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META-ANALYSIS

Circulating vitamin D and the risk of gestational diabetes: a systematic review and dose-response meta-analysis

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Abstract

Purpose Several meta-analyses of observational studies revealed a modest increase in the risk of gestational diabetes (GDM) among pregnant women with low levels of serum vitamin D. However, no study examined a dose-response meta-analysis as well as a high versus low analysis in this regard.

Methods We systematically searched PubMed, Embase, ISI Web of Science, and Scopus up to August 2019 to find prospective observational studies investigating the association of serum 25(OH)D with the risk of developing GDM. Using a random-effects model, the reported risk estimates were pooled.

Results Nine cohort studies and six nested case-control studies were included in the final analysis (40,788 participants and 1848 cases). Considering linear analysis, each 10 nmol/L increase in circulating 25(OH)D was associated with a 2% lower risk of GDM (effect size (ES): 0.98; 95% CI: 0.98, 0.99; $I^2 = 85.0\%$, $P < 0.001$). highest compared with the lowest category of circulating 25(OH)D was associated with a 29% lower risk of GDM, with low evidence of heterogeneity ($I^2 = 45.0\%$, $P = 0.079$).

Conclusions In conclusion, lower levels of serum 25(OH)D were associated with a higher chance of GDM. Differential results existed between the overall and subgroup analysis, either based on vitamin D detection methods or based on maternal age, although these subgroups partially lowered the heterogeneity.

Keywords Gestational diabetes mellitus · Vitamin D · Pregnancy · Dose-response meta-analysis

Introduction

Gestational diabetes (GDM) is a common outcome of pregnancy, defined as any grade glucose intolerance diagnosed during pregnancy, mostly after 24 weeks of gestation [1]. GDM is associated with an increased risk of short and long-term consequences for the health of the mother and the fetus [2]. In 2017, 21.3 million births (16.2%) were reported to be affected by hyperglycemia in pregnancy worldwide, of which 84.4% was diagnosed with GDM [3]. Vitamin D deficiency is widely prevalent among pregnant women [4]; such that higher prevalence was reported in South Asian, Middle Eastern, and African women [5]. Since the prevalence of vitamin D deficiency and insufficiency is growing worldwide, much attention has been directed toward how vitamin D may influence health outcomes in pregnancy [6].

Vitamin D is among the major risk factors for the incidence of GDM. The need for vitamin D is increased during pregnancy [7]. Evidence on the effect of vitamin D

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supplementation on the prevention or treatment of diabetes is controversial [8–11]. Moreover, recent reviews regarding supplemental vitamin D during pregnancy could not find robust evidence [12, 13]. During the last decade, several observational studies revealed a significant association between serum concentrations of vitamin D and the risk of GDM [14–16]. Although some individual studies could not find any significant association [17], several meta-analyses and reviews have found a modest increase in odds of GDM among women with low levels of serum vitamin D [18–21]. In the current study, we performed a dose-response meta-analysis and a high versus low analysis of relevant cohort and nested case-control studies that investigated the association of circulating 25(OH)D with incident GDM. Such an analysis utilizes all the population data of each study rather than just the extreme categories by which the classical meta-analysis has been done.

Methods

Search strategy

We searched four electronic databases including PubMed, Embase, ISI Web of Science, and Scopus up to August 2019. Eligible studies that examined the association of serum vitamin D and the risk of GDM were searched using keywords and MeSH terms as follows: ("vitamin D" OR "cholecalciferol" OR "25-hydroxyvitamin D" OR "25(OH) D" OR "1,25-(OH)2D2" OR "1,25-dihydroxyvitamin D2") AND ("Diabetes, Gestational" OR "gestational diabetes" OR "GDM"). The bibliography of relevant original and review articles was referred to in order not to miss any other articles.

Study selection

This meta-analysis is conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [22]. No restriction was performed in terms of the publication language. We included those reports with information on circulating vitamin D during pregnancy in relation to the risk of GDM. Nonhuman studies, review articles, editorials, and letters were not included in the current study. To be more conclusive, different screening criteria used for GDM diagnosis were accepted. Studies that reported a prepregnancy diagnosis of diabetes for included women were excluded. Studies were excluded if they did not report the odds ratio (OR), relative risk (RR), confidence interval (CI), or standard error (SE), the number of women in each category of serum 25(OH)D or insufficient data to compute such values. If several publications used the same population, only the latest publication was included.

Data extraction

Two researchers independently extracted following information: first author, publication year, country, study design, characteristics of participants (age, number of case/cohort), average serum 25(OH)D levels in each patient category, RRs or ORs and 95% CIs for GDM for each category, diagnostic criteria for GDM, method of vitamin D assessment, and variables adjusted for in the analysis. If the study reported several adjustment models, only the more complete one was considered.

Quality assessment of studies

The quality of included studies was determined using the Newcastle–Ottawa Scale specific methods for cohort studies [23]. A maximum of nine points was assigned to each cohort study according to this method: four for selection and assessment of exposure, two for comparability, and three for assessment of outcomes. We defined the quality scores of >6 as high-quality studies; otherwise, it was deemed to be low-quality. Disagreements were resolved by consensus. Findings from the risk of bias assessment are presented in Table 1.

