Original Article

Association between vitamin D levels in early pregnancy and gestational diabetes mellitus: A systematic review and meta-analysis

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Abstract

Background: This meta-analysis aimed to pool all the available data to provide a well-powered assessment of the role of maternal Vitamin D levels in developing gestational diabetes mellitus (GDM) because already published studies evaluating this association are small in sample size and yielded conflicting findings. **Material and Methods:** A systematic review and meta-analysis of observational studies was performed. We searched electronic databases (PubMed and Cochrane Central) from inception to April 2021 for published and unpublished observational studies that determined the association between the reduction of Vitamin D levels and the risk of developing GDM in pregnant women. Results from studies were pooled as mean ± standard deviation (SD) and odds ratios (OR) using the random-effects model. **Results:** Forty-four studies, consisting of 37,838 pregnant women were included in this meta-analysis. Dichotomous studies showed a significant association between maternal Vitamin D deficiency and increased risk of GDM (OR = 1.38; 95% confidence interval [CI] = 1.21-1.57; $P < 0.00001$). Studies with continuous data also showed a significant association between maternal Vitamin D deficiency and the risk of developing GDM (weighted mean difference (WMD): –5.14 nmol/L, 95% CI = –6.28 to -4.00; $P < 0.00001$). Moderate heterogeneity was also detected. **Conclusion:** In conclusion, all studies demonstrated that lower levels of maternal serum Vitamin D were associated with a higher risk of developing GDM in pregnancy.

Keywords: Early pregnancy, GDM, gestational diabetes, gravidity, meta-analysis, vitamin D

Introduction

Gestational diabetes mellitus (GDM) commonly defined as glucose intolerance or insulin resistance, continues to be the most common metabolic disorder among pregnant women caused by several modifiable (body mass index[BMI], diet, physical activity, smoking) and non-modifiable (maternal age >35, type-II diabetes family history) risk factors.[1] According to a recent study, the global prevalence of GDM in pregnant women is reported to be 14.2%.[2] GDM can lead to several maternal (preeclampsia and cesarean section) and fetal (macrosomia) complications.[3] It is therefore essential to identify and curb risk factors of GDM because Vitamin D deficiency has been proposed to be a possible risk factor.

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The prevalence of Vitamin D deficiency in pregnant women ranges from 18 to 84%.[4] Vitamin D has been shown to influence insulin sensitivity by affecting the metabolism of calcium and phosphorus and by upregulating the insulin receptor gene, resulting in the reduction of insulin resistance.[5] Therefore, it has been suggested that its deficiency may predispose pregnant women to GDM.[6] However, individual studies evaluating the association between Vitamin D deficiency and incidence of GDM are small in sample size and have yielded conflicting findings. Therefore, we conducted a systematic review and meta-analysis to provide a holistic, well-powered assessment of the association between Vitamin D levels and GDM.

Materials and Methods

This systematic review and meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[7] Because this is a compilation of publicly accessible results, no Institutional Review Board permission (IRB) or patient informed consent was required for this report.

Data sources and search strategy

PubMed and Cochrane CENTRAL were searched from their inception to April 2021, without any language and time restriction. The search string used for both databases was (Vitamin D OR 25 (OH) D OR 25-hydroxyvitamin D OR cholecalciferol OR calcitriol OR ergocalciferol OR calcifediol) AND (Pregnan* OR gravid OR Matern*) AND (Diabetes). A detailed search string has been provided in [Table S1] of Supplements. The reference list of retrieved trials, meta-analyses, and review articles were then manually screened to find any suitable studies.

Study selection

Articles were included based on the following eligibility criteria: (a) the target patient population was pregnant women; (b) the outcome was GDM, with a group of pregnant women with normal glucose tolerance being in the control group and with a group of pregnant women with deficient Vitamin D levels in the experimental group; (c) the relation between Vitamin D deficiency and the risk of GDM was investigated; (d) for comparisons of Vitamin D insufficiency and sufficiency, an effect estimate (odds ratios [OR]) with 95% confidence intervals (CI) was provided or could be calculated.

All studies, including case reports, meta-analyses, or not released as published reports and studies measuring prenatal and postnatal Vitamin D levels were excluded.

Data extraction and quality assessment

The selected articles and related reports from the systemic search were exported to the EndNote Reference Library Software (X7 v17.0.0.7072) where duplicate studies were assessed and then removed. The remaining articles were blind-screened by two reviewers and only those that met the above eligibility criteria were finalized. We searched gray and white literature. Assessment for relevancy was first done based on title and abstract, and then full text. The difference in opinion among reviewers was resolved by group discussion. The concordance rate between the reviewers was 97.5%. We also looked up the bibliographies of related review articles.

Statistical analysis

RevMan (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. The results of the report were calculated as OR with a 95% CI and pooled using a random-effects model. Sensitivity analysis was performed on all results to examine the individual impact of each study. A forest plot was created to visually verify the pooled results. I^2 statistics are used to assess heterogeneity between studies, with 25% to 50% of I^2 values being considered mild heterogeneity and 50% to 75% being considered moderate heterogeneity. A value greater than 75% is considered severe heterogeneity.[8] A P value of <0.05 was considered significant in all cases. Funnel plots and Egger's regression test were inspected to eliminate publication bias.

Results

Literature search results

An initial search of three electronic databases identified 575 potential studies. After exclusion, 44 studies remained for analysis. The results of our literature study are summarized in the PRISMA flowchart [Figure 1].

