

Serum vitamin D deficiency and risk of gestational diabetes mellitus: a meta-analysis

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Abstract

Introduction: This meta-analysis was performed to confirm the relationship of gestational diabetes mellitus (GDM) and vitamin D.

Material and methods: PubMed and CNKI databases were searched for relevant articles. Standard mean difference (SMD) along with 95% CI was used to compare vitamin D level between women with GDM and healthy subjects. The correlation coefficient between the vitamin D and homeostasis model assessment-insulin resistance index (HOMA-IR) was analyzed.

Results: The vitamin D level of GDM subjects was much lower than healthy subjects (SMD = -0.71, 95% CI: -0.91, -0.50). Vitamin D deficiency was associated with high risk of GDM (OR = 1.15, 95% CI: 1.07–1.23). Vitamin D was negatively correlated with HOMA-IR ($r = -0.62$, 95% CI: -0.85, -0.39). The analysis showed no publication bias (Egger's: $p = 0.197$; Begg's: $p = 0.786$).

Conclusions: Vitamin D is closely associated with the onset of GDM.

Key words: vitamin D, gestational diabetes mellitus, 25(OH)D, meta-analysis.

Introduction

Vitamin D, a secosteroid, is synthesized in skin and then metabolized in kidneys and liver of humans. It plays an important role in maintaining phosphorus and calcium homeostasis and accelerating bone mineralization. Emerging evidence shows that vitamin D deficiency is associated with high risk of cardiovascular disease [1–3], hypertension [4, 5], and cancers [6–8]. In addition, it has been demonstrated that vitamin D maintains normal glucose homeostasis [9, 10]. Vitamin D deficiency is reported to be associated with insulin resistance, high risk of pre-diabetes and type 2 diabetes mellitus (DM) [11].

Both of vitamin D and parathyroid hormone (PTH) contribute to maintaining calcium (Ca) homeostasis [12]. Vitamin D is associated with intestinal Ca absorption. Low serum Ca level promotes PTH secretion to stimulate the resorption of Ca from bone and the renal reabsorption of Ca [12], which is defined as secondary hyperparathyroidism that could increase the risk of DM [13, 14].

Gestational diabetes mellitus (GDM) is a growing health problem. It is defined as glucose intolerance, which commonly occurs during pregnancy [15]. Its relationship with adverse newborn and pregnancy outcomes is well known [16]. Obesity and lifestyle are the main risk factors for GDM [17, 18]. Some studies have reported a significant relationship between 25(OH)D deficiency and GDM, while others did not find such an association [19–22]. The opinions about the relationship of GDM and 25(OH)D levels are inconsistent [19–22]. Previously published meta-analyses analyzed the relationship of 25(OH)D deficiency and GDM [23–25], but studies published in Chinese were not considered in these meta-analyses.

The present meta-analysis included articles in Chinese and the results seem to be much more accurate. Levels of vitamin D in GDM subjects and healthy ones were analyzed. Meanwhile, the relationship of vitamin D with risk of GDM was also investigated.

Material and methods

Search strategy

The present meta-analysis was conducted according to the PRISMA statement about meta-analysis [26]. Two researchers independently performed searches for the related articles (up to September 2019) in the PubMed and CNKI databases. Keywords included 1,25-dihydroxycholecalciferol or 25(OH)D or vitamin D or 25-hydroxy vitamin D and GDM or gestational diabetes mellitus. The obtained articles were scanned and the reference lists of all articles were checked manually. To decrease bias, two researchers performed the searches and any inconsistent opinions were resolved with a discussion.

Inclusion and exclusion criteria

The obtained articles were selected according to inclusion and exclusion criteria. During evaluation, abstracts and titles of obtained articles were screened carefully. Only studies that conducted analysis among pregnant woman without illness were considered. Meanwhile, papers that compared vitamin D level between women with GDM and women with normal glucose tolerance (NGT) would be selected. In addition, papers that reported an estimation of effect (odds ratio – OR) to compare sufficient and insufficient vitamin D values were also selected. Studies based on non-human experiments, duplicate publications, reviews, meta-analysis, and those that provided insufficient data were excluded from the analysis.

Data extraction

The following data were extracted from included studies: name of first author, year of publica-

tion, sample size, gestational age, vitamin D levels and status among GDM and healthy subjects. For more information, the authors would be contacted for supplementary data. Disagreements were resolved via a discussion.