Statistical analysis

We used reported HRs or ORs and their 95% CIs for the risk of GDM to calculate log HR and log RR and its SEs. A linear dose-response meta-analysis per 10 nmol/L increment of serum levels of 25(OH)D was performed using generalized least squares trend estimation (GLST). These methods require the number of cases or person-year and the total number of subjects for at least three quantitative exposure categories. GLST also requires mean intake for each category of exposure levels. In cases that the range of serum vitamin D than mean levels was reported, the midpoint of the upper and lower limits in each category was chosen as the assigned dose. Then, we conducted a two-stage random-effects dose-response meta-analysis to determine the linear trend between serum 25(OH)D levels (dose) and GDM risk. First, we used a method suggested by Greenland and Longnecker [24] and Orsini et al. [25] to calculate the correlation within each study. Second, we combined study-specific estimates using a random-effects meta-analysis. Moreover, the effect sizes of the highest compared with the lowest categories were combined using the DerSimonian and Laird random-effects model [26]. To evaluate possible factors causing heterogeneity, we conducted subgroup analysis based on prespecified subgroups, including study design (cohort vs. nested case-control), study location (the US vs. non-US), vitamin D assessment method (immunoassay vs. non-immunoassay), the number

Table 1 The main characteristics of cohort studies examined the association between serum levels of 25(OH)D and GDM

Ref.	Country	Study type	Age (mean ± SD)	Number of cases/cohort size	Exposure	Exposure assessment	Outcome assessment	Adjustment	Quality score
Zhang et al. [44]	United States	Cohort	34.3 ± 4.8	57/953	Combined 25(OH)D3 and 25(OH)D2	ELISA	ADA	3, 4, 12, 16	9
Burris et al. [14]	United States	Cohort	32 ± 3.6	68/1314	Combined 25(OH)D3 and 25(OH)D2	CLIA	ADA	3, 4, 5, 6, 7, 8, 15, 16, 17, 18	8
Tomedi et al. [16]	United States	Cohort	11–29 (84.6%) 30–42 (15.4%)	12/674	Combined 25(OH)D3 and 25(OH)D2	RIA	C&C	2, 3, 4, 6, 7, 12, 16	9
Rodriguez [45]	Spain	Cohort	32 ± 4.2	93/2644	25(OH)D3	HPLC	NDDG	1, 2, 3,4, 6, 7, 8, 9, 10	9
Loy et al. [46]	Singapore	Cohort	30.5 ± 5.1	155/940	Combined 25(OH)D3 and 25(OH)D2	LC–MS	WHO	1, 3, 4, 6, 7, 8, 12, 13, 16, 18	9
Nobles et al. [47]	United States	Cohort	39.1 ± 1.9	31/252	Combined 25(OH)D3 and 25(OH)D2	CLIA	ADA	2, 3, 4, 15, 16	9
Flood-Nichols et al. [48]	United States	Cohort	24.3 ± 4.4	5/310	Combined 25(OH)D3 and 25(OH)D2	ELISA	ACOG	4, 8, 15, 16	8
Wilson et al. [49]	Australia	Cohort	28 ± 6	92/3229	Combined 25(OH)D3 and 25(OH)D2	IDS-iSYS	IADPSG	3, 4, 8, 9, 10, 16, 17	9
Eggemoen et al. [50]	Norway	Cohort	29.8 ± 0.18	235/823	Combined 25(OH)D3 and 25(OH)D2	RIA	WHO	3, 6, 7, 10, 15, 16, 19	9
Baker et al. [51]	United States	Nested case-control	35 (31–37)	60/4225	Combined 25(OH)D3 and 25(OH)D2	LC–MS	NDDG	2, 3, 4, 6, 15	9
Parlea et al. [52]	Canada	Nested case-control	34.3 ± 4.3	116/335	Combined 25(OH)D3 and 25(OH)D2	CLIA	NDDG	2, 3	9
Schneuer et al. [53]	Australia	Nested case-control	34.5 ± 4.6	376/11358	Combined 25(OH)D3 and 25(OH)D2	AIAS	ADPS	3, 5, 6, 7, 8, 10, 12, 13, 15	8
Park et al. [54]	Korea	Nested case-control	34.8 ± 3.6	23/523	Combined 25(OH)D3 and 25(OH)D2	ECLIA	C&C	2, 3, 4, 11, 14, 15	8
Arnold et al. [55]	United States	Nested case-control	33.5 ± 4.6	135/4000	Combined 25(OH)D3 and 25(OH)D2	LC–MS	ADA	3, 4, 12, 15, 16	8
Dodds et al. [56]	Canada	Nested case-control	NR	390/9208	Combined 25(OH)D3 and 25(OH)D2	ECLIA	CDA	2, 3, 4, 10, 15	8