Study characteristics and patients' baseline characteristics

Baseline characteristics of all included studies are summarized in the supplementary file [Table S2]. Forty-four studies were included in our meta-analysis, which consisted of 20 cohort studies, 8 nested case-control studies, 9 case-control studies, and 7 cross-sectional studies. The earliest study was published in 2008, whereas the latest one was published in 2021.

The sample size of participants in each study ranged from 76 to 4,984. The 44 studies showed a total of 37,838 pregnant women, with 6,694 GDM patients. Different criteria were used for the assessment of Vitamin D levels and the presence of GDM. There were different levels of 25 (OH) D in GDM cases in each study, ranging from 14.19 ± 4.46 to 80.0 ± 21.2 nmol/L. For the Vitamin D cut-off value, 34 studies used 50 nmol/L, 6 studies used 73.5–75 nmol/L, and the remaining 7 studies used 25–37.5 nmol/L.

Quality assessment and publication bias

All studies were of a markedly high methodological quality, with the Newcastle–Ottawa scale ranging from six to nine as depicted by the quality assessment table provided in [Table S3–S5] of supplements/appendix.

The publication bias was evaluated using Funnel plots, Begg's test, and Egger's test. The symmetrical funnel plots [Figure 2a and b] reveal that our analysis holds no small study or publication bias.

Results of the meta-analysis

Out of 44 selected studies, 33 of them in [Figure 3] showed that the maternal Vitamin D deficiency was significantly associated with an increased risk of GDM (OR = 1.28; 95% CI = 1.16–1.42; $P < 0.00001$). Sensitivity analyses by removing two studies did not lead to a significant change in the results (OR = 1.38; 95% CI = 1.22–1.57; $P < 0.00001$), but gave us a moderate heterogeneity across the included studies ($I^2 = 49\%$; $P = 0.001$).

On subgroup analyses by the type of study, case control studies (OR = 1.54; 95% CI = 1.12–2.10; $P = 0.007$), nested case control studies (OR = 1.51; 95% CI = 1.35–1.69; $P < 0.00001$), and cross-sectional studies (OR = 1.83; 95% CI = 1.35–2.48; $P = 0.0001$) showed a significantly increased risk of GDM. No significant increased risk was noted in cohort studies (OR = 1.16; 95% CI = 0.92–1.47; $P = 0.22$).

Out of 44 studies, there were 32 studies (25,760 participants, 5,136 GDM patients, and 20,132 control group) in [Figure 4], which demonstrated that Vitamin D deficiency was significantly associated with an increased risk of GDM. It was observed that the Vitamin D levels were significantly lower in the GDM group than in the control group. However, the mean difference for each study ranged from –33.57 to 11.00. The pooled effect was (WMD: –4.99 nmol/L (95% CI = –6.73 to –3.26; $P < 0.00001$). Sensitivity analyses by removing four studies led to a significant change in the results and the pooled effect changed to (WMD: –5.14 nmol/L (95% CI = –6.28 to –4.00; $P < 0.00001$), which shows that Vitamin D level in the experimental group decreased by 5.14 nmol/L when compared with the control group. Moderate heterogeneity was also observed ($I^2 = 51\%$, $P = 0.001$), [Figure 4].

Discussion

This meta-analysis consists of data pooled from 44 studies to evaluate the association between Vitamin D levels and the risk of GDM. These studies comprise a total of 37,838 pregnant women,