Data synthesis and statistical analysis

STATA software was used for statistical analyses. OR with 95% confidence interval (CI) was applied to evaluate the relationship of vitamin D with the risk of GDM. Standard mean difference (SMD) along with 95% CI was used to compare vitamin D level between women with GDM and healthy subjects. Meanwhile, the correlation coefficient between vitamin D and the homeostasis model assessment-insulin resistance index (HOMA-IR) was analyzed as well. Heterogeneity was assessed with Q and I^2 statistics. When heterogeneity was observed, a random-effects model was used in the analysis. Publication bias was tested by Egger's and Begg's analyses. All statistical tests were two sided.

Results

Selection process of articles

After the initial search, 248 potential articles were obtained. Eight additional articles were identified through manual search of the references. Overall, 256 potential articles were confirmed. After screening the abstracts and titles, 97 articles were removed. After a full-text review, 106 articles were excluded. Fifty-three studies were selected [19, 20, 22, 27–76]. The selection process is shown in Figure 1. Basic information of included articles is listed in Table I.

Comparison in vitamin D level between women with GDM and healthy subjects

A total of 43 articles with a population of 28,827 compared the vitamin D level between women with GDM and healthy subjects (Figure 2). During analysis, the SMD statistic was applied due to inconsistent units. In the analysis, we found that vitamin D level of GDM subjects was much lower than that of healthy subjects (SMD = -0.71 , 95% CI: $-0.91, -0.50$).

Relationship of vitamin D with GDM risk

Altogether 21 articles with a population of 16,177 reported a relationship of vitamin D and risk of GDM (Figure 3). Two studies reported a significant relationship, and 19 studies reported no significant relationship. Due to significant heterogeneity ($p < 0.001$), the meta-analysis was performed with a random-effects model. It showed that vitamin D deficiency was associated with high risk of GDM (OR = 1.15, 95% CI: 1.07–1.23).

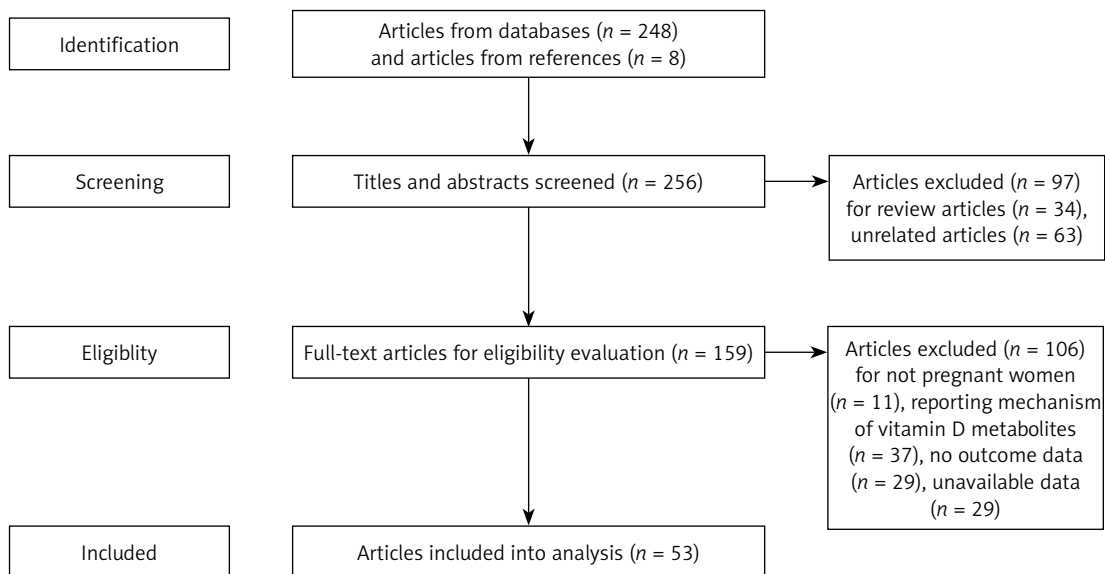


Figure 1. Selection process of included articles. Fifty-three studies were included in the present meta-analysis