1: child's sex; 2: gestational age; 3: maternal age; 4: body mass index; 5: maternal weight, 6: socioeconomic status; 7: parity; 8: smoking status; 9: alcohol consumption; 10: study site; 11: previous GDM; 12: family history or previously diagnosed diabetes; 13: previously diagnosed hypertension; 14: vitamin D intake; 15: season of sampling; 16: race/ethnicity; 17: physical activity; 18: dietary intakes of fish and calcium; 19: skinfolds

M male, *F* female, *NR* not reported, *OR* odds ratio, *RR* risk ratio, *HR* hazard ratio, *GDM* gestational diabetes mellitus, *RIA* radiaimmunoassay, *HPLC* high-performance liquid chromatography, *ECLIA* electrochemical luminescence immunoassay, *IDS-iSYS* immunodiagnostic systems, *LC–MS* liquid chromatography–mass spectrometry, *CLIA* chemiluminescent immunoassay, *ELISA* enzyme-linked immunosorbent assay, *AIAS* automated immunoassay system, *ADA* American Diabetes Association, *NDDG* National Diabetes Data Group, *C&C* Carpenter–Coustan, *WHO* World Health Organization, *ACOG* American College of Obstetricians and Gynecologists, *IADPSG* International Association of Diabetes and Pregnancy Study Groups, *ADPS* Australasian Diabetes in Pregnancy Society, *CDA* Canadian Diabetes Association

of cases (<100 vs. >100), maternal age (>30 vs. <30 years), GDM diagnostic criteria, and adjustment for important risk factors including body mass index, gestational age, study site, family history of diabetes or previously diagnosed diabetes, smoking status, socioeconomic status, the season of sampling, and race/ethnicity. The heterogeneity was evaluated using I^2 value and Cochran's Q test (by metaan command in STATA) [27, 28]. P values for heterogeneity within studies in each subgroup (P-within) were obtained by comparing Q with a $\chi 2$ distribution with k-1 degree(s) of freedom, where k is the number of studies [29, 30]. To determine whether a statistically significant subgroup differences were detected, we considered the P values from the fixed-effect model (P-between) using the inverse variance-weighted estimation [31]. Sensitivity analysis was performed to explore the extent to which references might depend on a particular study or group of studies and the effect size was recalculated to estimate the statistical validity of the effect size [32]. Publication bias was assessed using visual inspection of funnel plots and the use of Egger's regression asymmetry test. All the analyses were performed by the use of Stata, version 11.2 (Stata Crop). We considered P values of <0.05 as statistically significant. When serum 25(OH)D concentration was reported in different units, we converted them to the most frequently used unit.

Results

Findings from the systematic review

Out of 784 records identified through database searching, a total of 253 articles remained after removing duplicate publications. Following the first screening, 223 articles were removed based on their title and abstract and a total of 30 studies were reviewed through full-text assessment. We excluded ten more studies since they reported ORs or HRs for less than three categories of serum vitamin D [17, 33–41]. We also removed three review articles as well as two studies in which the number of cases or controls were not reported for each category of serum levels of vitamin D [42, 43]. Finally, nine cohort studies [14, 16, 44–50] and six nested case-control studies [51–56] were included in the final analysis (Fig. 1). Table 1 represents the characteristics of the included studies. A total of 40,788 pregnant women with an average age of 11 to 42 years participated in these studies, of which 1848 women developed GDM. Studies were published between 2008 and 2018, of them seven studies were from United States (US) [14, 16, 44, 47, 48, 51, 55], two studies were from Australia [49, 53], two studies were from Canada [52, 56], one study was from Korea [54], one study was from Norway [50], one study was performed in Singapore [46], and one study was conducted in Spain [45]. In 11 studies, serum 25(OH)D levels were measured using immunoassay methods including electrochemical luminescence immunoassay (ECLIA) [54, 56], immunodiagnostic systems (IDS-iSYS) [49], chemiluminescent immunoassay (CLIA) [14, 47, 52], enzyme-linked immunosorbent assay (ELISA) [44, 48], radioimmunoassay (RIA) [16, 50], and automated immunoassay system (AIAS) [53]. Whereas, other studies used chromatography methods including high-performance liquid chromatography (HPLC) [45] and liquid chromatography–mass spectrometry (LC–MS) [46, 51, 55]. Different criteria were used to diagnose GDM including American Diabetes Association (ADA) ($n = 4$), National Diabetes Data Group (NDDG) ($n = 3$), Carpenter–Coustan (C&C) ($n = 2$), World Health Organization (WHO) ($n = 2$), American College of Obstetricians and Gynecologists (ACOG) ($n = 1$), International Association of Diabetes and Pregnancy Study Groups (IADPSG) ($n = 1$), Australasian Diabetes in Pregnancy Society (ADPS) ($n = 1$), and Canadian Diabetes Association (CDA) ($n = 1$). One study evaluated only 25(OH)D3 [45] while other studies evaluated combined 25(OH)D3 and 25(OH)D2.