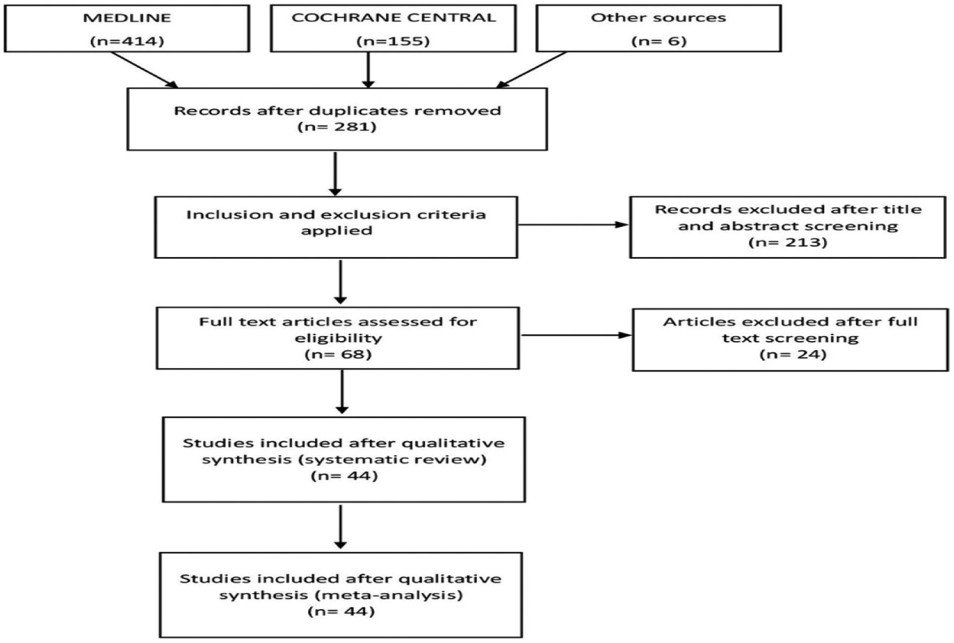

Figure 1:PRISMA flowchart summarizing results of literature search

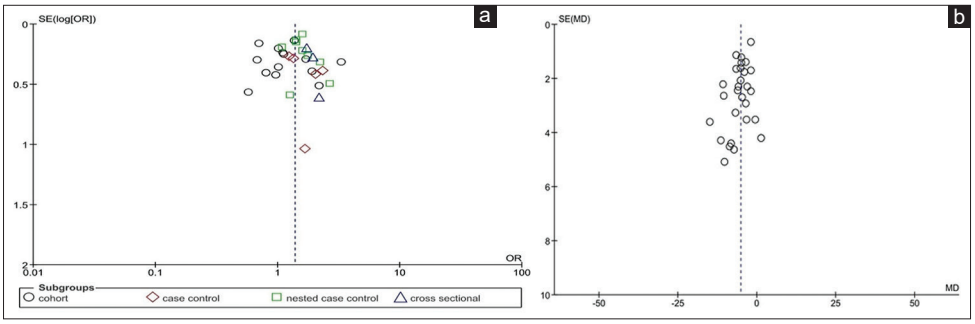

Figure 2: (a) Funnel plot for dichotomous outcomes. (b) Funnel plot for continuous outcomes

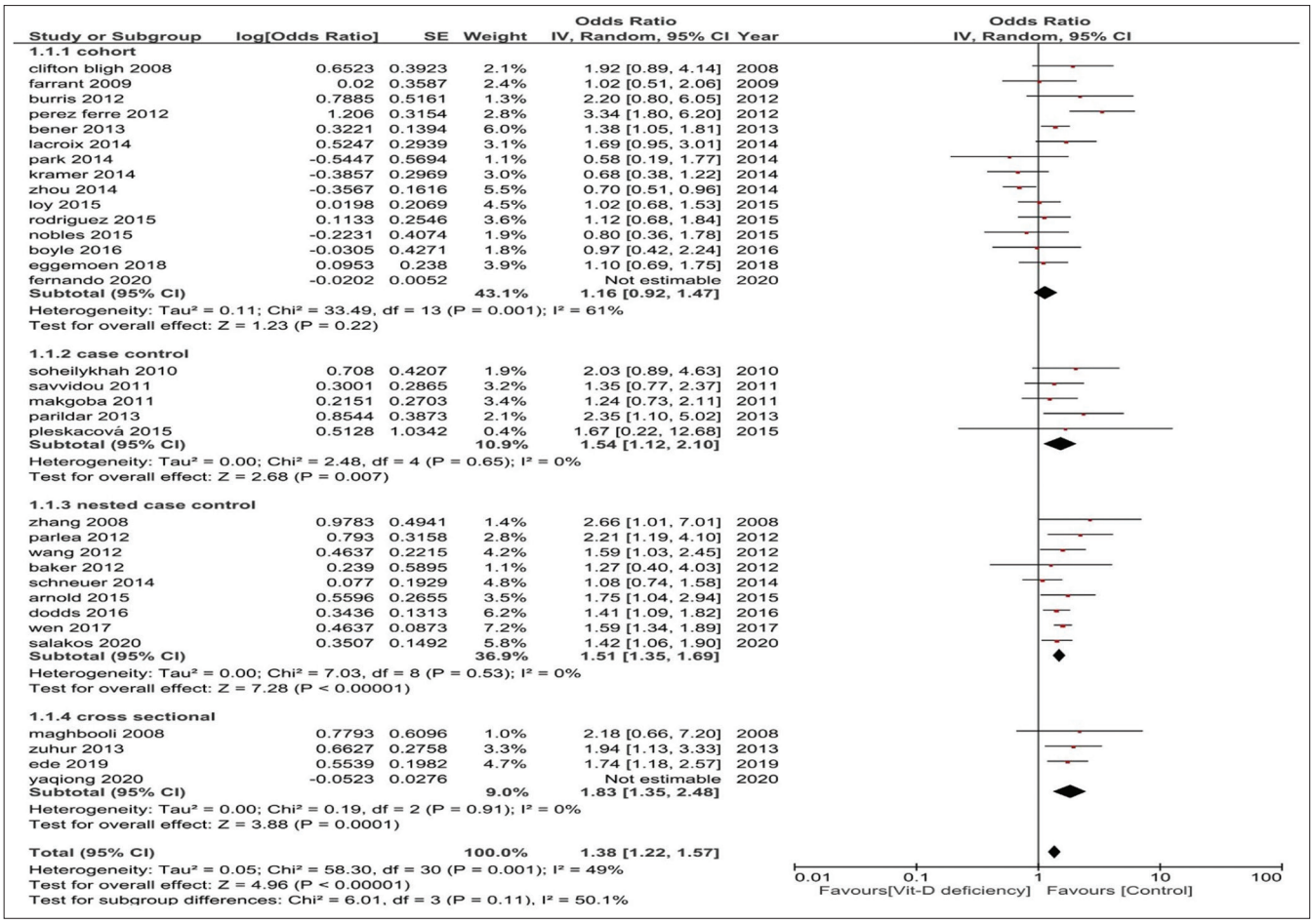

Figure 3: Forest plot depicting the odds of developing GDM due to vitamin D deficiency. CI, confidence interval; GDM, Gestational Diabetes Mellitus

out of which, 6,694 were GDM patients. Our results suggested a significant association depicting that Vitamin D deficiency can cause GDM in pregnant women, as 25 (OH) D levels in GDM patients dropped by 5.14 nmol/L when compared with the control group. This result corresponds with those of previous meta-analyses on prospective studies that indicated a significantly lower risk of GDM concerning higher levels of 25 (OH) D.[9-11]

Previous meta-analyses have suggested the association between Vitamin D insufficiency and increased risk of GDM; however, those studies missed some vital observational studies and did not assess the association in terms of study designs. Our meta-analysis includes data from all the important observational studies conducted up till now determining the association between decreased Vitamin D levels and risk of GDM in pregnant women considering study designs as well.

