Review Article

Significance of Vitamin D on the Susceptibility of Gestational Diabetes Mellitus – A Meta-Analysis

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Abstract

Vitamin D plays an important role in glucose tolerance by stimulating insulin secretion and evidences suggest a contradictory result on the association between vitamin D status and risk of developing gestational diabetes mellitus (GDM). The present updated meta-analysis has been undertaken to find out the joined effect of vitamin D status on the risk of effect GDM considering previously published articles. Data were collected through literature search using electronic databases to retrieve relevant published research articles using various combinations of the following keywords, "vitamin D," "vitamin D deficiency," "cholecalciferol," "25-hydroxyvitamin D," "25(OH) D," "gestational diabetes mellitus," and "GDM." A total of 36 studies including 7,596 GDM cases and 23,377 non-GDM controls were involved in this study. Overall, pooled meta-analysis showed that pregnant women diagnosed with GDM have 18% higher risk of GDM risk when compared with controls [odds ratio (OR) = 1.18, 95% confidence interval (CI) 1.10–1.25; $P = 0.00$] with high heterogeneity ($I^2 = 73.29$). The mean difference was also significantly different between cases and controls (OR = −0.18, 95% CI − 0.22 to − 0.14; $P = 0.00$). Subgroup analysis showed significant results with age more than 30 years, Asian and European regions, and case–control, cross-sectional, and nested case–control study design. Low concentration of vitamin D is associated with the development of GDM. Although in future more studies especially systematically designed clinical trials based on vitamin D supplementation with large sample size on different population are needed to elucidate the exact concentration of vitamin D during pregnancy as well as before and after pregnancy.

Keywords: Cholecalciferol, GDM, gestational diabetes mellitus, meta-analysis, vitamin D

Introduction

Gestational diabetes mellitus (GDM) is a condition in which a pregnant women loss the ability to tolerate glucose due to progressive changes in maternal carbohydrate metabolism, and consequently the glucose level gets elevated and the symptoms of diabetes become visible. GDM is mostly diagnosed during the second or third trimester of pregnancy, and women diagnosed with diabetes mellitus (DM) during her first trimester are classified as pre-existing type 1 or type 2 diabetic patients rather than GDM.[1] However, soon after delivery normal glucose metabolism restores, whereas women diagnosed with GDM and their children have substantial risk (35%–60%) of developing type 2 diabetes mellitus (T2DM), metabolic syndrome, and obesity in future.[2,3] The worldwide prevalence of GDM is increasing rapidly ranged between 15% and 20% depending on the population, and therefore much interest in the domain of GDM etiology is increasing rapidly.[2] The relationship between GDM and T2DM and associated risk factors is needed to elucidate to understand the etiology of disease and this advancement will help in possible prevention of T2DM in women.

Vitamin D has a significant role in cancer, hypertension, T2DM, and pregnancy due to the presence of vitamin D receptors (VDRs) in most of the tissues.[1] In physiologic condition, the active form of vitamin D (1,25 dihydroxy vitamin D) exerts its direct effects via binding to VDRs or indirectly by calcemic hormones and inflammation and involves in several mechanisms in addition to bone metabolism and glucose metabolism. Sufficient amount of vitamin D is required for the normal production and secretion of insulin,[4] and therefore, vitamin D deficiency may affect the risk

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of developing GDM and postpartum T2DM. In addition, supplementation of vitamin D in GDM subjects had positive effects on fasting blood glucose and insulin level.[5,6] However, the optimal level of vitamin D during pregnancy and the association between maternal vitamin D deficiency and glucose intolerance remain unclear due to various conflicting reports. Therefore, we performed a meta-analysis on published research articles to systematically evaluate the relationship between maternal vitamin D status and the GDM risk.

Materials and Methods

Publication search for identification of related studies

We performed literature search using electronic databases "PubMed," "Medline, "ScienceDirect," "Embase," and "Google Scholar" to retrieve relevant published research articles using various combinations of the following keywords, "vitamin D," "vitamin D deficiency," "cholecalciferol," "25-hydroxyvitamin D," "25(OH) D," "gestational diabetes mellitus," and "GDM." Broad search terms were used to assist the identification of all appropriate articles, with the last search performed on the 30 August 2018. The search was limited to the studies conducted on human subjects and articles published in English language. The full-text articles were obtained for all the related studies. In addition, we evaluate the references cited in the retrieved articles to obtain additional studies that may be eligible. All the studies thus retrieved were evaluated and filtered by two independent arbiters considering the following inclusion and exclusion criteria.

Inclusion criteria: (i) the study should be based on pregnant women, (ii) GDM outcome as per the World Health Organization guidelines, (iii) studies investigating the association between maternal vitamin D status and risk of GDM in GDM (case) and non-GDM (control) women during pregnancy, (iv) studies with sample size and level of vitamin D for both cases and controls, and (v) ethnicity of the participating women.

Exclusion criteria: (i) studies that were review articles, case reports, clinical trials, and meta-analysis, (ii) studies designed on animal models, (iii) studies with irrelevant data and study design, (v) studies that were duplicate publications, and (vi) studies published in language other than English.

Data extraction

The retrieved articles were examined carefully by two specialists who worked individually and extracted information according to the inclusion criteria. The retrieved information by independent arbiters was compared later and discussed for eligibility of the studies. From each eligible articles, the following information was collected and tabulated into Microsoft Excel including the first author's last name, year of publication, ethnicity of the study population, study design, number of subjects (cases and controls) participated in the study, maternal age, and gestational age and mean [standard deviation (SD)] value of serum 25(OH) D in GDM and non-GDM subjects.