Except one study [48], studies had controlled the analyses for maternal age. Out of 15 studies, 12 studies had controlled the analyses for body mass index [14, 16, 44–49, 51, 54–56]. Seven studies adjusted the analyses for gestational age [16, 45, 47, 51, 52, 54, 56]. Five studies controlled the analyses for study site [45, 49, 50, 53, 56] and five other studies performed adjustments for family history of diabetes or previously diagnosed diabetes [16, 44, 46, 53, 55]. Only six studies performed adjustment for parity [14, 16, 45, 46, 50, 53] and smoking status [14, 45, 46, 48, 49, 53]. Most studies adjusted the analyses for socioeconomic status [5, 14, 16, 45, 46, 51, 53], season of sampling [14, 47, 48, 50, 51, 53–56], and race/ethnicity [14, 16, 44, 46–50, 55]. Other studies further adjusted the analysis for child's sex ($n = 2$), maternal weight ($n = 2$), alcohol consumption ($n = 2$), previous GDM ($n = 1$), previously diagnosed hypertension ($n = 2$), vitamin D intake ($n = 1$), dietary intakes of fish and calcium ($n = 2$), physical activity ($n = 2$), and skinfolds ($n = 1$). According to New-Castle Ottawa Scale, all of the included studies were of high quality (Table 1).

Findings from the dose-response meta-analysis

Nine studies including three cohort studies and six nested case-control studies reported sufficient information for dose-response meta-analysis on serum levels of 25(OH)D and the risk of GDM. We observed an inverse linear association between serum levels of 25(OH)D and the risk of developing GDM. Each 10 nmol/L increase in circulating

