	194.4	42	590	205.8	47	7.4%	0.49 [0.07, 0.92]
Roshanravan 2018	610	203.9	46	719.7	300.5	35	7.3%	-0.43 [-0.88, 0.01]
Wang 2002	1,080	270	46	1,130	330	90	7.5%	-0.16 [-0.52, 0.20]
Wibell 1985	700	100	20	700	80	13	6.5%	0.00 [-0.70, 0.70]
Subtotal (95% CI)			630			2069	85.2%	-0.56 [-1.07, -0.04]
Heterogeneity: Tau² = 0.76; Chi² = 249.52, df = 11 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.12 (P = 0.03)								
1.3.2 Plasma								
Borella 1990	766.6	117.6	18	627.5	150	35	6.8%	0.98 [0.38, 1.58]
Luo 2020	661	197	752	653	200	744	8.0%	0.04 [-0.06, 0.14]
Subtotal (95% CI)			770			779	14.8%	0.46 [-0.45, 1.38]
Heterogeneity: Tau² = 0.39; Chi² = 9.12, df = 1 (P = 0.003); I² = 89%								
Test for overall effect: Z = 0.99 (P = 0.32)								
Total (95% CI)			1400			2848	100.0%	-0.40 [-0.80, 0.00]
Heterogeneity: Tau² = 0.53; Chi² = 298.85, df = 13 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.94 (P = 0.05)								
Test for subgroup differences: Chi² = 3.62. df = 1 (P = 0.06). I² = 72.3%								