Statistical analysis

Meta-analysis was performed using the Comprehensive Meta-Analysis (CMA) software (version 3). Odds ratio (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of association between vitamin D deficiency and GDM risk based on the vitamin D status in GDM cases and non-GDM controls. *P* value < 0.05 was considered as statistically significant result. Statistical heterogeneity among the studies was measured by a Chi-square-based *Q*-test and I^2 statistic. I^2 value statistics as suggested by Higgins and Thompson were used to estimate the magnitude of heterogeneity, namely, 25%, 50%, and 75%, which correspond to low, medium, and high heterogeneity, respectively.[7] When I^2 >50%, the heterogeneity was considered significant. A fixed-effects model was used to calculate pooled ORs when heterogeneity was not significant; otherwise, random-effects model was used. Subgroup meta-analysis was stratified by study design, age, and region undertaking random-effects model to combine studies within each subgroup. Funnel plot (Begg's test) was generated to verify potential publication bias using the standard error of log (OR) for each publication plotted against its log (OR). Asymmetry of the funnel plot was assessed by Egger's regression test of significance. *t*-test was applied to measure the significance of the asymmetry, and *P* value was <0.05, indicating the presence of publication bias.[8] All statistical tests were two-sided.

Results

Literature search

A total of 1769 studies were identified as a result of PubMed, Medline, ScienceDirect, Embase, and Google Scholar search with relevant keywords during initial search and these studies were screened thoroughly. The procedure followed for screening and selection of potential studies has been described using the flowchart [Figure 1].

The present meta-analysis comprising 36 observational studies was published between 2008 and 2017 and involved 11 case–

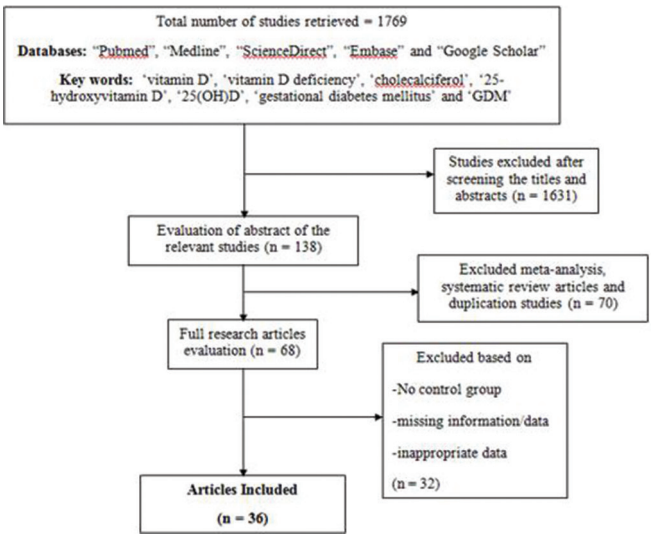

Figure 1: Flow diagram of literature search for this meta-analysis

control studies, 9 nested case–control studies, 9 cohort studies, and 7 cross-sectional studies. All the 36 retrieved articles along with their characteristics and information are presented in Table 1.

Meta-analysis

Pooled analyses

Overall, the pooled meta-analysis showed a statistically significant relationship between vitamin D deficiency and