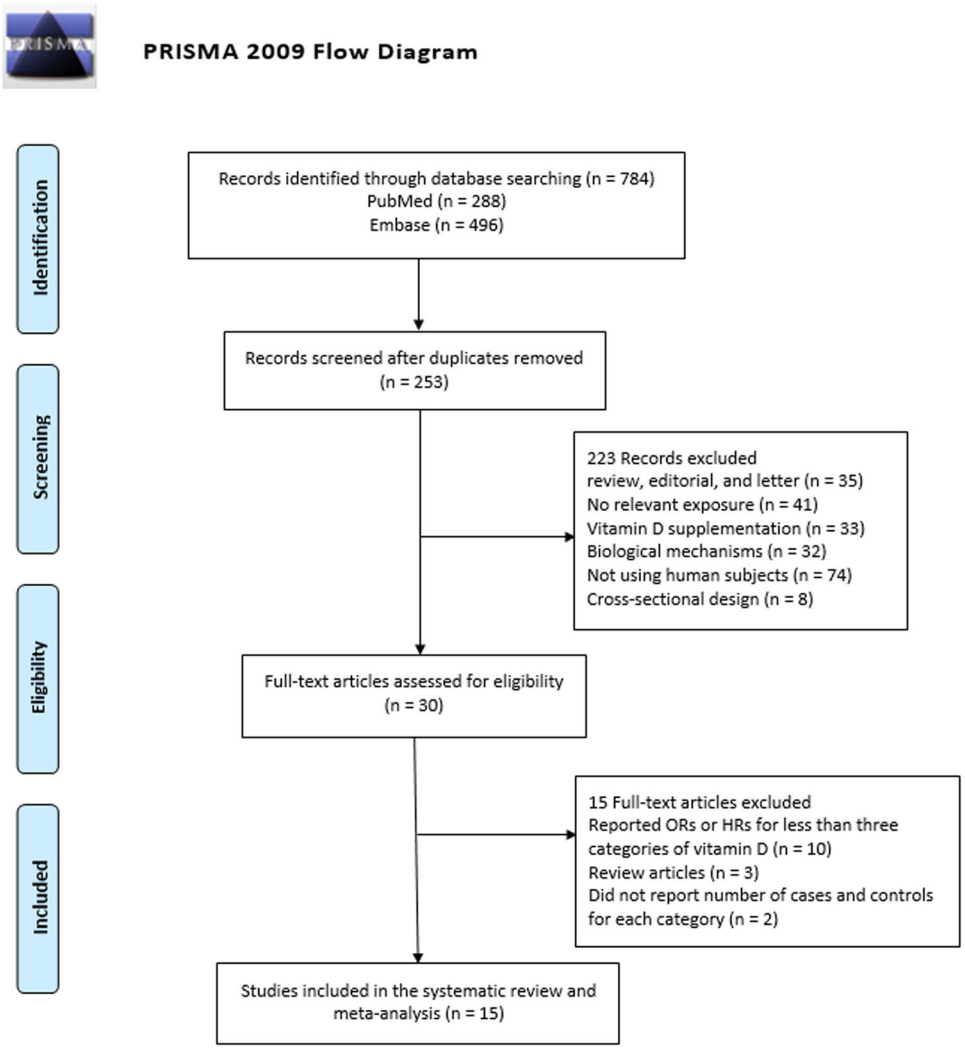

Fig. 1 Flowchart of the study selection process

25(OH)D was associated with a 2% lower risk of GDM (effect size (ES): 0.98; 95% CI: 0.98, 0.99), with an evidence of high heterogeneity ($I^2 = 85.0\%$, $P < 0.001$) (Fig. 2). To address the main sources of heterogeneity, we implemented sensitivity analysis as well as subgroup analyses according to the prespecified characteristics. Findings from the subgroup analysis revealed that study design, vitamin D assessment methods, GDM criteria, and the number of cases could explain the source of heterogeneity. Findings from subgroup analysis showed a significant linear association in both cohort and nested case-control studies, studies conducted either in US or non-US countries, studies with <100 or >100 cases, and those that adjusted their analyses for <4 or ≥4 important variables. In addition, subgroup analysis showed no significant association in studies that used non-immunoassay methods to evaluate serum 25(OH)D (ES: 0.99; 95% CI: 0.99, 1.00; $I^2 = 0.00$), those that diagnosed GDM using NDDG criteria (ES: 0.99; 95% CI: 0.99, 1.00; $I^2 = 0.00$), and studies that recruited women with <30 (ES: 0.95; 95% CI: 0.88, 1.02; $I^2 = 0.00$) (Table 2). In the sensitivity test that omitted one study each time to obtain the pooled effect size from the random-effects model, no study could significantly change the association between serum 25(OH)D and GDM risk (data not shown). There was not any publication bias based on Egger's test ($P = 0.88$) and the symmetry of the funnel plot (Fig. 4a).

High vs. low meta-analysis

Seven cohort prospective studies [14, 16, 44, 46–48, 50] and one nested case-control study [52] reported sufficient information for high vs. low analysis. Highest compared with the lowest category of circulating 25(OH)D was associated with a 29 % lower risk of GDM (ES: 0.71; 95% CI: 0.51, 0.99), with low evidence of heterogeneity ($I^2 =$ 45.0 %, $P = 0.079$) (Fig. 3). In the subgroup analysis, the association remained significant if the mean age of the mother was more than 30 years (ES: 0.71, 95% CI: 0.54, 0.94), immunoassay methods were used to evaluate

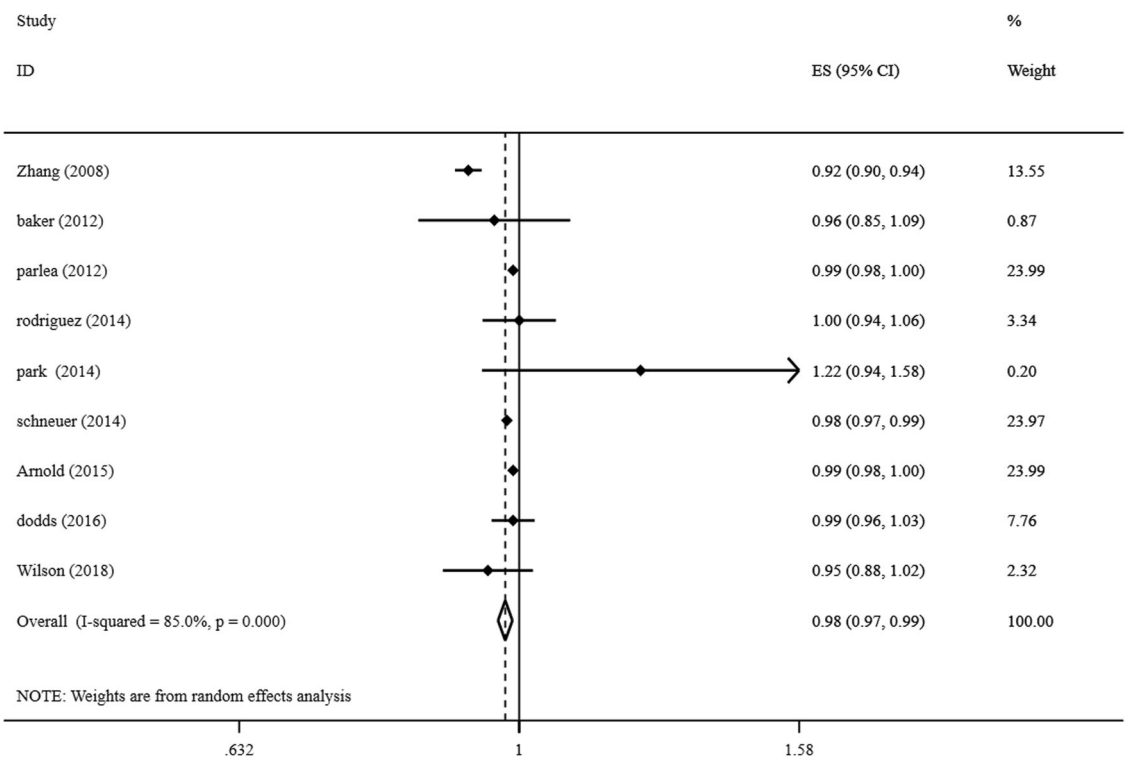

Fig. 2 Forest plot for the association between serum levels of 25(OH)D and the risk of gestational diabetes by the use of the random-effects model. ES effect size

circulating 25(OH)D (ES: 0.69, 95% CI: 0.53, 0.90), and the study was from US countries (ES: 0.62, 95% CI: 0.42, 0.93). Furthermore, there was no significant association in studies with adjustment for ≥4 principal variables (ES: 0.91, 95% CI: 0.71, 1.16), studies with more than 100 cases (ES: 0.95, 95% CI: 0.70, 1.27), those that used WHO criteria to diagnose GDM (ES: 0.95, 95% CI: 0.71, 1.27), and cohort studies (ES: 0.82, 95% CI: 0.65, 1.04) (Table 3). Findings from sensitivity analysis showed that excluding 4 studies [14, 44, 48, 52] resulted in a nonsignificant linear association. There was no evidence of publication bias based on Egger's test ($P = 0.20$) and visual inspection of the funnel plot (Fig. 4b).

