Review

Changes in anthropometric and blood 25-hydroxyvitamin D measurements in antenatal vitamin supplemented gestational diabetes mellitus patients: A systematic review and meta-analysis of randomized controlled trials

Saha and Saha. Antenatal vitamin D supplementation in GDM

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DOI: 10.4274/jtgga.galenos.2021.2020.0197

Received: 18 November, 2020 **Accepted:** 12 January, 2021

Abstract

Gestation weight (GW), body mass index (BMI), and the blood 25-hydroxyvitamin D (25(OH)D) level during pregnancy are important determinants of the gestational outcomes. This study aims to study how these parameters vary between antenatal vitamin D recipients and non-recipients in gestational diabetes mellitus (GDM) patients. The randomized controlled trials comparing these outcomes between vitamin D recipient and non-recipient GDM patients were searched in electronic databases (PubMed, Embase, and Scopus). The reviewed studies' data were abstracted and critically appraised by the Cochrane tool. The estimation of the weighted mean difference for GW and BMI and standardized mean difference (SMD) for 25(OH)D levels occurred by juxtaposing the interventions meta-analytically (random-effect model). The statistical inconsistency was determined by Chi^2 and I^2 method. The statistical significance was estimated at $p<0.05$ and 95% confidence interval (CI). Eleven eligible trials (all Iran-based, except one) sourcing data from about 875 GDM patients were reviewed. Overall, the risk of bias was low, except for selection and performance bias. On random-effect model meta-analysis, the 25(OH)D levels of the GDM patients favored the vitamin D recipients when compared to non-vitamin D (SMD: 1.97, 95%CI, 1.06, 2.88, p, <0.001, I^2, 96.2%, p of Chi^2, <0.001) and placebo (SMD, 1.86, 95% CI, 0.95, 2.77, p,<0.001, I^2, 95.3%, p of Chi^2,<0.001) recipients, respectively. On meta-regression, sample size was a predictor of the observed heterogeneity. For GW and BMI the interventions did not differ statistically significantly. In GDM patients, antenatal use of vitamin D aids in the rise of blood 25(OH)D levels; however, it doesn't influence GW and BMI change. PROSPERO registration number: CRD42020149613

Keywords: Gestational diabetes, vitamin D, dietary supplement

Introduction

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance that develops or is identified initially during gestation(1). Its global prevalence is about 7-10%(2–5). GDM diagnosis utilizes the glucose challenge tests between 24-28 weeks of gestation(1). Initial GDM management encompasses diet and exercise therapy, and on the failure of these to achieve glycemic control, physicians start insulin therapy(1).

GDM is a crucial health burden since it can affect both the GDM patient and her neonate. Gestational weight (GW) and body mass index (BMI) in pregnancy are two important anthropometric determinants of GDM-related outcomes. Studies on GDM patients suggest that an excessive GW accumulation increases the risk of maternal complications like cesarean delivery, large for gestational age, and gestational hypertension and fetal problems like macrosomia, large for gestational age, hypoglycemia in newborns, and poor APGAR score(6–11). It remains unclear if the Institute of Medicine's guideline (2009) for recommended GW gain for respective BMI categories can be applied to the GDM subpopulation or not(8,12). However, studies on overweight and obese GDM patients found that gaining GW less than that recommended for their respective BMI categories resulted in favorable obstetric and neonatal outcomes(8,13,14). Maintaining an optimum weight before and during pregnancy, therefore, can decrease the complications of pregnancy(9). Nevertheless, it remains unclear if any antenatal intervention in GDM patients may be beneficial in achieving an acceptable GW and BMI.