Significant heterogeneity was observed in 33 included studies, which is evident in the different study designs. We performed subgroup analysis and sensitivity analysis was performed to reduce overall heterogeneity. Sub-grouping was done on the basis of the types of study designs present. Sub-group analysis portrays that maternal Vitamin D deficiency and an inclined risk of having GDM are significantly associated only if the following study designs were chosen: Cross-sectionals, case–control studies, and nested case–control studies as depicted in [Figure 3]. The OR in the subgroup having only cohort studies was much lesser than ORs in other study designs, hence making cohort studies for this association less reliable in our study, which marks the novelty in our study.

Apart from Vitamin D levels, numerous variables increase the risk of GDM including BMI, age, ethnicity, maternal age, physical activity, and socioeconomic status, which were adjusted for [Table S2].

The positive association suggested by this meta-analysis is reasonable. According to McIntyre *et al.*[12] pregnancy is a condition that promotes physiological insulin resistance and GDM is the most prevalent medical condition during pregnancy as the pervasiveness of undiagnosed hyperglycemia and overt diabetes in young women is escalating. Maternal overweight and obesity, history of GDM, familial T2DM, and ethnicity are major risk factors involved. Vitamin D has been known to sway glucose by propelling the recovery of physiological insulin secretion through anti-inflammatory properties, increasing duodenal and renal absorption of calcium, which is then available for intracellular signaling activated by insulin, acting on insulin

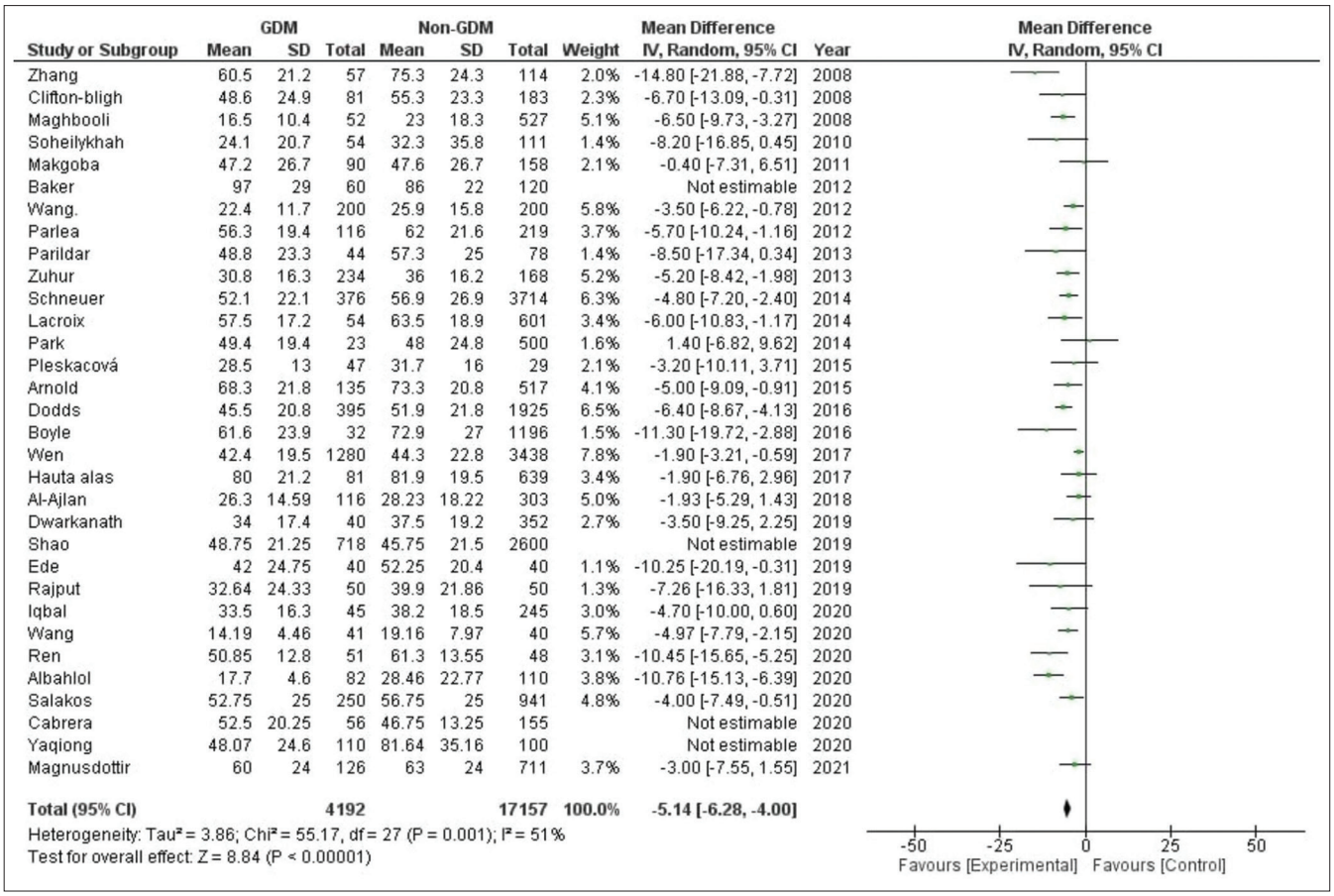

Figure 4: Forest plot comparing Vitamin D levels for the occurrence of GDM. CI, confidence interval; GDM, Gestational Diabetes Mellitus

receptors assisting in insulin sensitivity, and indirectly by reducing obesity.[13]