Table I. Basic information of studies

Author	Year	Country	Subjects, n	Gestational diabetes, n	Diagnosis time [weeks]	Assay method	Cut-off values [nmol/l]
Liu Y [27]	2015	China	174	85	24–28	Electrochemiluminescence	–
Wu YX [28]	2016	China	240	120	11	ELISA	50
Cai YQ [29]	2017	China	400	200	24–28	ELISA	50
Tao [30]	2015	China	176	88	24.28	Electrochemiluminescence	–
Zhou JL [31]	2017	China	7000	1012	24–28	ELISA	–
Ye [32]	2015	China	82	41	24–28	ELISA	50
Zhang SF [33]	2015	China	100	50	24–28	Electrochemiluminescence	–
Liu T [34]	2013	China	50	25	24–28	ELISA	–
Hou [35]	2016	China	70	30	24–28	ELISA	–
Liang [36]	2016	China	60	30	24–28	ELISA	25
Wang YL [37]	2016	China	100	50	24–28	Electrochemiluminescence	75
Guan [38]	2016	China	90	60	24–28	radioimmunoassay	–
Lei [39]	2014	China	433	118	24–28	Electrochemiluminescence	75
Zhang YJ [40]	2017	China	400	200	24–28	ELISA	–
Zhang CY [41]	2013	China	372	124	24–28	CLIA	50
Liu Y [42]	2017	China	72	36	24–28	ELISA	75
Song [43]	2015	China	180	78	24–28	ELISA	75
Hu [44]	2015	China	74	37	28	ELISA	50
Lu [45]	2010	China	55	29	24–30	ELISA	–
Zhu [46]	2016	China	110	55	24	Electrochemiluminescence	–
Cai F [47]	2016	China	1305	133	24–28	ELISA	–
Wang X [48]	2016	China	243	123	23–41	ELISA	–
Shen X [49]	2015	China	200	100	24–28	CLIA	50
Shen F [50]	2013	China	528	36	16–20	ELISA	–
Si [51]	2014	China	446	55	17–21	ELISA	–

Table I. Cont.

Author	Year	Country	Subjects, n	Gestational diabetes, n	Diagnosis time [weeks]	Assay method	Cut-off values [nmol/l]
Bei [52]	2014	China	100	50	24–28	LC–MS/MS	–
Yuan [53]	2017	China	717	478	24–28	ELISA	–
Zhou Y [54]	2016	China	7773	977	24–28	–	–
Zhang CL [55]	2008	America	171	57	24–28	ELISA	75
Parlea [56]	2012	Canada	335	116	24–28	CLIA	–
Wang [58]	2012	China	400	200	26–28	ELISA	50
Bener [59]	2013	Qatar	1873	260	24–28	Radioimmunoassay	75
Parildar [60]	2013	Turkey	122	44	24–32	CLIA	50
Zuhur [61]	2013	Turkey	402	234	24–28	Electrochemiluminescence	50
Arnold [62]	2015	America	652	135	24–28	LC–MS/MS	75
Dodds [63]	2016	Canada	2320	395	24–28	CLIA	50
Schneuer [64]	2014	Australia	4090	376	24.28	CLIA	50
Maghbooli [19]	2008	Iran	579	52	24–28	Radioimmunoassay	34.9
Clifton-Bligh [20]	2008	Australia	264	81	28.7	Nichols Advantage assay	–
Soheilykhah [65]	2015	Iran	54	165	24–28	ELISA	75
Makgoba [22]	2011	UK	248	90	24–28	LC–MS/MS	–
Savvidou [66]	2011	UK	1100	100	24–28	LC–MS/MS	–
Baker [67]	2012	America	180	60	24–28	LC–MS/MS	75
Burris [68]	2012	America	1246	68	26–28	CLIA	75
Fernandez-Alonso [69]	2012	Spain	466	36	24–28	Electrochemiluminescence immunoassay	75
Lacroix [70]	2014	Canada	655	54	24–28	Immunoassay system	75
Park [71]	2014	Korea	523	23	24–28	Electrochemiluminescence immunoassay	50
Boyle [72]	2016	UK	1544	32	24–28	LC–MS/MS	75
Hauta-Alus [75]	2017	Finland	723	81	24–28	CLIA	80
Shen [76]	2011	China	1030	52	24.28	ELISA	50
Yang [57]	2013	China	70	35	24–28	ELISA	50
Loy [73]	2015	Singapore	940	155	26–28	LC–MS/MS	75
Pleskacova [74]	2015	Czech Republic	76	47	24–30	ELISA	50

LC–MS/MS – liquid chromatography–tandem mass spectroscopy, CLIA – chemiluminescence immunoassay.