In this aspect, vitamin D has come up as an interesting agent that demands substantial research. In GDM patients, various clinical trials(15–18) have tested the maternal health effect of antenatal vitamin D supplementation, and due to the different relationships between GDM and vitamin D status in the body, such testing appears pertinent. For instance, inadequate vitamin D levels in the body are associated with the risk of GDM development(19–23). Vitamin D deficiency (<20ng/ml) has a nearly fourfold raised risk of GDM development than women with sufficient vitamin D level (>30ng/ml) after adjusting for the age of the mother, race, ethnicity, and family history of type-2 diabetes among first-degree family members(24). Moreover, studies showed a decreased GDM prevalence in prenatal vitamin D recipients(25,26). In this milieu, it's crucial to know how vitamin D supplementation in GDM mothers can affect their GW and BMI. Additionally, as the fetus entirely depends on maternal 25-hydroxyvitamin D (25(OH)D) levels,(27) its level in the GDM mothers after vitamin D supplementation also requires evaluation.

Intervention description

The inactive forms of the fat-soluble vitamin D are D2 (ergocalciferol) and D3 (cholecalciferol)(28,29). Both forms are available from diet and supplements; vitamin D3 is also produced in the skin on exposure to the sun(28,29). On hydroxylation of pre-vitamin D in the liver, the main circulating form (25(OH)D) of vitamin D is produced(27). In blood, it's either in bound form (to albumin) or free form(27). For its physiologic role, it is converted to its active calcitriol (1,25(OH)2D) form(28,30). Vitamin D's physiologic effect in pregnancy is mediated via calcitriol's action on the vitamin D receptors in uteroplacental tissue(28,30). Compared to calcitriol, which has a half-life of 4-6 hours(27), the relatively longer half-life of 25(OH)D (2-3 weeks)(31) makes the latter an ideal marker for vitamin D status(32).

In GDM patients, contemporary trials have supplemented vitamin D in various dosages. For oral preparations, while some trials used it at a dose of 50,000 IU 2-3 weeks apart for three to eight weeks(33–36), other trials used it twice daily at 200-500 IU for 6-1six weeks(17,37). One trial used a single intramuscular injection of vitamin D at a dose of 300,000 IU(38). Furthermore, while few trials used the vitamin as a single supplement(33,37,38), others co-supplemented it with various micronutrients like zinc, magnesium, and calcium(17,34).

What this review adds?

In contemporary medicine, several clinical trials have tested the changes in GW, BMI, and plasma 25(OH)D level in GDM mothers, after antenatal vitamin D supplementation(15,34–36). Recent reviews have studied the effect of antenatal vitamin D supplementation on certain maternal (e.g., cesarean section, pre-eclampsia, preterm delivery, macrosomia, polyhydramnios) and neonatal (e.g., hyperbilirubinemia, hypoglycemia, and hospitalization) complications(39–41). However, best known to us, there is no systematic review and meta-analysis that studied how maternal GW, BMI, and 25(OH)D levels change in the blood on vitamin D supplementation in GDM patients. Therefore, this study explores this under-reviewed area of modern medicine by a systematic literature search, critical appraisal, and meta-analysis.

Aims

This study compares the GW, BMI, and 25(OH)D levels among vitamin D supplemented and not supplemented GDM patients.

Methods

This systematic review is registered in the PROSPERO (CRD42020149613) and has a pre-published protocol(42,43). This report adheres to the PRISMA 2009 reporting guideline (Table S1)(44).

Inclusion criteria

1. Study design: Parallel arm randomized controlled trials of any number of intervention arms.
2. Population: Pregnant females of any age were eligible irrespective of their pre-pregnancy BMI and 25(OH)D levels. They must be diagnosed with GDM during their concurrent pregnancy.
3. Intervention arm: The treatment arm/s should have received vitamin D as a sole or co-supplement.
4. Comparator arm: The comparator arm/s may have received a placebo or any other supplement except vitamin D. Comparator arm/s not receiving any intervention were also eligible.
5. Outcomes: The trials must report the GW (kg), BMI (kg/m^2), and 25(OH)D (in ng/mL or mmol/L) in the above GDM patients before and after receiving these interventions (before childbirth).