Worldwide, 21.3 million pregnancies are associated with hyperglycemia and of these, 18.4 million pregnancies are associated with GDM.[14] It has been documented that low Vitamin D levels not only cause GDM but primary caesarian section, periodic pregnancy loss, high blood pressure in diabetic pregnancy, preterm labor, and postpartum depression can be the major consequences.[15] Our meta-analysis highlights the importance of prenatal management and routine screening of pregnant women for early recognition and suitable commencement of treatment and supplementations. Such attentiveness can potentially countervail the remarkable morbidity associated with GDM.

Our findings suggest that screening should be performed by primary care physicians or obstetricians in women of childbearing age and those in the early stages of pregnancy for Vitamin D deficiency. Vitamin D supplementation should be prescribed in early pregnancy in deficient women.

Limitations

This meta-analysis has certain limitations. Firstly, the diagnostic criteria adopted by different studies were broad as it was determined by different health organizations. Secondly, there were contrasting approaches for methods of assessment of Vitamin D, and cutoff values varied overall. Moreover, there is a confounding bias as some adjusted models were found to differ, whereas some of them could not get adjusted for in the studies. Furthermore, our study does not report any data regarding exposure to sunlight and long-term detrimental outcomes in mothers and their children.

Conclusion

In conclusion, all studies consisting of dichotomous or continuous variables demonstrated that lower levels of maternal serum Vitamin D were associated with a higher risk of developing GDM in pregnancy. We suggest further studies be conducted to assess the usefulness of Vitamin D supplementation in women who are deficient before pregnancy or during pregnancy.

Keypoints

-The meta-analysis was performed to clear the prevailing confusion regarding the association between Vitamin D deficiency in early pregnancy and GDM.

-Lack of locally performed research on this issue and an inadequate number of observational studies included in

international meta-analyses are the two factors that pushed us to perform this meta-analysis, making it the most comprehensive and conclusive study on this topic to date.

-The data from 44 studies comprising 37,838 pregnant women were analyzed to reveal a significant association between Vitamin D deficiency and GDM.

-Previously conducted research has pointed out inconsistencies in the screening and management practice of GDM, that is, studies analyzed in our meta-analysis aim to fix by providing primary care physicians with clinically relevant and evidence-based data, which they can incorporate into their daily practice for an overall more streamlined diagnosis and management of GDM.

Key take-home message

Pregnant women with Vitamin D deficiency are more prone to suffer from GDM.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jamilian M, Amirani E, Asemi Z. The effects of vitamin D and probiotic co-supplementation on glucose homeostasis, inflammation, oxidative stress and pregnancy outcomes in gestational diabetes: A randomized, double-blind, placebo-controlled trial. ClinNutr 2019;38:2098-105.
2. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, *et al.* IDF diabetes atlas: Estimation of global and regional gestational diabetes mellitus prevalence for 2021 by International Association of Diabetes in pregnancy study group's criteria. Diabetes Res ClinPract 2022;183:109050.
3. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: A clinical update. World J Diabetes 2015;6:1065-72.
4. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J ObstetGynecol 2010;202:429.e1-9.
5. Maestro B, Molero S, Bajo S, Dávila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D (3). Cell BiochemFunct 2002;20:227-32.
6. Burris HH, Camargo CA Jr. Vitamin D and gestational diabetes mellitus. CurrDiab Rep 2014;14:451.
7. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med 2015;162:777-84.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
9. Milajerdi A, Abbasi F, Mousavi SM, Esmaillzadeh A. Maternal vitamin D status and risk of gestational diabetes mellitus: A systematic review and meta-analysis of prospective cohort studies. ClinNutr 2021;40:2576-86.
10. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: Asystematic review and meta-analysis. Eur J Intern Med 2012;23:465-9.
11. Sadeghian M, Asadi M, Rahmani S, AkhavanZanjani M, Sadeghi O, Hosseini SA, *et al.* Circulating vitamin D and the risk of gestational diabetes: Asystematic review and dose-response meta-analysis. Endocrine 2020;70:36-47.
12. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers 2019;5:47.
13. Rizzo G, Garzon S, Fichera M, Panella MM, Catena U, Schiattarella A, *et al.* Vitamin D and gestational diabetes mellitus: Is there a link?Antioxidants (Basel) 2019;8:511.
14. Mdoe MB, Kibusi SM, Munyogwa MJ, Ernest AI. Prevalence and predictors of gestational diabetes mellitus among pregnant women attending antenatal clinic in Dodoma region, Tanzania: An analytical cross-sectional study. BMJ NutrPrev Health 2021;4:69-79.
15. Mithal A, Kalra S. Vitamin D supplementation in pregnancy. Indian J EndocrinolMetab 2014;18:593-6.