Discussion

Giving great importance for vitamin D and the risk of GDM, an extensive body of evidence has been published to find the association between serum levels of vitamin D and the risk of GDM. During the past decade, seven meta-analyses of observational studies were published [18–21, 57–59]. They adopted nearly the same inclusion and exclusion criteria and updated each other. They reported a significant inverse relationship between serum levels of 25(OH)D and the risk of GDM. However, the optimal 25(OH)D levels for GDM prevention remain unknown. In the current study, we observed a 2% lower risk of GDM per 10 nmol/L increment of circulating 25(OH)D, although findings had high heterogeneity. The association was not significant anymore in the subgroups of studies with non-immunoassay methods, NDDG diagnostic criteria, and studies that included mothers younger than 30 years. Moreover, the highest compared with the lowest category of circulating 25(OH)D was associated with a 29% lower risk of GDM, with low evidence of heterogeneity. The result was not replicated in some subgroups.

Our meta-analysis suggests that each 10 nmol/L increase in circulating 25(OH)D was associated with a 2% lower risk of GDM, and the risk of developing GDM decreases by 29% for the highest compared with the lowest category of 25(OH)D levels. Our results are in line with those of previous meta-analyses on prospective studies that indicated a significantly lower risk of GDM in relation to higher levels of 25(OH)D [18, 19, 57]. Earlier evidence suggested that vitamin D deficiency was associated with insulin resistance and type 2 diabetes given its role in supporting insulin secretion and pancreatic β-cell function [60]. Moreover, serum 25(OH)D has been inversely associated with poorer glycemic control including higher levels of fasting glucose and fasting insulin during pregnancy [41, 61]. Several mechanisms have been suggested for the relationship

Table 2 Subgroup analysis for the dose-response association between serum levels of 25(OH) D and the risk of gestational diabetes

	Effect sizes (*n*)	Overall effect (95% CI)	*P*-within[a]	I^2 [b] (%)	*P*-between[b]
Overall	9	0.98 (0.97, 0.99)	0.0001	85.0	
Study design					<0.001
Cohort	3	0.93 (0.91, 0.95)	<0.001	70.9	
Nested case-control	6	0.99 (0.98, 0.99)	<0.001	61.2	
Study location					0.72
US	3	0.99 (0.98, 0.99)	<0.001	95.5	
Non-US	6	0.99 (0.98, 0.99)	<0.001	56.4	
Vitamin D assessment method					0.03
Immunoassay methods	6	0.98 (0.98, 0.99)	<0.001	89.6	
Non-immunoassay methods	3	0.99 (0.99, 1.00)	0.13	0	
Gestational diabetes criteria[a]					0.02
NDDG	3	0.99 (0.99, 1.00)	0.13	0	
ADA	2	0.99 (0.98, 0.99)	<0.001	97.6	
Other	4	0.98 (0.98, 0.99)	<0.001	19.6	
Number of cases					<0.001
<100	5	0.93 (0.91, 0.95)	<0.001	64.4	
>100	4	0.99 (0.98, 0.99)	<0.001	70.4	
Maternal age[c]					0.60
>30	7	0.99 (0.98, 0.99)	<0.001	88.5	
<30	1	0.95 (0.88, 1.02)	0.173	0	
Number of eight adjusted variables[d]					0.67
<4	3	0.99 (0.98, 0.99)	<0.001	95.5	
≥4	6	0.99 (0.98, 0.99)	<0.001	44.5	

NDDG The National Diabetes Data Group, *ADA* American Diabetes Association

[a]*P* value for Cochran's *Q* test

[b]Obtained from the fixed-effect model

[c]*n* may not add up to the total because one study did not report participants' age

[d]The eight adjusted variables were body mass index, gestational age, study site, family history of diabetes or previously diagnosed diabetes, smoking status, socioeconomic status, the season of sampling, and race/ethnicity