FIGURE 5 Subgroup analysis of zinc level in gestational diabetes mellitus (GDM) or healthy pregnant women based on serum and plasma. The random effect model (inverse variance method) was applied
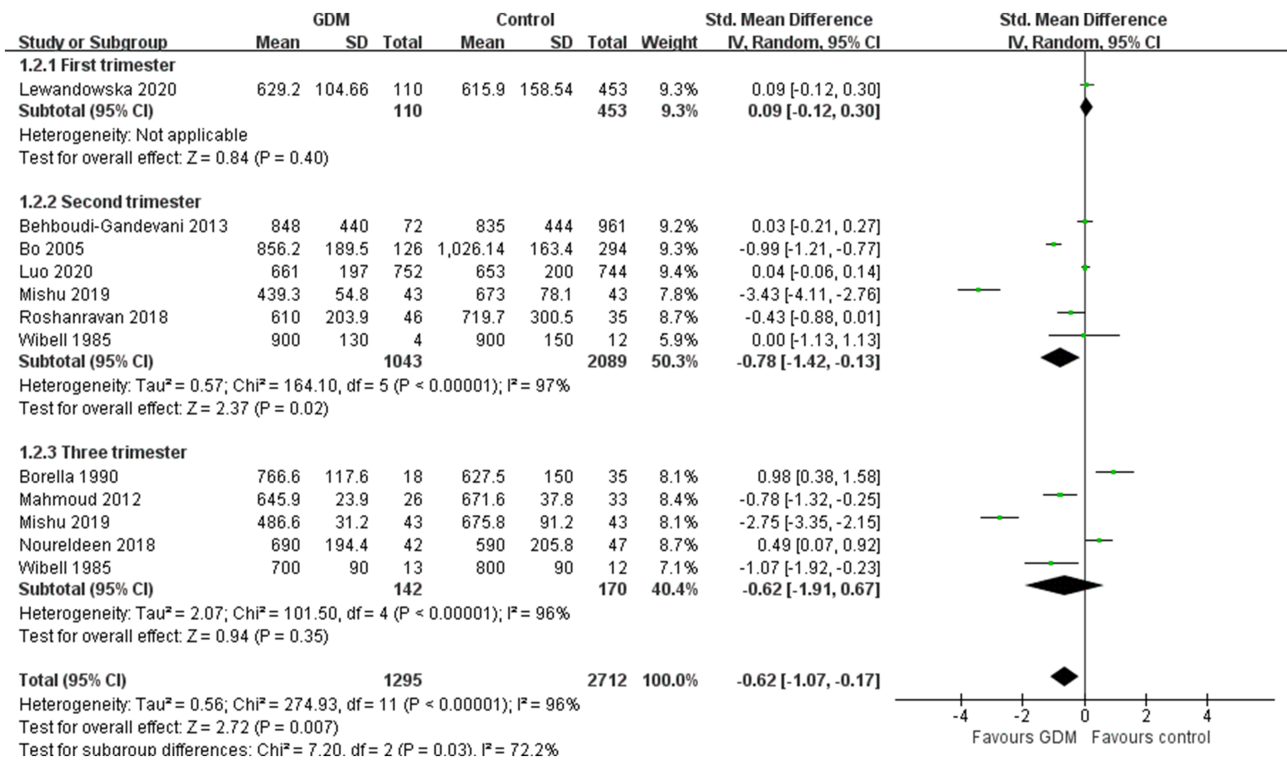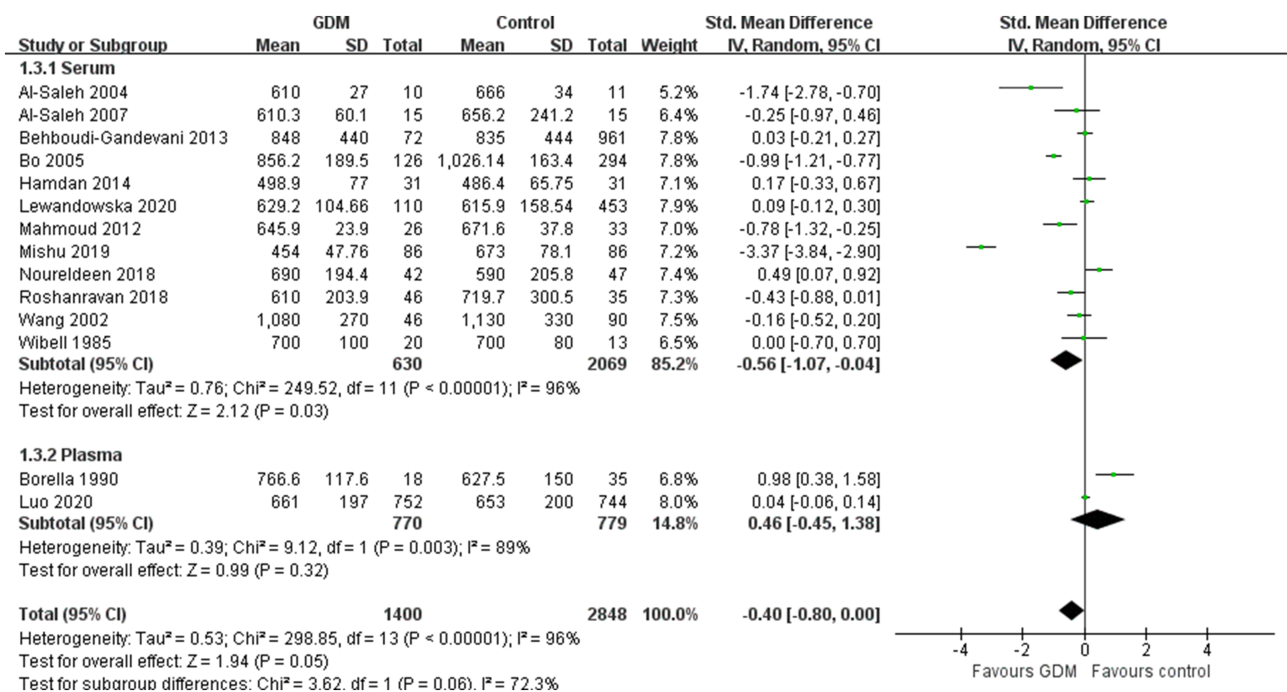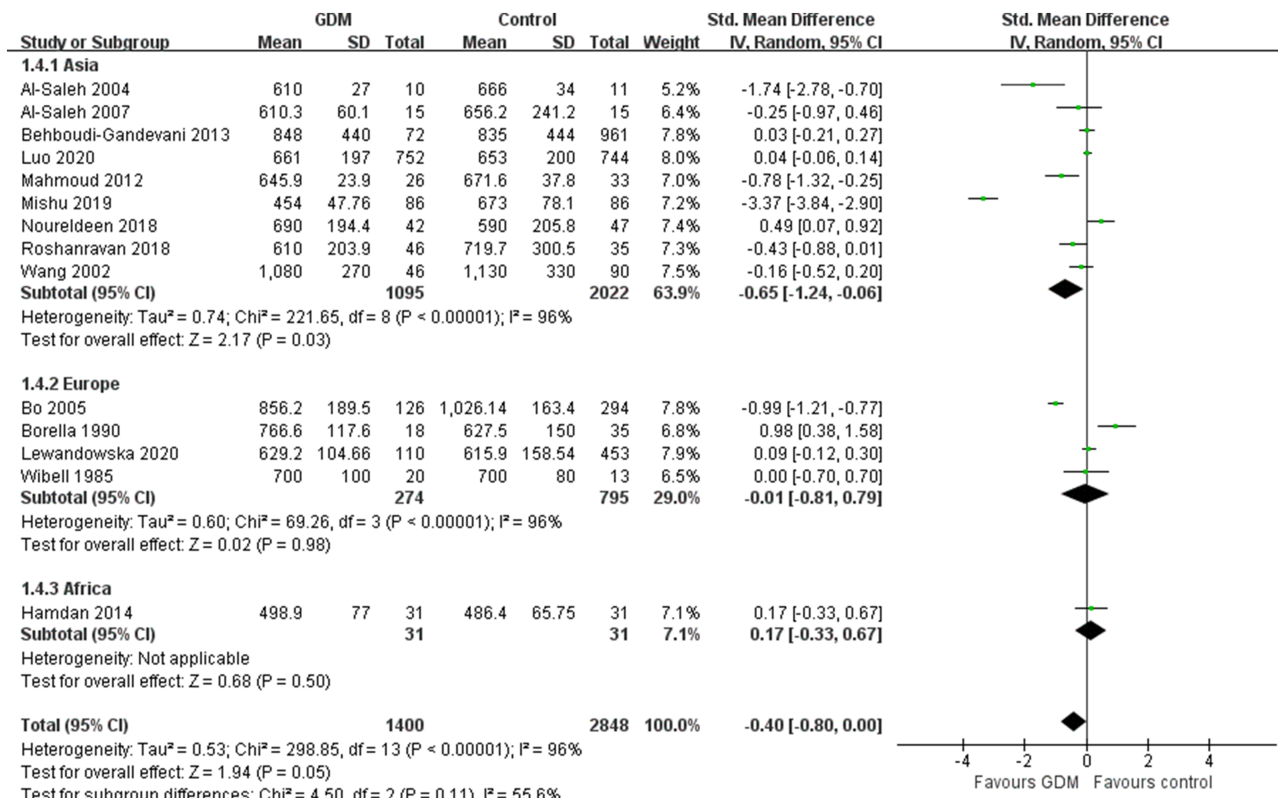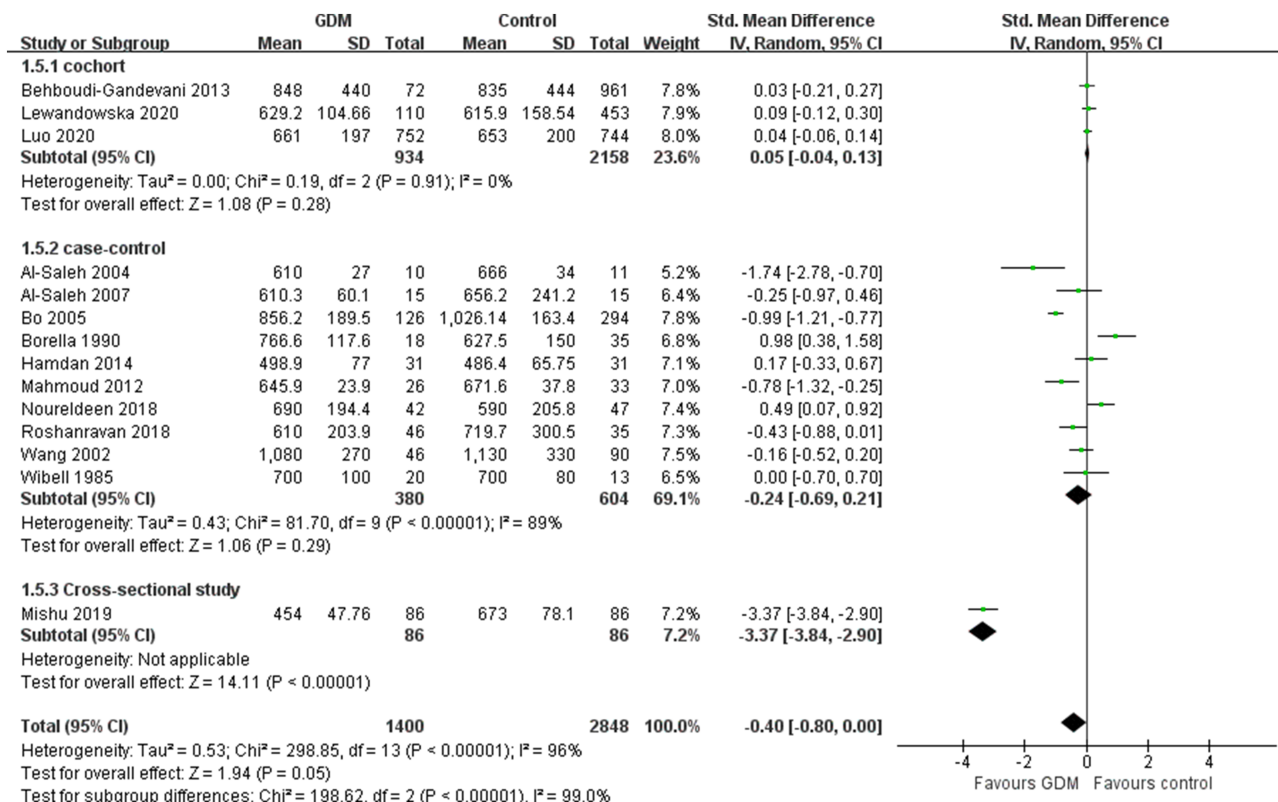
Study or Subgroup	GDM Mean	GDM SD	GDM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Asia								
Al-Saleh 2004	610	27	10	666	34	11	5.2%	-1.74 [-2.78, -0.70]
Al-Saleh 2007	610.3	60.1	15	656.2	241.2	15	6.4%	-0.25 [-0.97, 0.46]
Behboudi-Gandevani 2013	848	440	72	835	444	961	7.8%	0.03 [-0.21, 0.27]
Luo 2020	661	197	752	653	200	744	8.0%	0.04 [-0.06, 0.14]
Mahmoud 2012	645.9	23.9	26	671.6	37.8	33	7.0%	-0.78 [-1.32, -0.25]
Mishu 2019	454	47.76	86	673	78.1	86	7.2%	-3.37 [-3.84, -2.90]
Noureldeen 2018	690	194.4	42	590	205.8	47	7.4%	0.49 [0.07, 0.92]
Roshanravan 2018	610	203.9	46	719.7	300.5	35	7.3%	-0.43 [-0.88, 0.01]
Wang 2002	1,080	270	46	1,130	330	90	7.5%	-0.16 [-0.52, 0.20]
Subtotal (95% CI)			1095			2022	63.9%	-0.65 [-1.24, -0.06]