Correlation coefficient between vitamin D and HOMA-IR

A total of 8 articles with a population of 2,376 analyzed the correlation coefficient between vitamin D level and HOMA IR (Figure 4). The outcome indicated that vitamin D was negatively correlated with HOMA-IR ($r = -0.62$, 95% CI: $-0.85, -0.39$).

Sensitivity analysis

Sensitivity analysis was performed. Each study was sequentially removed and the overall results did not change, which indicated that the results were robust.

Publication bias

Potential publication bias was detected via funnel plot (Figure 5). Egger's and Begg's tests showed no publication bias (Egger's: $p = 0.197$; Begg's: $p = 0.786$).

Discussion

The pathogenesis of disease involves many factors, such as genes, infections, environment and nutrition supplementation [77–85], which regulates the metabolism of some molecules, thus resulting in the diseases [86, 87]. GDM is a well-known complication with high prevalence

during pregnancy. It shows an imbalance between insulin secretion and insulin resistance, resulting in maternal hyperglycemia [88]. The risk factors for GDM include maternal age, obesity prior to and during pregnancy, family history of diabetes and previous history of GDM [89]. However, these factors cannot serve as predictors of GDM development in half of all cases [90]. Lower 25(OH)D concentrations have been demonstrated to be associated with insulin resistance, ma-

ternal glycemia, and high risk of GDM. However, the relationship of 25(OH)D with risk of GDM has not been well defined. The present meta-analysis was performed to reach a definite conclusion on this topic.

Some studies suggested a relationship of 25(OH)D with increased risk of GDM [20, 21, 55, 65, 91]. A recent study did not find evidence for the relationship of 25(OH)D with GDM [22]. Another study reported a similar result, but it sug-