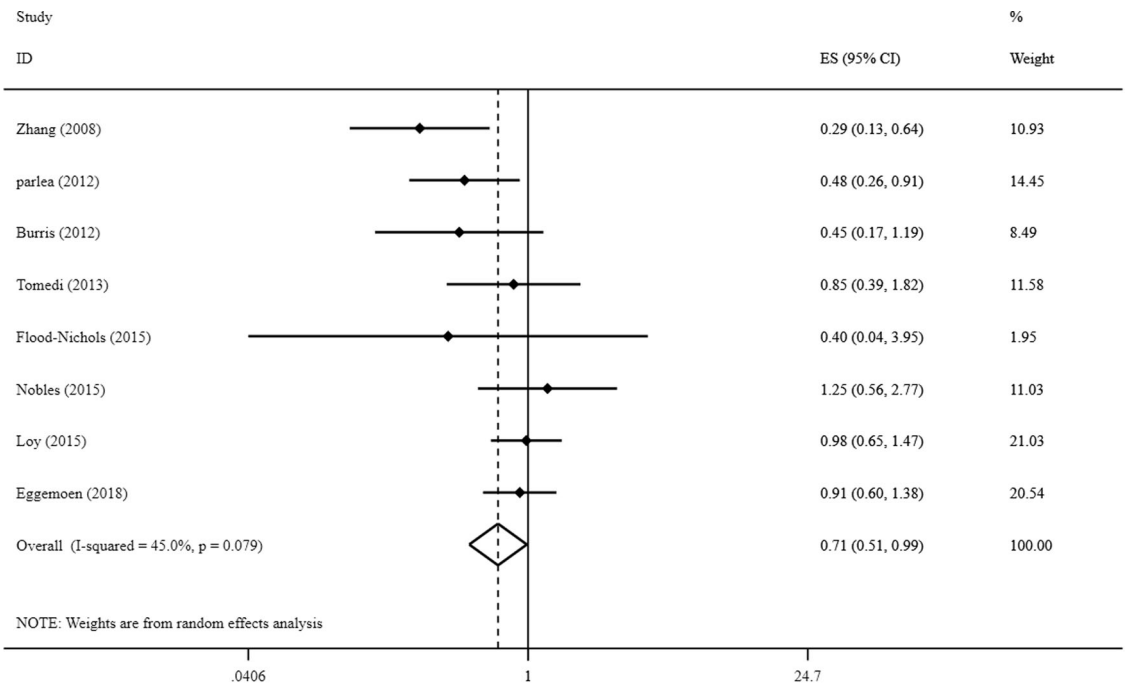

Fig. 3 Forest plot for the association of the highest compared with the lowest category of serum levels of 25(OH)D and the risk of gestational diabetes by the use of the random-effects model. ES effect size

Table 3 Subgroup analysis for the relative risk of incident gestational diabetes for the highest compared with the lowest category of circulating 25 (OH)D

	Effect sizes (*n*)	Overall effect (95% CI)	*P*-within[a]	*I*[b] (%)	*P*-between[b]
Overall	8	0.71 (0.51, 0.99)	0.041	45.0	
Study design					0.13
Cohort	7	0.82 (0.65, 1.04)	0.10	42.2	
Nested case-control	1	0.48 (0.26, 0.91)	0.02	0	
Study location					0.23
US	5	0.62 (0.42, 0.93)	0.02	47.6	
Non-US	3	0.84 (0.64, 1.10)	0.19	44.9	
Vitamin D assessment method					0.16
Immunoassay methods	7	0.69 (0.53, 0.90)	0.007	44.2	
Non-immunoassay methods	1	0.98 (0.65, 1.47)	0.92	0	
Gestational diabetes criteria[a]					0.10
ADA	3	0.56 (0.35, 0.91)	0.02	70.1	
WHO	2	0.95 (0.71, 1.27)	0.706	0	
Other	3	0.60 (0.37, 0.96)	0.03	0	
Number of cases					0.03
<100	6	0.58 (0.41, 0.81)	0.002	38.1	
>100	2	0.95 (0.71, 1.27)	0.706	0	
Maternal age					0.37
<30	3	0.88 (0.61, 1.26)	0.48	0	
>30	5	0.71 (0.54, 0.94)	0.02	65.0	
Number of eight adjusted variables[c]					0.004
<4	2	0.40 (0.24, 0.65)	<0.0001	0	
≥4	6	0.91 (0.71, 1.16)	0.43	0	

ADA American Diabetes Association, *WHO* World Health Organization

[a]*P* value for Cochran's *Q* test

[b]Obtained from the fixed-effect model

[c]The eight adjusted variables were body mass index, gestational age, study site, family history of diabetes or previously diagnosed diabetes, smoking status, socioeconomic status, the season of sampling, and race/ethnicity

between vitamin D and GDM including the effect of vitamin D on the performance of pancreatic β cells [62], intracellular calcium regulation [63], and the effect on systemic inflammation together with insulin resistance in patients with diabetes mellitus [64].

In the subgroup analysis, we observed a significant association in studies conducted on pregnant women older than 30 years. This might be influenced by the expected risk of GDM and vitamin D deficiency among older pregnant women [65, 66]. We also found that different vitamin D measurement tools may affect the final results; such that significant associations were only observed in studies that used immunoassay methods. The selected studies used different methods for the determination of 25(OH)D, among which immunoassays were the most widely used technique [67, 68]. Studies have shown that assay variations can affect the results of vitamin D measurement [68, 69]. However, the low number of studies in the non-immunoassay subgroup limited statistical power, and therefore more work is required to find out if the association reported here persists when using other methods. Notably, in the high vs low analysis, the significant association disappeared after the exclusion of one case-control study. Thus, the true association may result from potential biases of case-control studies such as selection bias, recall bias, and inverse causal bias [70]. In this regard, several meta-analyses confirmed the current results, showing that heterogeneity among studies included in a meta-analysis can be explained by study design [18, 57, 66]. Moreover, nonsignificant result among non-US countries is probably due to the paucity of studies in this subgroup since only one study came from Asia, one study was from Canada, and one study was from Europe. In addition, the significant association disappeared among studies with adjustment for ≥4 major confounders. Since the pathophysiology of GDM is multifactorial [71], some confounding bias may play a role in evaluating the association of serum vitamin D and the risk of GDM. Thus, the possible effect of vitamin D on GDM cannot be regarded as the sole causative factor.