Table 1: Characteristic of the selected studies included in the meta-analysis

Author	Year	Region	Study design	Control	Case	Maternal Age		Gestational age	25(OH) D nmol/L		Reference
						Case	Control		GDM	Non-GDM	
									Mean (± SD)		
Clifton-Bligh *et al.*	2008	Australian	Cross-sectional	226	81	32.6±5.1	NR	ST or TT	48.6 (24.9)	55.3 (23.3)	[9]
Zhang *et al.*	2008	USA	Nested case-control	114	57	34.3±4.8	33.1±3.9	24-28 weeks	60.4 (21.22)	75.13 (24.21)	[10]
Maghbooli *et al.*	2008	Asian	Cross-sectional	579	52	30.23±5.7	25.14±4.44	23.9±5.32	16.49 (10.44)	22.97 (18.25)	[11]
Farrant *et al.*	2009	Asian	Cohort	560	39	NR	NR	<32 weeks	49.3 (31.2	46.4 (30.9)	[12]
Soheilykhah *et al.*	2010	Asian	Case-control	111	54	27.39±5.08	27.39±5.08	24-28 weeks	24.1 (20.7)	32.3 (35.8)	[13]
Savvidou *et al.*	2011	European	Case-control	1,000	100	31.7	NR	11-19 weeks	NR	NR	[14]
Makgoba *et al.*	2011	European	Case-control	158	90	34.2±4.9	33.1±4.7	FT	47.2 (26.7)	47.6 (26.7)	[15]
Parlea *et al.*	2011	Canadian	Nested case-control	218	116	34.3±4.3	34.3±4.1	27.5±1.4	56.3 (19.4)	62 (21.6)	[16]
Wang *et al.*	2012	Asian	Nested case-control	200	200	NR	NR	ST	22.4 (11.7)	25.9 (15.8)	[17]
Fernandez-Alonso *et al.*	2012	European	Cross-sectional	466	36	NR	NR	NR	NR	NR	[18]
Perez-Ferre *et al.*	2012	European	Cross-sectional	266	49	NR	NR	24-28 weeks	NR	NR	[19]
Burris *et al.*	2012	USA	Cross-sectional	1,264	68	NR	NR	NR	NR	NR	[20]
Baker *et al.*	2012	USA	Nested case-control	120	60	35 (31-36)	33 (30-36)	FT and ST	97 (29)	86 (22)	[21]
Zuhur *et al.*	2013	European	Cross-sectional	168	234	31.6±6.0	29.8±5.2	26.4±1.5	26.7 (5.37)	24.2 (3.79)	[22]
Bener *et al.*	2013	Asian	Cohort	1,613	260	NR	NR	>24 weeks	44.19 (20.01)	NR	[23]
Cho *et al.*	2013	Asian	Case-control	20	40	33.45	NR	24-28 weeks	28.95 (22.73)	85.78 (47.88)	[24]
Parildar *et al.*	2013	European	Case-control	78	44	33.4±5.2	29.9±4.1	24-32 weeks	44.8 (23.3)	57.3 (25)	[25]
Soheilykhan *et al.*	2013	Arabian	Case-control	111	54	NR	NR	24-28 weeks	24.01 (20.62)	32.2 (35.74)	[26]
McManus *et al.*	2014	Canadian	Case-control	37	36	31.6	NR	24-28 weeks	77.3 (24.3)	93.2 (19.2)	[27]
Zhou *et al.*	2014	Asian	Cohort	100	2,960	29.7	NR	16-20 weeks	NR	NR	[28]
Kramer *et al.*	2014	Canadian	Cohort	125	142	34.4	NR	NR	NR	NR	[4]
Lacroix *et al.*	2014	Canadian	Cross-sectional	601	54	30.4±5.4	28.4±4.5	6-13 weeks	57.5 (17.2)	63.5 (18.9)	[29]
Park *et al.*	2014	Asian	Cohort	500	23	34.8±3.6	33.6±3.7	36.00±10.19	49.4 (19.4)	48 (24.8)	[30]
Schneuer *et al.*	2014	Australian	Nested case-control	3,714	376	34.5±4.6	33.1±4.7	FT	52.1 (22.1)	56.9 (26.9)	[31]
Pleskacova *et al.*	2015	European	Case-control	29	47	33 (28-35)	31 (28-33)	ST	28.5 (13)	31.7 (16)	[32]
Arnold *et al.*	2015	USA	Nested case-control	517	135	33.5±4.6	32.6±4.4	15.2±2.9	59.7 (23.5)	66.6 (22)	[33]
Nobles *et al.*	2015	USA	Cohort	206	31	NR	NR	15.2 weeks	NR	NR	[34]
Loy *et al.*	2015	Asian	Cohort	785	155	NR	NR	26-28 weeks	NR	NR	[35]
Rodriguez *et al.*	2015	European	Cohort	2,289	93	32±4.2	32±4.2	13.5 week	28.42 (4.39)	28.41 (0.96)	[36]
Jain *et al.*	2015	Asian	Nested case-control	19	51	NR	NR	24-28 weeks	29.64 (8.49)	55.3 (37.96)	[37]
Shahgheibi *et al.*	2016	Asian	Case-control	44	43	31.28	NR	FT	13.5 (7.6)	17.4 (14.9)	[5]
Dodds *et al.*	2016	Asian	Nested case-control	1,924	395	NR	NR	ST	45.5 (20.8)	51.9 (21.8)	[38]
Boyle *et al.*	2016	Australian	Cohort	1,710	32	30.8±5.1	30.3±4.7	15 weeks	61.6 (23.9)	72.9 (27)	[39]
Muthukrishna and Dhruv	2016	Asian	Case-control	19	51	26.5	NR	<28 weeks	24.7 (17.6)	45.8 (28)	[40]
Wen *et al.*	2017	Asian	Nested case-control	3,438	1,280	30.2±3.7	28.8±3.3	NR	42.4 (19.5)	44.3 (22.3)	[41]
Gashlan *et al.*	2017	Arabian	Case-control	48	55	33.67±0.75	29.90±0.90	30.80±0.88	25.34 (2.15)	28.98 (1.99)	[42]

GDM: Gestational diabetes mellitus; SD: Standard deviation; TT: Third trimester; ST: Second trimester; NR: Not reported; FT: First trimester

risk of developing GDM (OR = 1.18, 95% CI 1.10–1.25; $P = 0.00$) [Figure 2] with the fixed-effects model and (OR = 1.43, 95% CI 1.23–1.67; $P = 0.00$) with the random-effects model. Heterogeneity among the analyzed studies was significant ($P_{heterogeneity} = 5.07$, $I^2 = 73.29$). Meta-analysis of the difference between mean ± SD serum level of vitamin D of GDM and non-GDM women also showed a statistically significant relationship either taking fixed-effects model (OR = −0.18, 95% CI −0.22 to −0.14; $P = 0.00$) [Figure 3] as the heterogeneity ($P_{heterogeneity} = 0.00$, $I^2 = 90.95$) was significant or by taking random-effects model (OR = −0.39, 95% CI − 0.54 to −0.24; $P = 0.00$).