Table S1: Search strategy used in each database

Database	Search strategy	Obtained articles
Medline	((("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields] OR 25[UID]) AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "oh"[All Fields])) AND "D"[All Fields]) OR ("25 hydroxyvitamin d"[Supplementary Concept] OR "25 hydroxyvitamin d"[All Fields] OR "25 hydroxyvitamin d"[All Fields] OR "calcifediol"[MeSH Terms] OR "calcifediol"[All Fields]) OR ("cholecalciferol"[MeSH Terms] OR "cholecalciferol"[All Fields] OR "cholecalciferols"[All Fields] OR "colecalciferol"[All Fields]) OR ("calcitriol"[MeSH Terms] OR "calcitriol"[All Fields] OR "calcitriols"[All Fields]) OR ("ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields] OR "ergocalciferol"[All Fields]) OR ("calcifediol"[MeSH Terms] OR "calcifediol"[All Fields])) AND ("pregnan*"[All Fields] OR ("gravid"[All Fields] OR "gravids"[All Fields]) OR "matern*"[All Fields]) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields])	414
Cochrane central	(Vitamin D OR 25(OH)D OR 25-hydroxyvitamin D OR cholecalciferol OR calcitriol OR ergocalciferol OR Calcifediol) AND (Pregnan* OR gravid OR matern*) AND (Diabetes)	155

Table S2: Baseline characteristics of patients in included studies

Study (study year)	Population	Study Design	Participants	GDM (*n*)	GDM Criteria*	Assessment of Vitamin D†	Gestational Age	25(OH)D nmol/L Mean (SD)		Significant‡	Cut Off value (nmol/L)	Adjustments§
								Vit D in GDM	Vit D in non-GDM			
Clifton-Bligh (2008)	Australia	Cohort	307	81	ADPS	LC-MS	second/ third trimester	48.6 (24.9)	55.3 (23.3)	yes	50	(1), (2), (3)
Zhang (2008)	US	Nested case control	171	57	ADA	ELISA	24-28 weeks	60.5 (21.2)	75.3 (24.3)	yes	50	(1), (2), (3), (4)
Maghbooli (2008)	Iran	Cross sectional	579	52	C&C	RIA	24-28 weeks	16.5 (10.4)	23.0 (18.3)	yes	35	(1), (2)
Farrant (2009)	India	Cohort	599	39	C&C	RIA	<32 weeks	38.8 (NR)	37.8 (NR)	no	50	(1), (2), (5)
Soheilykhak (2010)	Iran	Case control	165	54	C&C	ELISA	24-28 weeks	24.1 (20.7)	32.3 (35.8)	NR	50	NR
Savvidou (2011)	UK	Case control	1100	100	WHO	LC-MS	11-13 weeks	NR	NR	NR	75	(1), (2), (3), (6), (7), (8)
Makgoba (2011)	UK	Case control	248	90	WHO	LC-MS	first trimester	47.2 (26.7)	47.6 (26.7)	no	50	(1), (2), (3), (4), (5), (6)
Burris (2012)	US	Cohort	1155	68	ADA	CLIA	26-28 weeks	NR	NR	NR	25	(1), (2), (3), (6), (7), (9), (12), (13), (14), (15), (16), (17)
Perez ferre (2012)	Spain	Cohort	266	49	ADA	CLIA	24-28 weeks	NR	NR	NR	50	(1), (3), (4), (11)
Baker (2012)	US	Nested case control	180	60	NDDG	LC-MS	first trimester	97.0 (29.0)	86.0 (22.0)	yes	50	(1), (2), (6), (9)
Wang (2012)	China	Nested case control	400	200	ADA	ELISA	26-28 weeks	22.4 (11.7)	25.9 (15.8)	yes	25	(1), (4), (11)
Parlea (2012)	Canada	Nested case control	335	116	NDDG	CLIA	15-18 weeks	56.3 (19.4)	62.0 (21.6)	yes	73.5	(9), (10)
Bener (2013)	Qatar	Cohort	1873	260	WHO	RIA	>24 weeks	NR	NR	NR	75	NR
Parildar (2013)	Turkey	Case control	122	44	IADPSG	CLIA	24-32 weeks	48.8 (23.3)	57.3 (25.0)	no	50	NR
Zuhur (2013)	Turkey	Cross sectional	402	234	IADPSG	ECLIA	24-28 weeks	30.8 (16.3)	36.0 (16.2)	yes	50	(1), (2), (4), (5)
Lacroix (2014)	Canada	Cohort	655	54	IADPSG	LC-MS	6-13 weeks	57.5 (17.2)	63.5 (18.9)	yes	50	(1), (2), (4), (5), (6), (17), (21), (22), (23)
Park (2014)	Korea	Cohort	523	23	C&C	ECLIA	24-28 weeks	49.4 (19.4)	48.0 (24.8)	no	50	(1), (2), (5), (6), (9), (20)
Kramer (2014)	Canada	Cohort	524	142	NDDG	ECLIA	Second/third trimester	NR	NR	NR	50	(1), (2), (3), (4), (6), (14), (15), (20)
Zhou (2014)	China	Cohort	1953	331	IADPSG	ECLIA	16-20 weeks	NR	NR	NR	50	(1), (2), (24), (25)
Schneuer (2014)	Australia	Nested case control	4090	376	ADPS	AIA	first trimester	52.1 (22.1)	56.9 (26.9)	yes	37.5	(1), (3), (5), (6), (7), (10), (17), (18), (19)
Nobles (2015)	US	Cohort	237	31	ADA	CLIA	15.2 Weeks	NR	NR	NR	75	(1), (2), (3), (6), (9), (14)
Loy (2015)	Asian	Cohort	940	155	WHO	LC-MS	26-28 weeks	NR	NR	NR	75	(1), (2), (3), (5), (7), (12), (15), (17), (26)
Rodriguez (2015)	Spain	Cohort	2382	93	NDDG	HPLC	13.5 weeks	71.1 (NR)	71.0 (NR)	no	50	(1), (2), (3), (7), (9), (12), (17), (19), (26),(27)
Pleskacová (2015)	Czech	Case control	76	47	WHO	ELISA	24-30 weeks	28.5 (13.0)	31.7 (16.0)	no	50	(2)
Arnold (2015)	US	Nested case control	652	135	ADA	LC-MS	<20 weeks	68.3 (21.8)	73.3 (20.8)	yes	50	(1), (2), (3), (4), (6)
Boyle (2016)	New Zealand	Cohort	1544	32	ADHB	LC-MS	15 weeks	61.6 (23.9)	72.9 (27.0)	yes	50	(2), (3)
Dodds (2016)	Canada	Nested case control	2320	395	CDA	AIA	before 20 weeks	45.5 (20.8)	51.9 (21.8)	NR	50	(1), (2), (3), (6), (9), (28), (29)