Heterogeneity: Tau² = 0.74; Chi² = 221.65, df = 8 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.17 (P = 0.03)								
1.4.2 Europe								
Bo 2005	856.2	189.5	126	1,026.14	163.4	294	7.8%	-0.99 [-1.21, -0.77]
Borella 1990	766.6	117.6	18	627.5	150	35	6.8%	0.98 [0.38, 1.58]
Lewandowska 2020	629.2	104.66	110	615.9	158.54	453	7.9%	0.09 [-0.12, 0.30]
Wibell 1985	700	100	20	700	80	13	6.5%	0.00 [-0.70, 0.70]
Subtotal (95% CI)			274			795	29.0%	-0.01 [-0.81, 0.79]
Heterogeneity: Tau² = 0.60; Chi² = 69.26, df = 3 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.02 (P = 0.98)								
1.4.3 Africa								
Hamdan 2014	498.9	77	31	486.4	65.75	31	7.1%	0.17 [-0.33, 0.67]
Subtotal (95% CI)			31			31	7.1%	0.17 [-0.33, 0.67]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Total (95% CI)			1400			2848	100.0%	-0.40 [-0.80, 0.00]
Heterogeneity: Tau² = 0.53; Chi² = 298.85, df = 13 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.94 (P = 0.05)								
Test for subgroup differences: Chi² = 4.50, df = 2 (P = 0.11), I² = 55.6%								