We accepted the diagnosis and management of GDM and the dosage and regimen of interventions received by the participants in the respective treatment arms as per the trialists.

Exclusion criteria

1. Study design other than those described above, e.g., observational studies and crossover studies.
2. Participants with diabetes types besides GDM, like type 1 or type 2 diabetes.
3. Studies conducted on animals.
4. Editorials, abstracts from conference presentations (where a full published manuscript is not available), letters, or any other brief communications.

Database search

We searched the title and abstract of prospective trials matching the above eligibility criteria in PubMed, Embase, and Scopus databases irrespective of the date and language of publication and geographical boundary. The following search terms were used "vitamin D" OR “calciferol” OR "vitamin D2" OR “ergocalciferol” OR "vitamin D3" OR “cholecalciferol” AND “GDM" OR "gestational diabetes" along with these MeSH terms- "Cholecalciferol," "ergocalciferols," and "diabetes, gestational." To identify the clinical trials

in PubMed (“Clinical Trial” and “Randomized Controlled Trial”) and Embase (“controlled clinical trial” and “randomized controlled trial”), we used filters. In Scopus, instead of filters, the following search terms were used: “trial,” “randomised,” “randomized,” and “controlled.” The last date of the search was 17-Sep-2020. Additionally, we reviewed the references of the papers included in this review.

We uploaded the retrieved citations (from database search) in the Rayyan systematic review software(45) and eliminated the duplicate articles. Successively, skimming of the remaining citations' titles and abstracts against the eligibility criteria commenced. Articles were read in full-text when it seemed to meet the inclusion criteria, or a decision of its incorporation in this review was doubtful.

Data abstraction and risk of bias (RoB) assessment

We extracted data about the study design, consent, ethics, registration number of the trial, participant features, interventions contrasted, and the outcomes of interest in a pre-piloted form. With the Cochrane collaboration tool, individual trial's risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias was determined, and each of these RoB components was categorized as low, high, or unclear(46). To assess selection bias, the random allocation sequence generation method, and its concealment method from participants, were judged. The blinding mechanism of study participants and personnel and that of outcome assessors were used to evaluate the performance and detection bias, respectively. By evaluating missing outcome data, and its reason among the intervention arms, the risk of attrition bias, was evaluated. Any additional bias besides the above comprised the other bias type. For a visual presentation of the RoB, we prepared an RoB graph and an RoB summary using the Review Manager (RevMan) software(46,47).

The review authors independently performed study selection, data abstraction, and RoB assessment, and resolved any disagreement in an opinion by discourse.

Meta-analysis

The juxtaposed interventions' effect on each of the outcomes was contrasted by random-effects meta-analysis (using DerSimonian and Laird method) since we assumed clinical heterogeneity among the trials attributable to the different types of vitamin D co-supplements used in these. The use of endpoint means of the respective outcomes and their SDs ensued to conduct the meta-analysis. We estimated the meta-analytic effect sizes of GW and BMI in weighted mean differences (WMD) and that of 25(OH)D levels in standardized mean differences (SMD) due to the identical and non-identical types of measuring units used in the trials, respectively. A decrease in the summary effect of GW and BMI, and its increase in 25(OH)D levels, denoted a favorable meta-analytic finding. For any outcome, when multiple treatment arms tested an intervention, the post-intervention means and their SDs of those intervention groups were combined for meta-analysis(46). Outcome reported in the median were not considered for meta-analysis.

Heterogeneity and meta-regression

The statistical heterogeneity was determined by Chi^2 (statistically significant at $p<0.1$) and I^2 (categorized as low, moderate, and high at I^2 values of 25, 50, and 75%, respectively)(48) statistics. To account for any substantial heterogeneity, we performed univariate meta-regression by presence or absence of missing outcome data and sample size (categorized as <100 and ≥ 100). Using the predictor identified by meta-regression, we did a subgroup analysis to see how heterogeneity changes across the different categories of the predictor.