Contd...

Table S2: Contd...

Study (study year)	Population	Study Design	Participants	GDM (*n*)	GDM Criteria*	Assessment of Vitamin D†	Gestational Age	25(OH)D nmol/L Mean (SD)		Significant‡	Cut Off value (nmol/L)	Adjustments§
								Vit D in GDM	Vit D in non-GDM			
Wen (2017)	China	Nested case control	4718	1280	ADPS	ELISA	Second/ third trimester	42.4 (19.5)	44.3 (22.8)	yes	50	(1), (2), (3), (4), (5), (6), (17), (30), (31), (32), (33), (34)
Hauta-alus (2017)	Finland	Cross sectional	723	81	ADA	CLIA	7-25 week	80.0±21.2	81.9±19.5	no	50	NR
Eggemoen (2018)	Oslo, Norway	Multi-ethnic cohort	745	235	WHO	RIA	First-second trimester	47.7 (44.0, 51.3)	51.4 (49.2, 53.7)	no	50	(1), (3), (6), (12), (17), (35), (36)
Al ajlan (2018)	Saudi Arabia	Cohort	419	116	IADPSG	ECLIA	first trimester	26.3 (14.59)	28.23 (18.22)	yes	50	(1), (2), (4), (6), (11), (14), (15), (17), (20), (37), (38), (39)
Rajput (2019)	India	Cross sectional	100	50	NR	ELISA	second trimester	32.64±24.33	39.90±21.86	yes	50	NR
Dwarkanath (2019)	India	Cohort	392	40	IADPSG	LC-MS/MS	~12 weeks	34.0±17.4	37.5±19.2	no	50	(1), (6), (10), (12), (15), (17)
Shao (2019)	Chinese	Cohort	3318	718	IADPSG	LC-MS/MS	first-second trimester	48.75±21.25 (T1)	45.75±21.5 (T1)	yes	50	(6),
Ede (2019)	Turkey	Cross sectional	80	40	C&C	HPLC	second trimester	42±24.75	52.25±20.40	yes	35	(1), (2), (14), (17)
Fernando (2020)	Australia	Cohort	304	55	ADIPS	CLIA	<20 week	55.6±19.2	50.7±24.4	yes	75	(1), (2), (3)
Wang (2020)	China	Case control	81	41	IADPSG	ECLIA	24-28 weeks	14.19±4.46	19.16±7.97	yes	NR	NR
Salakos (2020)	France & Belgium	Nested case control	1191	250	WHO	NR	first trimester (11-15 weeks)	52.75±25	56.75±25	no	25	NR
Iqbal (2020)	India	Cohort	290	45	IADPSG	LC-MS/MS	first trimester	33.5±16.3	38.2±18.5	no	50	(1), (6), (10), (12), (15), (17)
Cabrera (2020)	Philippines	Cross sectional	211	56	ADA	ECLIA	NR	21.0±8.1	18.7±5.3	no	50	(1), (2), (5), (17)
Ren (2020)	China	Case control	99	51	NR	ELISA	NR	50.85±12.8	61.3±13.55	NR	57.7	NR
Albahlol (2020)	Saudi Arabia	Cross sectional case control	322	82	NR	ELISA	22-37	17.7±4.6	28.46±22.77	yes	50	NR
Yaqiong (2020)	China	Cross sectional	210	110	ADA	ECLIA	after 24 weeks	48.07 (24.6)	81.64 (35.16)	yes	25	(1), (2), (4), (5), (12)
Magnusdottir (2021)	Iceland	Cohort	837	126	IADPSG	ECLIA	11-14 weeks	60±24	63±24	no	50	(1), (2), (7), (17)