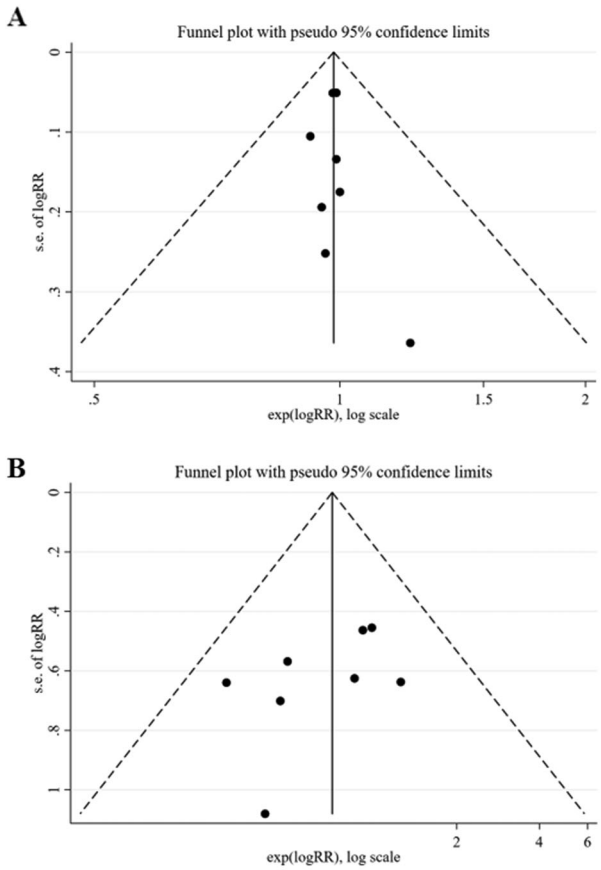

Fig. 4 Funnel plots for the dose-response (**a**) and high vs low (**b**) associations between serum levels of 25(OH)D and the risk of gestational diabetes

Although we found a significant association of circulating vitamin D and GDM, findings from randomized controlled trials (RCTs) showed weak or even negative effects of vitamin D on diabetes prevention or treatment [8]. Most of these studies have suffered from more than one study design limitation such as recruiting participants without vitamin D deficiency [9–11] and insufficient dosage of vitamin D supplementation [72, 73]. Nevertheless, recent trials with the robust design did not find a significant effect of vitamin D supplementation on the glycemic profile of prediabetic and diabetic patients [74, 75]. Similarly, data from RCTs regarding vitamin D supplementation on GDM have also been inconsistent. Recent reviews on vitamin D supplementation during pregnancy could not find robust evidence related to GDM [12, 13].

Some limitations should be considered for our meta-analysis. First, since the included studies adjusted their analyses for separate confounders, high heterogeneity was apparent in the dose-response meta-analysis. However, based on a previous study, the results of the meta-analysis would not differ substantially when adopting fully adjusted models than using models that control only the most common confounders [76]. Moreover, other sources of heterogeneity among the original studies were partially explained by our subgroup analysis and sensitivity analysis. Second, due to a lack of relative data, we could not find the impact of potential confounding factors including skin color, weight gain during pregnancy, dietary intake of vitamin D, and sunlight exposure. Another limitation is the point that the included studies had used different methods and standards to diagnose GDM. Although we performed subgroup analysis in this regard, the interpretation of the results is complicated given the little number of studies in each subgroup. The strength of our study is that the present work was the first dose-response meta-analysis that examined the association between serum 25(OH)D and the risk of GDM using large-scale, high-quality, prospective cohort studies. The included studies were all population-based research, and therefore the results could be extended to the general population. Besides, to find the source of heterogeneity, we stratified our meta-analysis based on study design, study location, vitamin D assessment method, GDM criteria, maternal age, and adjustment for confounders, suggesting a possible independent association between serum 25(OH)D and GDM risk. The lack of publication bias indicates that we were unlikely to miss studies that could have changed the results of our meta-analysis.

Conclusion

Combining these findings, it seems that lower levels of serum 25(OH)D were associated with a higher chance of GDM. These results should be interpreted with caution due to high heterogeneity among the included studies. Although it is biologically plausible that low 25-OHD levels could be responsible for the GDM, owing to the observational nature of the data reviewed and inconsistency in RCTs we cannot infer causality from these findings. There is a need for well-conducted and adequately powered studies, especially in non-western regions, with different ethnic origins.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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