FIGURE 6 Subgroup analysis of circulating zinc level in gestational diabetes mellitus (GDM) or healthy pregnant women based on geographic location. The random effect model (inverse variance method) was applied

Study or Subgroup	GDM Mean	GDM SD	GDM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 cochort								
Behboudi-Gandevani 2013	848	440	72	835	444	961	7.8%	0.03 [-0.21, 0.27]
Lewandowska 2020	629.2	104.66	110	615.9	158.54	453	7.9%	0.09 [-0.12, 0.30]
Luo 2020	661	197	752	653	200	744	8.0%	0.04 [-0.06, 0.14]
Subtotal (95% CI)			934			2158	23.6%	0.05 [-0.04, 0.13]
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%								
Test for overall effect: Z = 1.08 (P = 0.28)								
1.5.2 case-control								
Al-Saleh 2004	610	27	10	666	34	11	5.2%	-1.74 [-2.78, -0.70]
Al-Saleh 2007	610.3	60.1	15	656.2	241.2	15	6.4%	-0.25 [-0.97, 0.46]
Bo 2005	856.2	189.5	126	1,026.14	163.4	294	7.8%	-0.99 [-1.21, -0.77]
Borella 1990	766.6	117.6	18	627.5	150	35	6.8%	0.98 [0.38, 1.58]
Hamdan 2014	498.9	77	31	486.4	65.75	31	7.1%	0.17 [-0.33, 0.67]
Mahmoud 2012	645.9	23.9	26	671.6	37.8	33	7.0%	-0.78 [-1.32, -0.25]
Noureldeen 2018	690	194.4	42	590	205.8	47	7.4%	0.49 [0.07, 0.92]
Roshanravan 2018	610	203.9	46	719.7	300.5	35	7.3%	-0.43 [-0.88, 0.01]
Wang 2002	1,080	270	46	1,130	330	90	7.5%	-0.16 [-0.52, 0.20]
Wibell 1985	700	100	20	700	80	13	6.5%	0.00 [-0.70, 0.70]
Subtotal (95% CI)			380			604	69.1%	-0.24 [-0.69, 0.21]
Heterogeneity: Tau² = 0.43; Chi² = 81.70, df = 9 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.5.3 Cross-sectional study								
Mishu 2019	454	47.76	86	673	78.1	86	7.2%	-3.37 [-3.84, -2.90]
Subtotal (95% CI)			86			86	7.2%	-3.37 [-3.84, -2.90]
Heterogeneity: Not applicable								
Test for overall effect: Z = 14.11 (P < 0.00001)								
Total (95% CI)			1400			2848	100.0%	-0.40 [-0.80, 0.00]
Heterogeneity: Tau² = 0.53; Chi² = 298.85, df = 13 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.94 (P = 0.05)								
Test for subgroup differences: Chi² = 198.62, df = 2 (P < 0.00001), I² = 99.0%								