Publication bias and sensitivity analysis

The publication bias assessment incorporated visual inspection of funnel plots and Egger's test. For each outcome, a sensitivity analysis included iteration of the meta-analysis using a fixed-effect model and by dropping a trial each time.

Supplementary analysis

Using random-effect and fixed-effect model, all outcomes were compared meta-analytically between vitamin D and placebo receiving GDM patients.

We estimated the statistical significance of meta-analysis derived effect sizes at $p<0.05$ and 95% confidence interval (CI). Stata statistical software (version 16) was used for analysis.

Results

Scope of the Review

The database search retrieved 271 citations. After eliminating the duplicates, 188 citations underwent skimming against the eligibility criteria. Out of the 22 articles needing full-text reading, 11 trials sourcing data from about 875 participants published between 2014-19, were included in this review (Figure 1)(15,16,51,17,18,33–35,37,49,50). All trials except the Chinese one(37) were Iran-based, and the average age of participants in the respective intervention arms was approximately 28-32 years. The intervention period of Iranian(16–18,33,49–51) and Chinese(37) trials were 6-8 and 16 weeks, respectively. In most trials(15–18,34,35,37,49–51), GDM was diagnosed primarily using American Diabetes Association criteria(52,53). Insulin was not used during the intervention period, except in the trial by Yazdchi et al. (2016)(33). Eight trials(15,16,18,33,34,37,49,50) used D3 form of the vitamin while this was not clear among the remaining trials(17,35,51). In most of the trials (81.8%), a co-supplement (e.g., calcium, magnesium, zinc, omega-3 fatty acid, evening primrose oil, probiotic) accompanied the vitamin D supplementation(15–18,34,35,37,50,51). The intervention was given between 24-28 weeks of gestation in nine trials,(15–18,33–35,49,50) at 16 weeks of gestation in one trial,(37) and in another, this was unclear.(51) Table 1 depicts the salient features of the trials.

RoB assessment

In most studies, the allocation concealment component of the selection bias and performance bias was unclear (Table 2 and Figure 2). Otherwise, the RoB was low.

Meta-analysis findings

11 trials comparing GW (15,16,51,17,18,33–35,37,49,50), and 10 trials contrasting BMI (15–18,33–35,49–51) (one study(37) excluded as it did not report the follow up BMI) and 25(OH)D (a trial(33) excluded for reporting follow up value in median) each were included in the meta-analytic juxtaposition between vitamin D recipients and its non-recipients.

The antenatal vitamin D use in GDM patients favored plasma 25(OH)D level attainment compared to its non-supplementation (random-effect model: SMD: 1.97, 95%CI, 1.06, 2.88, *p*, <0.001, I^2, 96.2%, *p* of Chi^2, <0.001).

The post-intervention GW (random-effect model: WMD, 0.18, 95%CI, -1.10,1.47, *p*, 0.773, I^2, 0%, *p* of Chi^2, 0.559) and BMI (random-effect model: WMD, 0.27, 95%CI, -0.28, 0.82, *p*, 0.331, I^2, 0%, *p* of Chi^2, 0.838) were not statistically significantly different between the juxtaposed interventions (Figure 3).

Meta-regression and subgroup analysis

The univariate meta-regression suggested that sample size was a statistically significant predictor of the observed heterogeneity in the effect size of 25(OH)D level (Table S2). Upon subgroup analysis by the sample size, heterogeneity was moderate when sample size was ≥100, and the effect size increased (random-effect model: SMD, 3.81, 95%CI, 3.03, 4.59, I^2,72.5%) (Figure S1).

Publications bias

For 25(OH)D, a small study effect was suggested by the asymmetric funnel plots (Figure S2) and Egger's test (p, 0.005). On trim-and-fill analysis no additional study was imputed. Funnel plots for the rest of the outcomes were approximately symmetric.