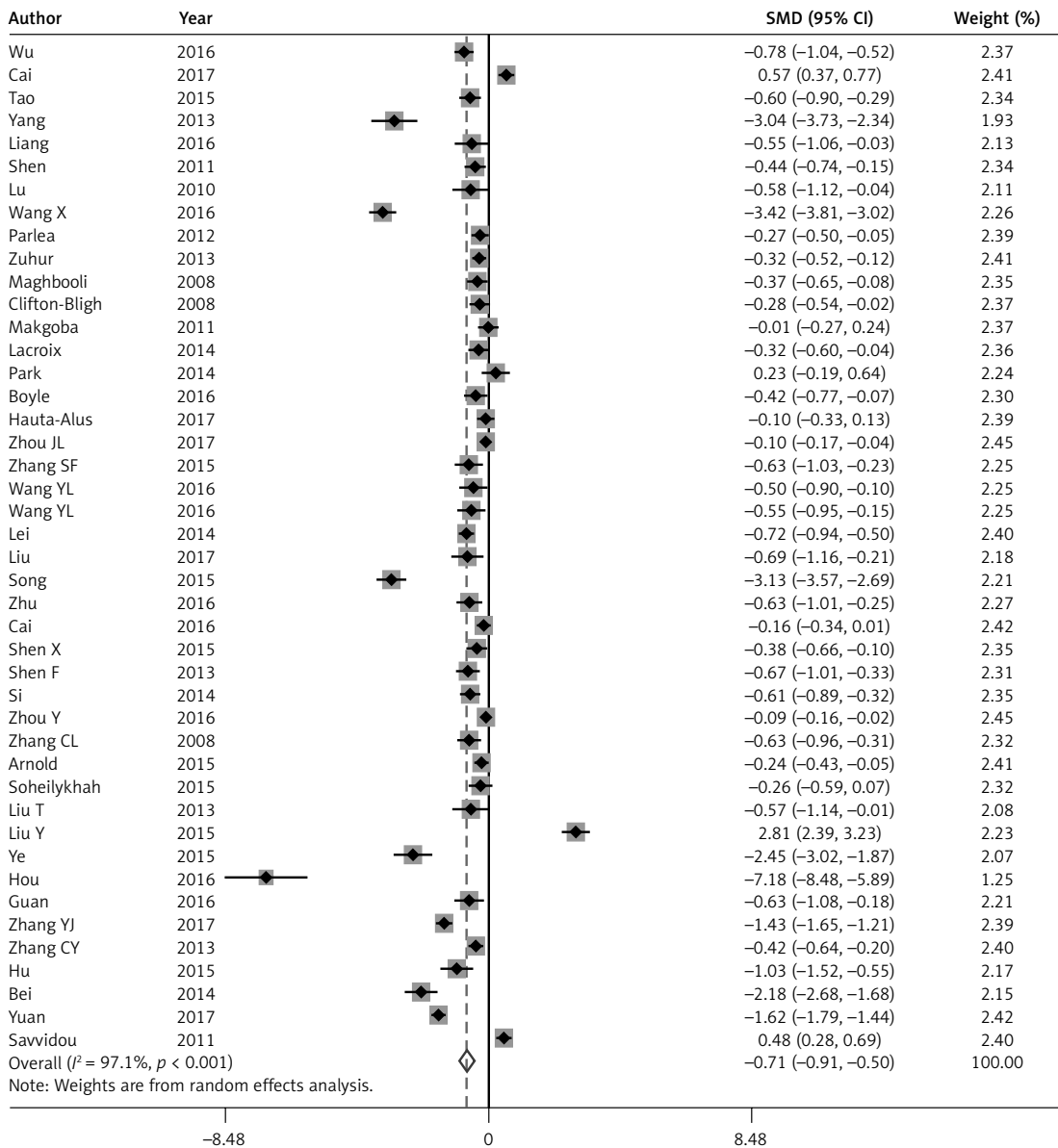


Figure 2. Comparison of vitamin D level between women with GDM and healthy subjects. Vitamin D level of GDM subjects was much lower than that of healthy subjects (SMD = -0.71, 95% CI: -0.91, -0.50). The horizontal line indicates the lower and upper limits of the 95% CI; the square indicates the SMD, with the size of the square indicating the weight of the study and the dotted red line indicating the combined SMD value. The diamond represents the combined effect size, and the larger the diamond, the larger the confidence interval. A cross between the diamond and the ineffective line indicates no statistical difference between GDM and healthy subjects in vitamin D level; if the diamond falls on the left side of the invalid line, it indicates a lower level of vitamin D among GDM subjects, compared to that of healthy subjects; if the diamond falls on the right side of the line, it indicates a higher level of vitamin D among GDM subjects, compared to that of healthy subjects

SMD – standard mean difference, CI – confidence interval.

gested an inverse relationship of glucose concentrations with 25(OH)D level 30 min after a 100 g glucose load [21]. Physical activity is an important confounder of the relationship of 25(OH)D and GDM. Thanks to sunlight exposure, active women have less risk of developing impaired glucose tolerance and seem to have higher 25(OH)D levels than less active women [92, 93].

In the analysis, a total of 43 articles compared the vitamin D level between GDM and healthy subjects. The overall outcome revealed that the vitamin D level of women with GDM was much lower than that of healthy subjects. Altogether 21 articles reported a relationship of vitamin D status and risk of GDM. Two articles reported a significant relationship and 19 articles reported no significant relationship. The outcome showed that vitamin D deficiency was significantly correlated with increased risk of GDM. Meanwhile, 8 articles analyzed the correlation coefficient between vitamin D and HOMA IR. We found that vitamin D was negatively correlated with HOMA-IR, which contributes to revealing the re-

lationship of vitamin D and GDM. It is common to compare the clinical efficacy of methods for disease [94–96]. There were articles reporting the beneficial effects of vitamin D supplementation on the GDM [97–100]. Zhang *et al.* reported that high-dose vitamin D supplementation significantly improved insulin resistance in pregnant women with GDM [97]. Yazdchi *et al.* concluded that vitamin D supplementation improved FG and HbA_{1c} in GDM patients [98]. The study by Shahgheibi *et al.* indicated that vitamin D supplementation in the first and second trimesters of pregnancy was effective in reducing GDM and controlling GTT and GTC [99]. Another study by Mahdih *et al.* indicated that 50,000 IU vitamin D every 2 weeks decreased the incidence of GDM [100]. All these results were consistent with our outcomes.