FIGURE 7 Subgroup analysis of circulating zinc level in gestational diabetes mellitus (GDM) or healthy pregnant women based on different study design. The random effect model (inverse variance method) was applied
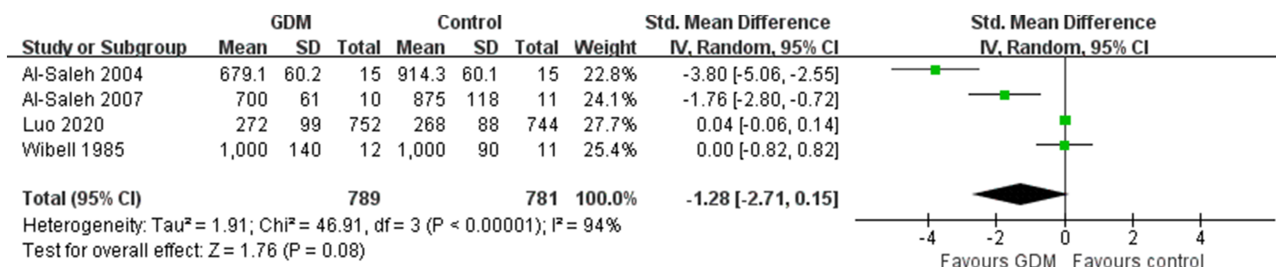
Study or Subgroup	GDM Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Al-Saleh 2004	679.1	60.2	15	914.3	60.1	15	22.8%	-3.80 [-5.06, -2.55]
Al-Saleh 2007	700	61	10	875	118	11	24.1%	-1.76 [-2.80, -0.72]
Luo 2020	272	99	752	268	88	744	27.7%	0.04 [-0.06, 0.14]
Wibell 1985	1,000	140	12	1,000	90	11	25.4%	0.00 [-0.82, 0.82]
Total (95% CI)			**789**			**781**	**100.0%**	**-1.28 [-2.71, 0.15]**