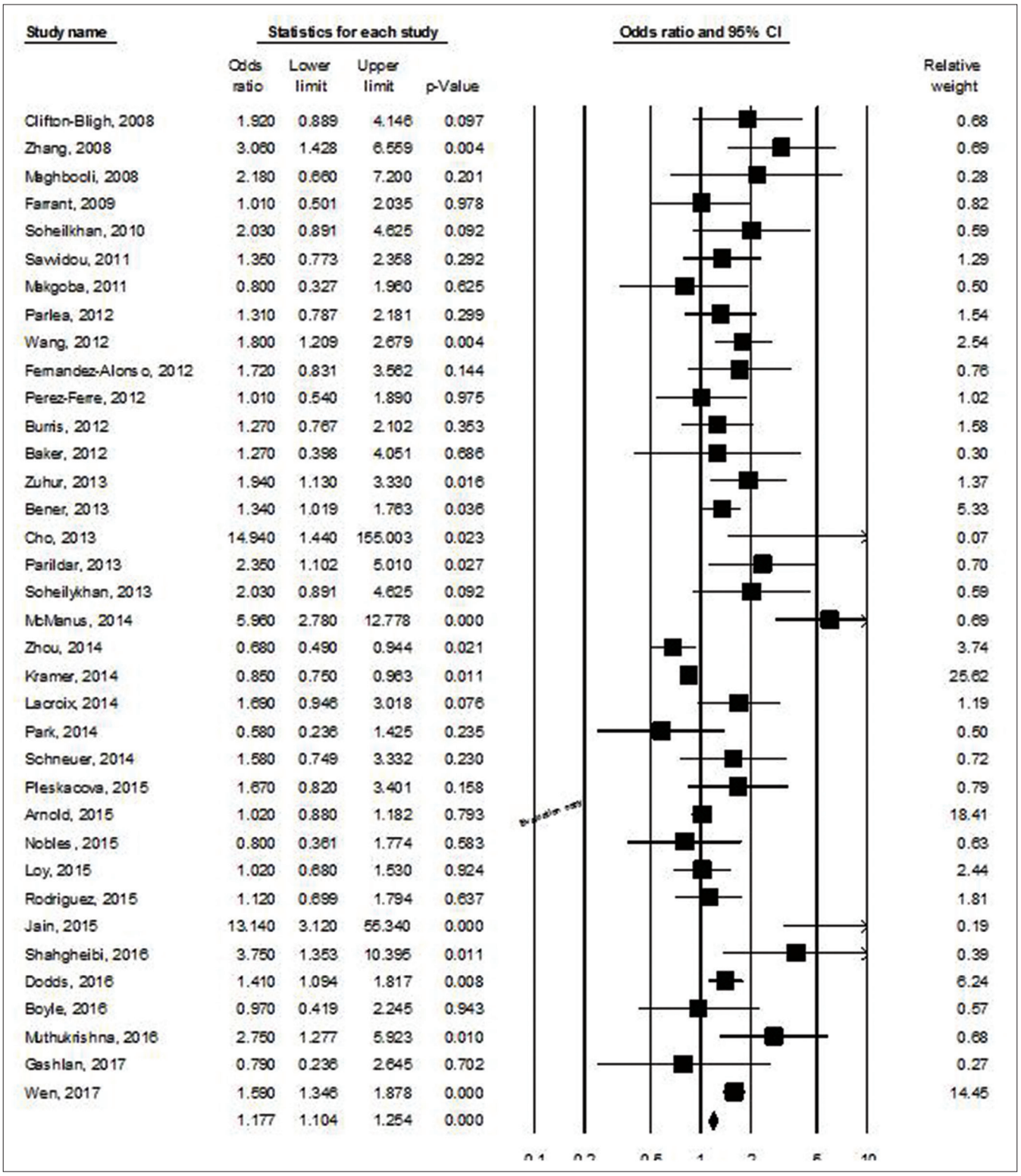

Figure 2: Association between vitamin D status and risk of GDM (fixed-effects model)

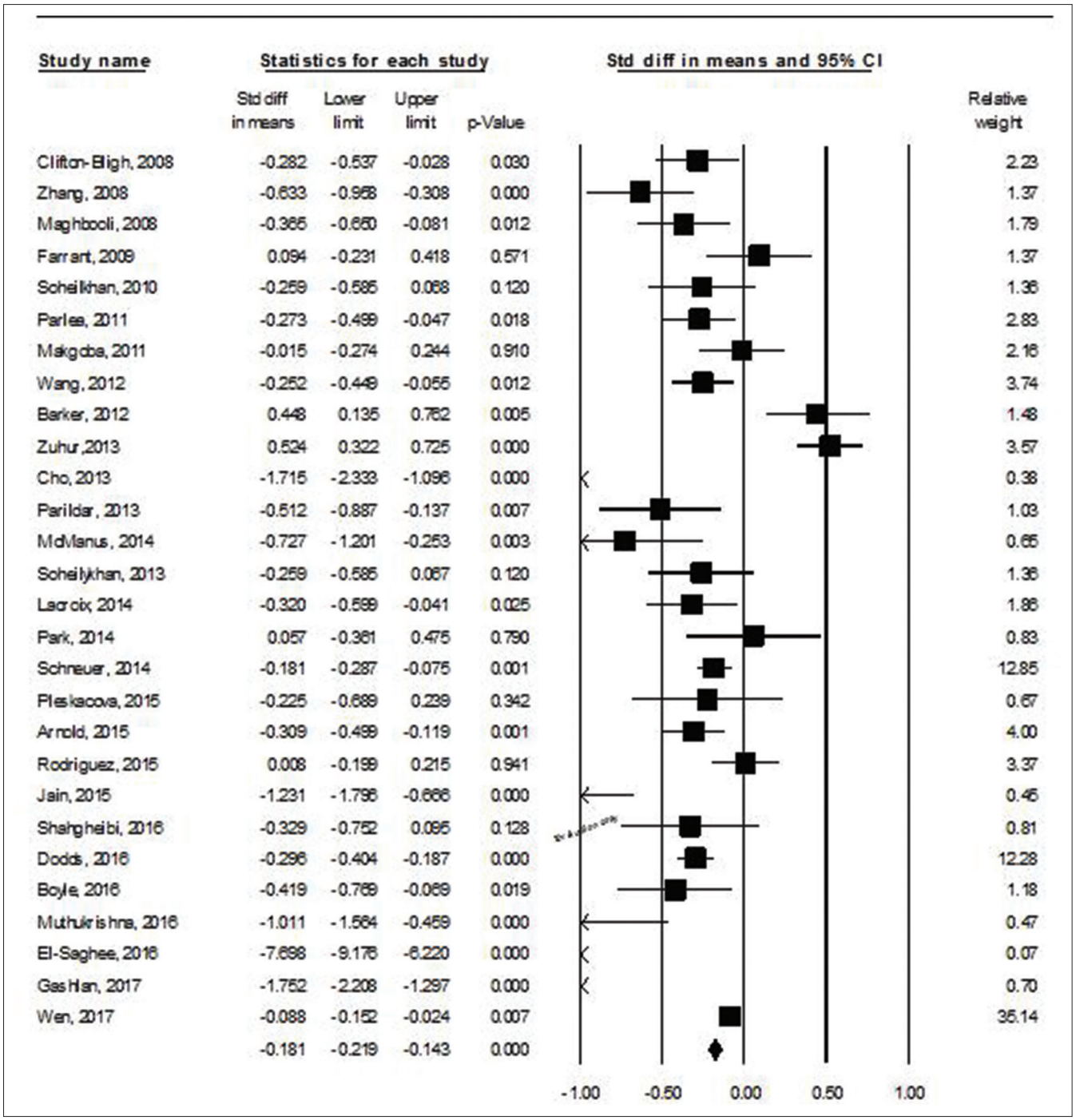

Figure 3: Association between serum vitamin D level and GDM (fixed-effects model)