The meta-analysis included 53 eligible articles, of which 30 articles were published in Chinese. The results seem to much more accurate; however, the analysis still has some limitations. First, the diagnostic time of GDM, detection method for 25(OH)D, and the cut-off value of vitamin D dif-

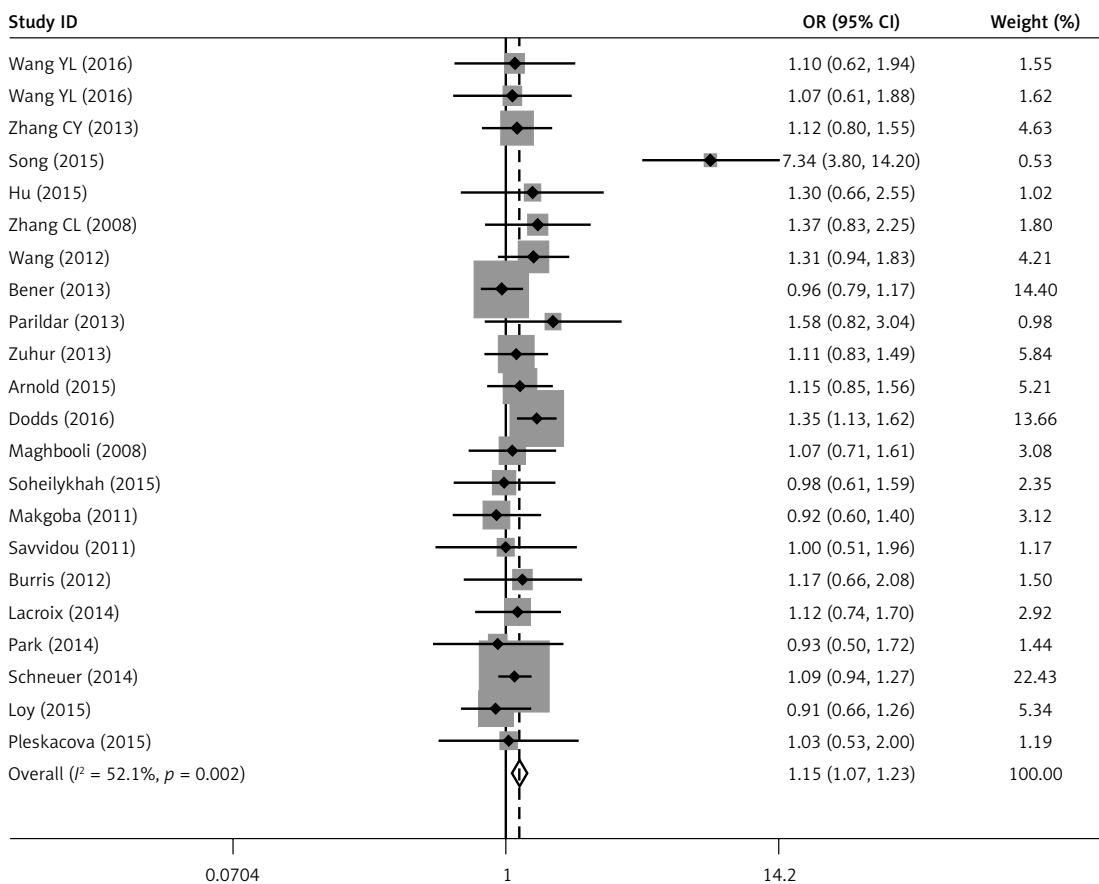


Figure 3. Relationship of vitamin D with GDM risk. Vitamin D deficiency was closely associated with high risk of GDM (OR = 1.15, 95% CI: 1.07–1.23). The horizontal line indicates the lower and upper limits of the 95% CI; the square indicates the OR, with the size of the square indicating the weight of the study and the dotted red line indicating the combined SMD value. The diamond represents the combined effect size, and the larger the diamond, the larger the confidence interval. A cross between the diamond and the ineffective line indicates no statistical correlation between the factors studied and the outcome; if the diamond falls on the left side of the invalid line, it indicates a protective factor; if the diamond falls on the right side of the line, it indicates a risk factor

OR – odds ratio, CI – confidence interval.