Heterogeneity: Tau² = 1.91; Chi² = 46.91, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.76 (P = 0.08)

FIGURE 8 Subgroup analysis of circulating zinc level in gestational diabetes mellitus (GDM) or healthy pregnant women based on umbilical vein blood. The random effect model (inverse variance method) was applied
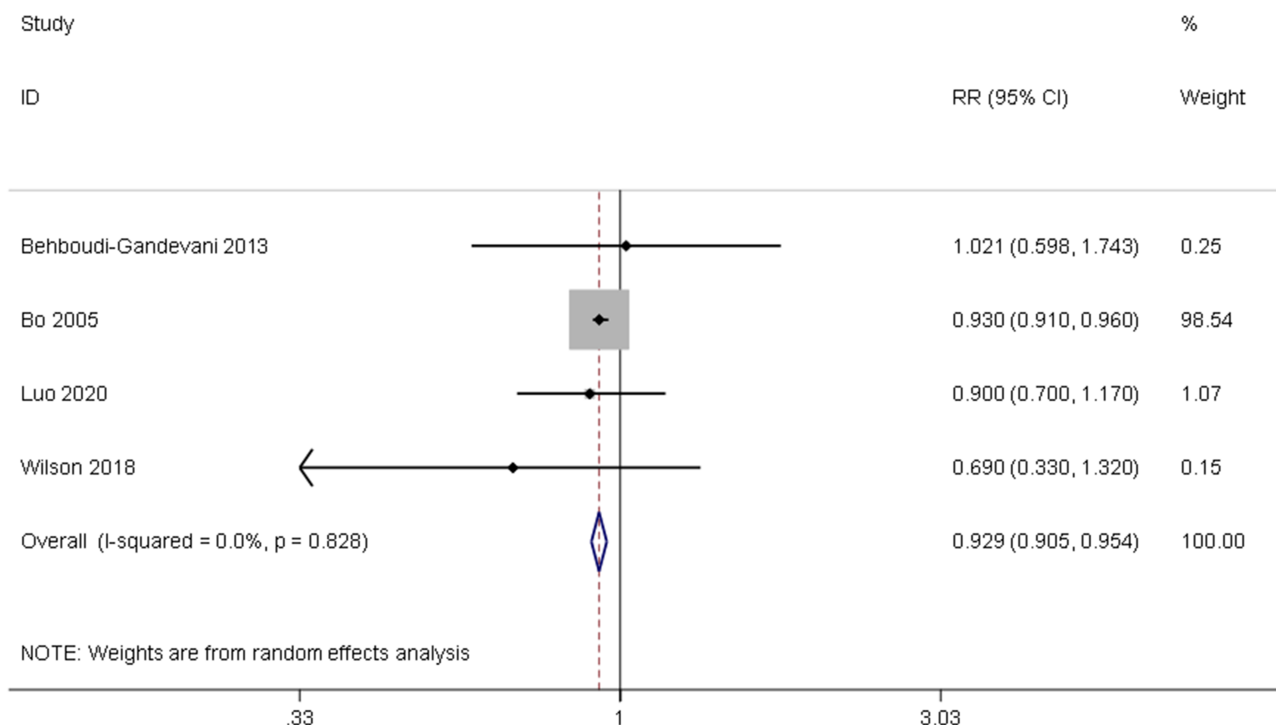
FIGURE 9 Forest plots (random effects model) of meta-analysis on the association between the concentration of zinc and the risk of gestational diabetes mellitus