Subgroup analyses

Meta-analysis on the basis of geographical area showed a significant association between vitamin D status and risk of GDM among the Asian and European population (OR = 1.49, 95% CI 1.15–1.93; $P = 0.002$) and (OR = 1.41, 95% CI 1.23–1.76; $P = 0.003$), respectively, undertaking random-effects model, while the other population did not reveal any association [Figure 4]. The results of age-based subgroup meta-analysis found that vitamin D status was significantly associated with GDM in women more than 30 years of age (OR = 1.42, 95% CI 1.90–1.71; $P = 0.00$) [Figure 5]. Meta-analysis on the basis of study design revealed that case–control (OR = 2.08, 95% CI 1.53–2.84; $P = 0.00$), nested case–control (OR = 1.55, 95% CI 1.14–2.09; $P = 0.005$), and cross-sectional (OR = 1.54, 95% CI 1.21–1.97; $P = 0.00$) studies were significantly associated with vitamin D status and risk of developing GDM [Figure 6].

Publication bias

Begg's and Mazumdar's funnel plot and Egger's test were performed to analyze the publication bias in the pooled analysis.

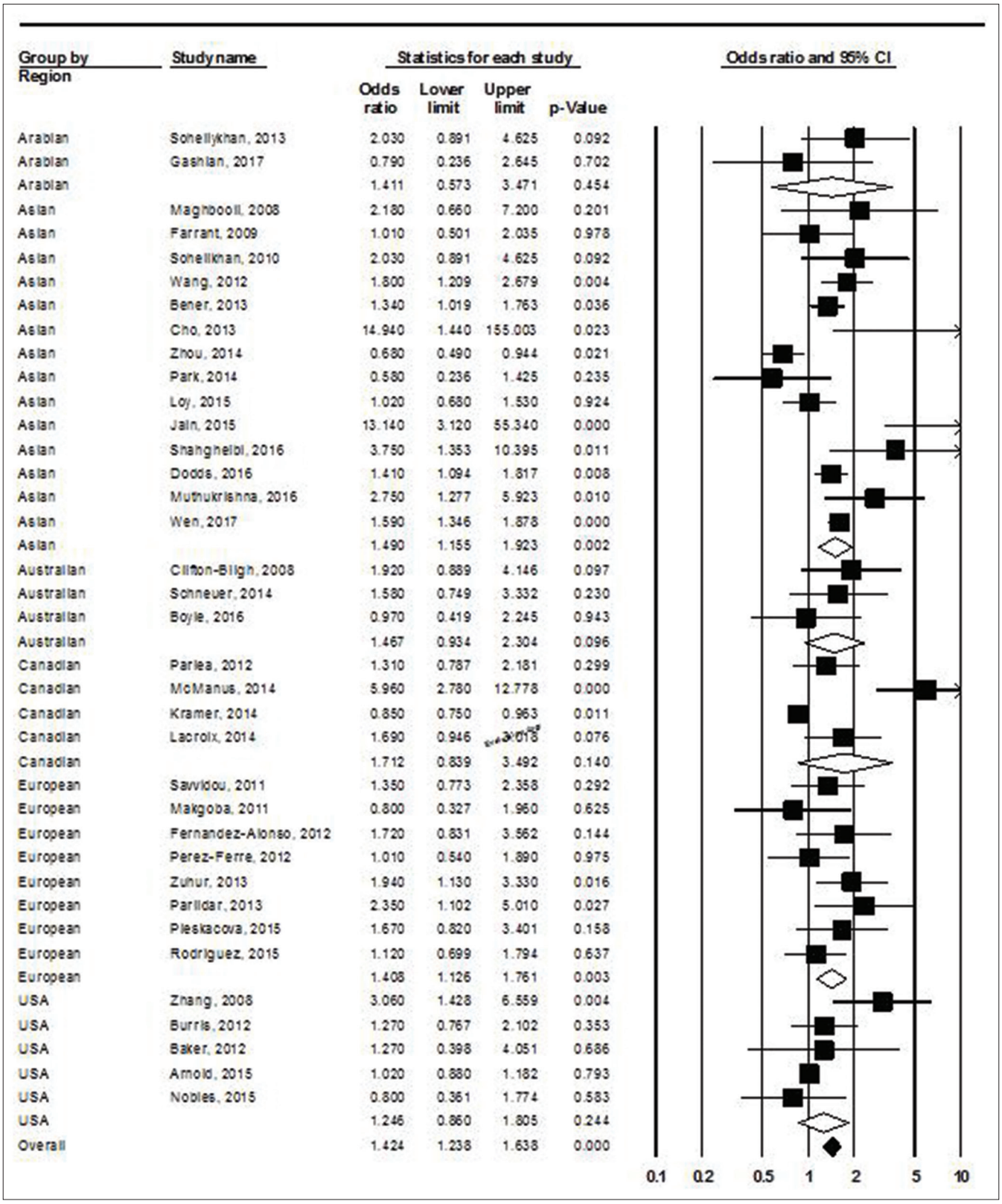

Figure 4: Relationship between vitamin D deficiency and risk of developing GDM based on region (random-effects model)

The distribution of studies on the Funnel plot [Figure 7] did not expose any obvious evidence of asymmetry suggesting the absence of publication bias. Furthermore, Egger's test analysis also provided evidence for the Begg's and Mazumdar's funnel plot symmetry as the *P* value was more than 0.05, suggesting the absence of any potential publication bias.