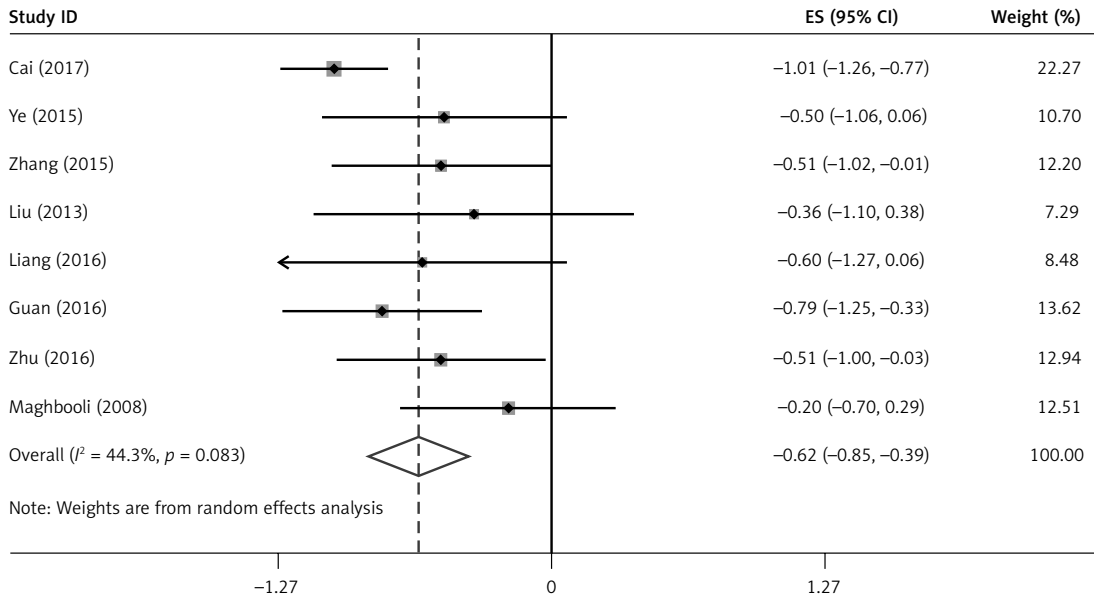


Figure 4. Analysis of the correlation coefficient between vitamin D level and HOMA-IR. Vitamin D was negatively correlated with HOMA-IR ($r = -0.62$, 95% CI: $-0.85, -0.39$). The horizontal line indicates the lower and upper limits of the 95%CI; the square indicates the effective size with the size of the square indicating the weight of the study and the dotted red line indicating the combined effective size value. The diamond represents the combined effect size, and the larger the diamond, the larger the confidence interval. A cross between the diamond and the ineffective line indicates the correlation coefficient between vitamin D level and HOMA-IR; if the diamond falls on the left side of the invalid line, it indicates a negative correlation; if the diamond falls on the right side of the line, it indicates a positive correlation

ES – effective size, CI – confidence interval.

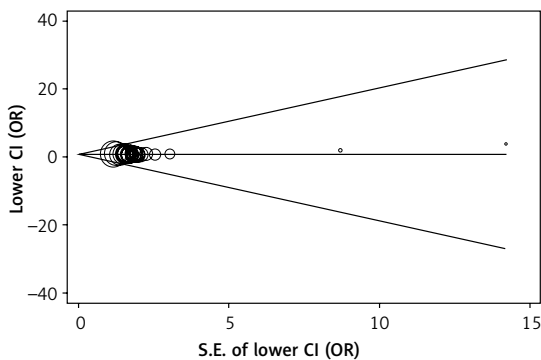


Figure 5. Begg's funnel plot. Egger's and Begg's tests showed no publication bias (Egger's: $p = 0.197$; Begg's: $p = 0.786$)

ferred among these studies. Second, the impact of some important factors may affect the relationship of vitamin D deficiency and GDM; however, some studies did not adjust the results for confounding factors. Further randomized controlled trials are necessary to assess this relationship and explore the effects of vitamin D supplementation on the prevention of GDM.

In conclusion, the vitamin D level of women with GDM is much lower than that of healthy subjects. Vitamin D deficiency is significantly correlated with increased risk of GDM. Vitamin D is negatively correlated with HOMA-IR. The conclusion indicates that vitamin D is valuable for pregnant

women. Detection of serum vitamin D should be performed on pregnant women, which helps in preventing GDM.

Conflict of interest

The authors declare no conflict of interest.

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