4 | DISCUSSION

As discovered in the present systemic review and meta-analysis, the serum zinc content, but not plasma zinc, markedly decreased among GDM cases compared with normal controls. This result was particularly true for subgroup analysis stratified by second trimester and Asian population. Previous systematic review searched literature assessing circulating zinc and dietary zinc intake during pregnancy and the associations with gestational adverse outcomes, for example, GDM (Wilson et al., 2016). Compared with the previous systemic review, the present meta-analysis was the first to comprehensively and thoroughly analysed related studies and put forward the more robust conclusion. In the present meta-analysis of relevant studies, GDM cases had markedly decreased circulating zinc contents compared to the health women.

Here, the present meta-analysis on 15 eligible articles strongly supported that, GDM cases had evidently decreased serum zinc contents relative to the normal controls. The specific mechanisms underlying such findings were not well understood, yet this meta-analysis considered the associations of decreased zinc contents with oxidative stress intensification. GDM probably occurs via three associated mechanisms, including the direct impacts of oxidative stress and trace elements on immunomodulation and insulin activity. Firstly, zinc participates in numerous biochemical events, which has anti-inflammation and anti-oxidation effects. Besides, zinc deficiency (and excess) relates to the increased inflammation and oxidative stress (Mistry & Williams, 2011). Secondly, the immunomodulation mechanisms in GDM are related to the effects of OS and trace elements on immune regulation (Mahmoud et al., 2012). Mahmoud et al. reported a significant decrease in zinc was shown in diabetics treated with diet

compared with the normal pregnant women, supporting that zinc might play an important role in immune response regulatory mechanisms (Beck et al., 1997). These results reflect the role of deficiencies of trace elements zinc and trace elements, for example, copper in regulation of lymphocyte activation. Oxidative stress can induce the apoptotic deletion in the CD8 + CD25 + activated populations among the GDM women. Such results suggested that circulating zinc might exert an important part in immune response regulatory mechanisms (Beck et al., 1997). Besides, the zinc complexes show activities similar to insulin. Consequently, zinc supplement may benefit the glucose homeostasis (Miranda & Dey, 2004; Salgueiro et al., 2001).

We also found that the circulating zinc levels were significantly different among GDM cases compared with normal controls when stratified by second trimester in subgroup analysis. For first trimester, GDM showed no prospective association with the zinc levels in pregnant women at the first trimester (Choi et al., 2016; Wilson et al., 2018). Nonetheless, little is known about the precise reason of aberrant circulating zinc during the first trimester in gestation period. Metabolic, genetic, and environmental factors should be taken into account as the major reasons, such as inflammation and OS (Mendes et al., 2019). In the uterus, Zn deficiency together with decreased antioxidative system activities, may result in trophoblast cell dysfunction. Deficiency in the anti-inflammation and antioxidation effects during the first trimester of gestation period is possibly related to the adverse pregnancy outcome (Mistry & Williams, 2011). For second trimester, Liu et al. reported that the blood zinc contents declined with the progression of pregnancy, even though no significant difference was detected in the first trimester and the blood zinc content increased following delivery relative to that in healthy controls. They suggested that such declined zinc content was related to the disproportional elevation of plasma volume and the transfer from the mother to the foetus. And also, the decreased zinc binding (Tamura et al., 2000), the reduced dietary bioavailability and the ultrahigh dietary iron or copper content competing with zinc for the absorption sites were also the possible causes (Sheldon et al., 1985). However, no plasma volume data were collected in this meta-analysis, as a result, no distinct association with GDM was detected. For third trimester, we did not find the difference of circulating zinc level between the GDM group and controls. Multiple factors, especially for an increased foetal zinc uptake, may be related to such phenomenon in the third trimester. As a result, in abnormal gestation, the decreased zinc transfer to foetus and/or the declined plasma volume expansion was the possibly cause of the increased plasma zinc contents in the mother at the third trimester (Borella et al., 1990).