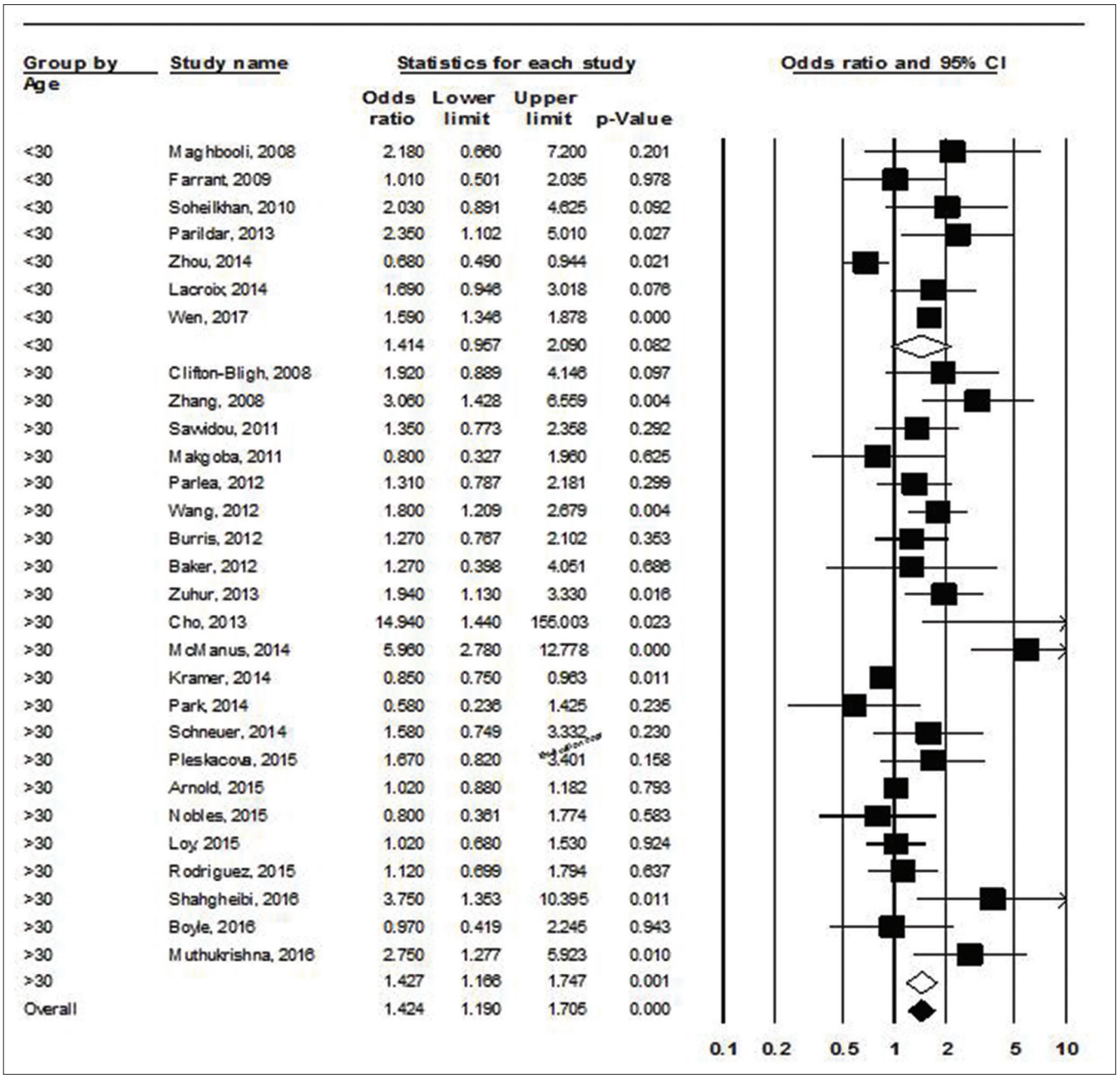

Figure 5: Relationship between vitamin D deficiency and risk of developing GDM based on age (random-effect model)

Discussion

Vitamin D plays a significant role in glucose metabolism considering the binding vitamin D (1,25 dihydroxy vitamin D) to VDRs presents on pancreatic beta-cells, the expression of 1-alpha-hydroxylase in pancreatic beta-cells,[43] insulin secretion and sensitivity by regulating extracellular calcium and calcium flux through cell membranes of pancreatic β-cell, and maintaining the intracellular cytosolic calcium pool.[44] Therefore, adequate amount of vitamin D is necessary for proper metabolism of glucose. According to the Institute of Medicine (IOM), serum vitamin D (25(OH) D) level <20 ng/mL maybe associated with the development of GDM. Consequently, several observational studies have been undertaken to observe the relationship between maternal vitamin D level and the risk of developing GDM.

The present meta-analysis has therefore been conducted to evaluate the relationship between vitamin D status and risk of developing GDM during pregnancy by considering 36 observational studies that comprised a total of 7,596 GDM cases and 23,377 non-GDM controls. Among the 36 studies, 14 studies observed a statistical significant relationship between vitamin D status and GDM risk, while the remaining 22 studies had non-significant association [Figure 2]. Considering fixed-effects model in the pooled meta-analysis, we observed that vitamin D deficiency is associated with 18% increased risk of GDM with a significant heterogeneity (I^2 = 73.29%;