‡Significant difference in serum 25(OH)D between gestational diabetes and controls. †Assay method of 25(OH)D. RIA: radioimmunoassay; LC-MS: liquid chromatography-tandem mass spectrometry; ELISA: enzyme-linked immunosorbent assay; CLIA: chemiluminescence immunoassay; ECLIA: electrochemiluminescence immunoassay; AIA: automated immunoassay; HPLC: High Performance Liquid Chromatography. *Diagnostic criteria of gestational diabetes C&C: Carpenter and Coustan; ADPS: Australasian Diabetes in Pregnancy Society; ADA: American Diabetes Association; WHO: World Health Organization; NDDG: National Diabetes Data Group; IADPSG: International Association of the Diabetes and Pregnancy Study Groups; ADHB: Auckland District Health Board; CDA: Canadian Diabetes Association. §Adjustments (1) age; (2) body mass index (BMI); (3) ethnicity; (4) family history of diabetes; (5) previous history of diabetes; (6) season; (7) smoking; (8) method of conception; (9) gestational age; (10) maternal weight; (11) triglyceride (TG); (12) education; (13) marital status; (14) pregnancy weight gain; (15) physical activity; (16) dietary intake of fish and calcium; (17) parity; (18) previously diagnosed hypertension; (19) socio-economic status; (20) vitamin D intake; (21) vitamin D lifestyle score; (22) parathyroid hormone (PTH); (23) waist circumference; (24) systolic/diastolic pressure; (25) serum calcium; (26) neonatal sex; (27) alcohol consumption; (28) study site; (29) year of blood collection; (30) menarche age; (31) menarche cycle; (32) trimester; (33) abnormal pregnancy history; (34) history of uterine fibroids; (35) sum of skin folds at visit 1; (36) change in skin folds from visit 1 to visit 2; (37) sun exposure; (38) HbA1c; (39) waist to hip ratio; (40) fasting blood glucose. NR, not reported.

Table S3: A detailed Newcastle-Ottawa Scale of each included cohort study

Study	Selection				Comparability		Outcome			Total Quality Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was present or not at start	Adjustment for the most important risk factors	Adjustment for other risk factors	Assessment of outcome	Follow-up length	Loss of follow-up length	
Clifton-Bligh (2008)	0	1	0	1	1	1	1	1	0	6
Farrant (2009)	1	1	0	1	1	1	1	1	0	7
Burris (2012)	1	1	0	1	1	1	1	1	0	7
Perez ferre (2012)	1	1	0	0	1	1	1	1	0	6
Bener (2013)	1	1	1	1	1	1	1	1	0	8
Lacroix (2014)	1	0	0	1	1	1	1	1	0	6
Park (2014)	1	1	0	1	1	0	1	1	0	6
Kramer (2014)	1	1	0	1	1	1	1	1	0	7
Zhou (2014)	1	1	1	1	1	1	1	1	0	8
Nobles (2015)	1	0	1	1	1	1	1	1	1	8
Loy (2015)	1	1	0	1	1	1	1	1	1	8
Rodriguez (2015)	1	0	1	1	1	1	1	1	1	8
Boyle (2016)	1	0	1	1	1	1	1	1	1	8
Eggemoen (2018)	1	1	1	1	1	1	1	1	1	9
Al ajlan (2018)	1	1	1	1	0	1	1	1	1	8
Dwarkanath (2019)	1	1	1	0	1	1	1	1	0	7
Shao (2019)	1	1	0	0	1	1	1	1	1	7
Fernando (2020)	1	1	1	0	1	1	1	1	1	8
Iqbal (2020)	0	1	0	1	1	1	1	1	1	7
Magnusdottir (2021)	1	1	0	1	1	1	1	1	0	7

Table S4: A detailed Newcastle-Ottawa Scale of each included case control study:

study	Selection				Comparability		Exposure			Total Quality Score
	Case definition adequate	Representativeness of the cases	Selection of control	Definition of controls	Adjustment for the most important risk factors	Adjustment for additional risk factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Zhang (2008)	1	1	1	1	1	1	0	1	0	7
Soheilykhak (2010)	1	1	1	1	1	0	1	1	0	7
Savvidou (2011)	1	1	1	1	1	1	1	1	0	8
Makgoba (2011)	1	1	1	1	1	1	0	1	0	7
Baker (2012)	1	1	1	1	1	1	1	0	0	7
Wang (2012)	1	0	1	1	1	0	1	1	0	6
Parlea (2012)	1	1	1	1	1	1	0	1	0	7
Parildar (2013)	1	0	1	1	0	1	1	1	0	6
Schneuer (2014)	1	1	1	1	1	1	1	1	0	8
Pleskacová (2015)	1	1	1	1	0	1	1	1	0	7
Arnold (2015)	1	1	1	1	1	1	1	1	0	8
Dodds (2016)	1	1	1	1	1	1	1	1	0	8
Wen (2017)	1	1	1	1	1	0	1	1	0	7
Wang (2020)	1	0	1	1	1	1	0	1	0	6
Salakos (2020)	1	1	1	1	1	1	1	1	0	8
Ren (2020)	0	1	1	1	1	0	0	1	1	6
Albahlol (2020)	1	1	1	1	1	0	1	1	0	7

Table S5 : A detailed Newcastle-Ottawa Scale of each included cross-sectional study:

Study	Selection				Comparability	Outcome		Total Quality Score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Confounding factors controlled	Assessment of outcome	Statistical test	
Maghbooli (2008)	1	1	0	1	2	1	1	7
Zuhur (2013)	1	1	0	1	2	1	1	7
Hauta-alus (2017)	1	1	0	1	1	1	1	6
Rajput (2019)	0	1	1	1	1	1	1	6
Ede (2019)	1	0	1	1	2	1	1	7
Cabrera (2020)	1	1	0	1	2	1	1	7
Yaqiong (2020)	1	1	0	1	2	1	1	7