In subgroup analysis stratified based on plasma or serum zinc for measuring the circulating zinc level among the pregnant females, there was distinct difference for serum zinc, but not plasma. As suggested by Brito et al. (Araujo Brito et al., 2013), plasma zinc level was reduced by 20%–30% in the 3rd trimester of the gestation period, which further decreased with the pregnancy progression. Goldenberg et al. reported an association between decreased plasma zinc and decreased albumin contents in plasma in the gestation period

(Goldenberg et al., 1991). As a result, the decreased zinc contents in plasma in the gestation period are possibly associated with plasma volume expansion observed among in almost each pregnant woman, and this will thus lead to the decreased albumin content (Tamura et al., 2004). The expanded plasma volume in the gestation period may not necessarily suggest the evidently decreased zinc plasma pool. It is suggested to determine the zinc content in red blood cells, because it represents a highly precise indicator for detecting cell zinc deficiency but not plasma zinc deficiency (Noureldeen et al., 2018).

Socio-economic variables, geographic position, race difference, and gender, may have certain influence on the trace element contents (Liang et al., 2019). The reduced socio-economic variables are related to the adverse lifestyle, such as inappropriate diet, smoking, obesity and incompliance with medical advice, such as in terms of vitamin supplement during the pregnancy (Choi et al., 2016). As suggested in present study, serum zinc contents of the Asians declined among GDM cases, but not European population. GDM possibly has greater impact by three relevant mechanisms. First, the geographic heterogeneities of soil element contents are primarily related to zinc, which have certain effects on the different zinc levels in animals and plants, finally in human beings (Rainbow & Black, 2005; Sturikova et al., 2018). Besides, the zinc levels in seeds and grains are determined by their growing soils. Second, no zinc deficiency is observed at present among the developed countries, and this is possibly due to the different nation-wide dietary interventions (Grieger et al., 2019). These observations may be induced by the eating habits among diverse positions, together with the increased risk of insulin resistance and elevated oxidative stress degree during the gestation period. Among them, diet is a primary zinc absorption source among the general populations. Zinc uptake in diet is primarily obtained based on animal proteins, such as shellfish, organ meat or muscle meat. Europeans take meat, milk and milled rice with embryo rich in zinc as the main course, which is not greatly changed during the gestation period. By contrast, the Asians most usually eat grains and vegetables, which cannot offer enough zinc, so the appropriately increased meat product uptake is recommended in gestation period. Such different eating habits possibly result in the heterogeneous findings among the European and the Asian populations.

Furthermore, this study also compared pregnant women with GDM in the highest level of circulating zinc and GDM in the lowest level of zinc yielded summarised risk ratios (SRR) of 0.929. To date, physicians and obstetricians, even those specialised in GDM, are not aware of a potential connection between zinc level and GDM. Studies on this subject are sparse, but evidence suggesting causality is accumulating, mainly based on studies with GDM and T2DM patients (Karamali et al., 2015; Marreiro et al., 2006; Sun et al., 2009). The results of our study showed significant association between low zinc level and GDM. Therefore, further studies are required to prove the causal relationship between zinc level and gestational diabetes.

Nonetheless, several limitations should also be noted in this work. Firstly, there were distinct heterogeneities. For clarifying the potential heterogeneity source, subgroup analysis was performed. Nonetheless, the remaining confounders among different studies were still a

concern in the present work. As a result, the unavoidable heterogeneity might impact the overall result accuracy. Moreover, only the English-language articles were searched, while the grey literature was not searched, yet the Egger test revealed that there was no obvious publication bias in analysing the relationship of zinc concentration in serum with the GDM incidence for all the enrolled articles.

As far as we know, this meta-analysis provides two primary implications for the clinic. The measurement of trace elements (in particular zinc) during the second trimester of gestation period helps to distinguish high-risk cases for GDM, so that these cases can receive more care. It is simple and feasible to measure the serum zinc. Besides, measuring zinc elements potentially indicates that it is necessary to alter the diet and change the health promotion behaviours (e.g., Asian pregnant women). Some modifications in the lifestyle are important for the pregnant females not just according to the decreased zinc element contents. More investigation is needed for the findings acquired. And more specially designed prospective articles should be carried out for understanding the dynamic relationship of zinc level with the incidence of GDM.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
JF and BZ contributed to conception and design; JF, TZ, YY and BZ contributed to acquisition of data; JF, YY and BZ analysis and interpretation of data; and JF and BZ were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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