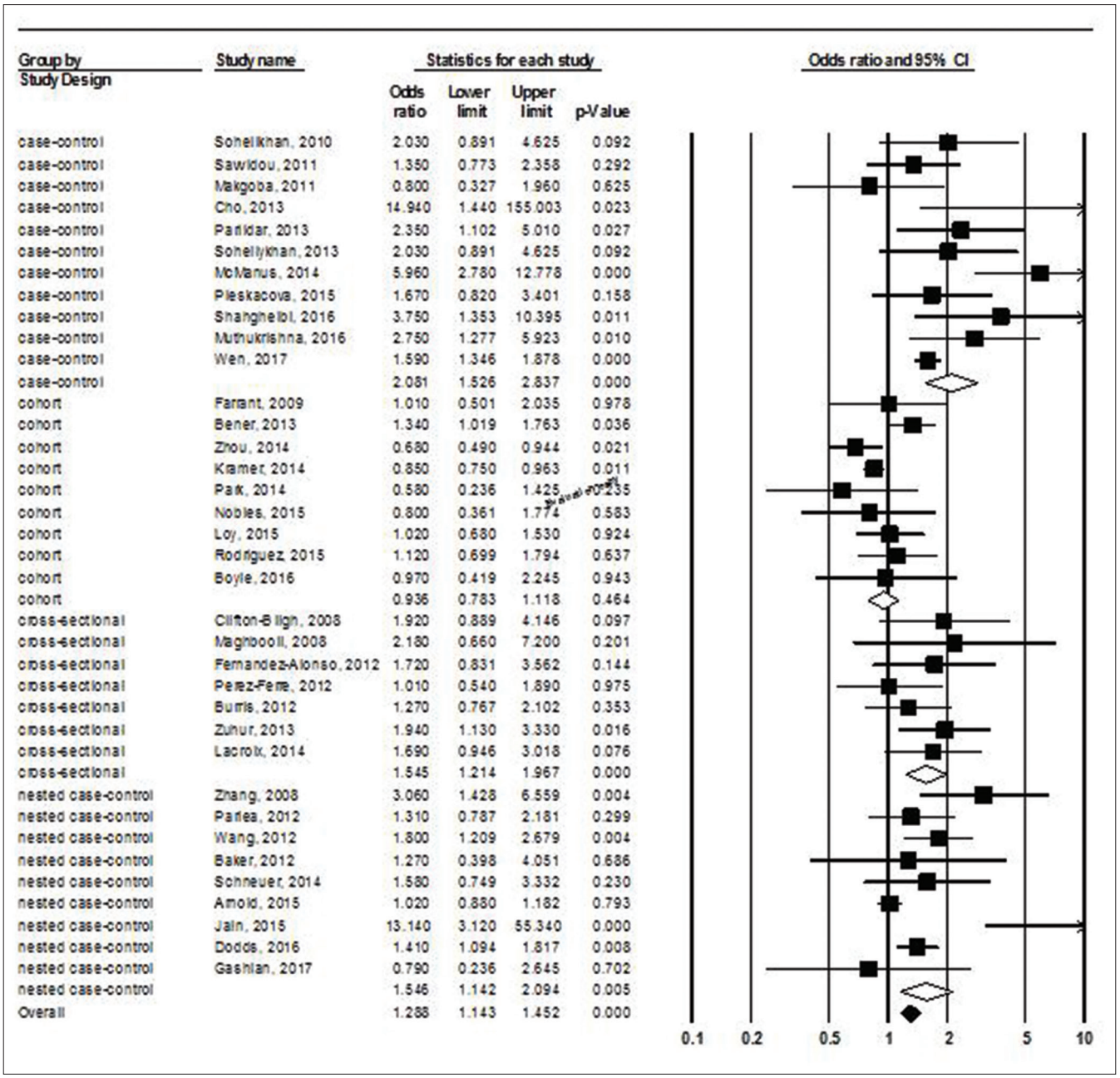

Figure 6: Relationship between vitamin D deficiency and risk of developing GDM based on study design (random-effects model)

$P_{heterogeneity}$ = 5.07). In a recent published meta-analysis considering 29 studies with a total of 14,497 participants, there was a significant association (OR = 1.15, 95% CI 1.00–1.30; P = <0.001) with random-effects model because the heterogeneity was low (I^2 = 31.6%; $P_{heterogeneity}$ = 0.055).[45] Another meta-analysis considering 26 studies also observed a significant association; however, the heterogeneity was much lower (I^2 = 8.1%; $P_{heterogeneity}$ = 0.346).[46] A meta-analysis conducted by Hu *et al*., 2018, comprising 29 observational studies with 28,982 controls and 4,634 GDM cases, also found a significant association with random-effects model (OR = 1.39, 95% CI 1.20–1.60) having moderate heterogeneity (I^2 = 50.2%; P = 0.001).[47] However, the total number of participants was not the representative of true population of cases and controls because they have added the total number of cases to the total number of controls in most of the studies.[47] In the current published meta-analysis, some studies with larger sample size shifted the whole effect to one effect side like that by Zhou *et al*. (2014) which comprised 2960 cases and 100 controls and showed a negative association,[28] although few studies with large sample size shifted the effect size to positive association.[31,38,41]

The lower and upper limits of OR for 95% CI were put into the CMA exactly as reported in the selected studies. As part of detailed calculations, the CMA calculates the standard errors using both the limits and reports the

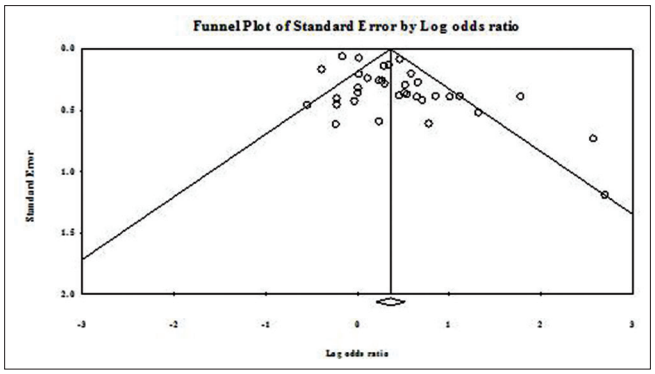

Figure 7: Funnel plot for the detection of the publication bias

average of these two standard errors if they are comparable, otherwise it flags an error. When the effect size data were put in CMA, the CMA flagged such error for a number of studies[5,11,17,22-25,27,32,37,40,41] as the values of the lower and upper limits were asymmetrical (ratio of calculated standard errors being more than the recommended value of 1.2). Hence, the CMA reported as input error and did not perform meta-analysis for these 12 studies. To avoid exclusion of such a large number of studies from meta-analysis, the allowable ratio of standard errors calculated based on the lower and upper limits of CIs was increased to a maximum possible value of 2. Even after this, the CMA reported error for four studies[5,24,27,32] and did not include them in meta-analysis. To include these studies in meta-analysis, the upper limit of 95% CI for these studies was removed from input to enforce the CMA to calculate the standard error based on the lower limit only. The rationale behind removing the upper limit instead of the lower limit was to avoid unnecessary exaggeration of effect size, that is, OR. As a result, the narrow 95% CI 1.10–1.25 value of fixed-effects model rather than 95% CI 1.23–1.67 value of random-effects model showed less sample error with fixed-effects model when compared with previously published meta-analysis which used random-effects model with wider 95% CI.

Out of the 36 studies, only 28 studies reported the mean ± SD value of serum vitamin D, and among these 28 studies, 18 studies found that vitamin D deficiency has a positive relationship with GDM development [Figure 3]. Overall, pooled meta-analysis also showed that pregnant women associated with GDM have lower level of vitamin D when compared with normal pregnant women considering the fixed-effects model (OR = −0.18, 95% CI − 0.22 to − 0.14; P = 0.00) with highly significant heterogeneity (I^2 = 90.95%; P = 0.00) that demonstrates that deficient level of vitamin D is associated with an increased risk of GDM. The results of the present meta-analysis are consistence with those of previously published meta-analysis.[45-47]

We have stratified meta-analysis on the basis of age, geographical region, and study design. The optimal serum level of vitamin D during pregnancy is controversial, as we found in the subgroup meta-analysis based on geographical region which showed that only Asian[5,11-13,17,23,24,28,30,35,37,38,40,41] and European[14,15,18,19,22,25,32,36] population have a significant relationship between vitamin D status and GDM risk considering random-effects model; however, the results of the present meta-analysis are contradictory than previously published meta-analyses.[45,46] Even though vitamin D status is dependent on sunshine exposure but within Europe, the serum 25(OH) D levels are elevated in Northern European when compared with Southern European countries.[48] The results based on study design showed significant results with case–control study design (I^2 = 55.55%; P = 0.01) and nested case–control study design (I^2 = 50.63%; P = 0.11) with moderate heterogeneity, while cross-sectional study design (I^2 = 0.0%; P = 0.69) showed lack of heterogeneity. Conflicting to the present results, Amraei *et al*. found a significant result only with nested case–control study design (I^2 = 0.0%; P = 0.65) with lack of heterogeneity.[46] This is the first meta-analysis that stratified findings on the basis of age considering <30 and >30 years old pregnant women and found significant association; women less than 30 years of age did not show positive association with the risk of developing GDM, while women more than 30 years of age showed 42% higher risk of developing GDM considering the random-effects model. The results showed that age associated with lower level of vitamin D is also an important factor for the development of GDM. On the basis of the present observations and previously published meta-analysis, the strategies to reduce the risk of GDM and optimal level of vitamin D according to geographical area and age should also be elucidated.

Other than these factors, the confounding factors such as obesity, higher pre-pregnant body mass index (BMI), reduced physical activity, season, exposure to sunlight, and consumption of multivitamins may also be associated with GDM risk. In addition, increase in incidence of obesity and a raise in BMI in women of child-bearing potential are associated with higher risk for developing GDM. Timing of sample collection for the estimation of serum 25(OH) D based on trimester (Gestational sampling), definition of vitamin D deficiency or insufficiency, and methods used for the assessment of vitamin D should also be considered during the execution of study to investigate the association between vitamin D status and GDM risk.

Strengths

The exhaustive literature search has included most of the published research articles according to inclusion and exclusion criteria, and therefore, this is the meta-analysis with a larger number studies till date; however, most of the previously published meta-analyses did not consider several potential observational studies. Stratification according to age is done for the first time and impactful results were found which can be potentially used to estimate the exact supplementation of vitamin D during pregnancy according to age. Only the upper limit of 95% CI for some studies was removed instead of the lower limit to avoid unnecessary exaggeration of effect size.

Limitation

Comparative analysis of some demographical details (pre-pregnant BMI, reduced physical activity, season, exposure to sunlight, etc.) has not been performed due to inconsistent

information available in the observational studies. Most of the studies[5,9-13,15,18-21,24-27,29,30,32,34,36,37,39-42] involved in the meta-analysis comprised small sample size (less than 100) which has a tendency to make the results less reliable. Diagnostic criteria and diagnosis methods were different among the studies and the cut-off values to evaluate vitamin D deficiency among pregnant women were also not similar in retrieved articles. As of now, there has been no consensus in diagnostic criteria for GDM. Even in India, controversy exists in different analytical methods to be used for diagnosis of GDM.

Conclusion

Overall, the present meta-analysis showed that pregnant women with GDM have 1.18 nmol/L decreased level of serum 25(OH) D when compared with normal pregnant women. Evidences suggest that vitamin D plays an important role in glucose tolerance by insulin secretion. Therefore, low concentration of vitamin D is associated with the development of GDM. Although in future more studies especially systematically designed clinical trials based on vitamin D supplementation with large sample size on different population are needed to elucidate the exact concentration of vitamin D during pregnancy as well as before and after pregnancy and to make proper guidelines for daily intake of vitamin D considering affecting factors.

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Conflicts of interest

There are no conflicts of interest.

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