Sensitivity analysis

On using a fixed-effect model meta-analysis, the summary estimate of 25(OH)D level, reduced slightly (SMD,1.74, 95% CI, 1.57,1.92, p<0.001). The fixed-effect meta-analysis results for the rest of the outcomes were identical to the preliminary analysis. The meta-analysis findings for all outcomes remained unchanged on dropping a study each time and repeating the meta-analysis.

Supplementary meta-analysis

Between vitamin D and placebo, ten trials(15–18,33–35,49–51) compared GW and BMI, and nine trials(15–18,34,35,49–51) juxtaposed 25(OH)D levels (one study(33) reported 25(OH)D values in the median hence excluded). Vitamin D recipients achieved a favorable blood 25(OH)D level compared to the placebo recipients (random-effect model: SMD, 1.86, 95% CI, 0.95, 2.77, *p*, <0.001, I^2, 95.36%, *p* of Chi^2, <0.001) (Figure 4). The effect size of 25(OH)D levels reduced slightly on using a fixed-effect meta-analysis model (SMD, 1.45, 95% CI, 1.25, 1.64). GW and BMI, when contrasted among the intervention arms, were not statistically significantly different. Since <10 studies were available for the 25(OH)D levels, we did not explore heterogeneity or assess the publication bias for it.

Discussion

Overall, 11 trials, mostly Iranian, tested the effect of antenatal vitamin D complementation (as a co-supplement primarily) on GW, BMI, and 25(OH)D on 875 GDM patients, were retrieved. The intervention favored a rise in blood 25(OH)D levels, and the sample size was the plausible predictor of the observed heterogeneity.

Evidence quality

Utilizing the GRADE Working Group's (2004)(54) approach of grading evidence quality we graded the evidence concerning the 25(OH)D level as of moderate-quality, due to the unclear risk of bias components and heterogeneity.

Comparison with what is known

As the context remains underexplored in contemporary literature, a direct juxtaposition of our findings to existing reviews is not possible. However, clinical trials studying the effect of vitamin D supplementation on 25(OH)D level in pregnant females with no glucose intolerance are available for a contrast. Two such trials found that vitamin D supplementation in the third trimester increased maternal plasma 25(OH)D levels compared to the control group(55,56). Another randomized trial found that vitamin D supplementation causes a statistically significantly greater increase in the 25(OH)D level than the placebo(57). Mirroring to these trials' findings(55–57), we observed that vitamin D3 supplementation in GDM patients increased the maternal 25(OH)D level.

Implications and strengths

The chief inference of this paper is that it informs about the rigor of the current evidence of the maternal benefits of prenatal vitamin D supplementation in GDM patients. From the maternal health's perspective, this study may help health authorities to determine, if such supplementation at large scale for all GDM pregnancies will be an appropriate public health initiative or not at the current time. Moreover, as the reviewed trials were primarily Iran-based, this paper might encourage future trialists to conduct identical trials globally to generate generalizable evidence. Concerning the strength, this systematic review is one of the preliminary efforts to investigate the maternal effects of antenatal vitamin D supplementation

in GDM patients. Next, the unbound nature of our electronic database searches to any date, language, or geographical boundary, adds comprehensiveness to our review. Finally, evidence generated from this systematic review and meta-analysis is likely to be rigorous as it's grounded on the highest level of epidemiological evidence, randomized controlled trials.

Limitations

Despite these strengths, this paper has a few weaknesses. As most trials were conducted in Iran, the external validity of this review is likely to be compromised. The heterogeneity observed for the 25(OH)D levels might have increased the risk of bias in our estimates, and this can be because one of the studies was not from Iran. Besides, the maternal health effects of vitamin D supplementation remains inseparable from other supplements that were simultaneously given to the participants in most trials.

Conclusion

Using vitamin D as the chief ingredient of antenatal supplements favors in blood 25(OH)D level rise in GDM patients. However, these supplements on GW and BMI didn't vary with its non-recipients.

Conflict of Interest: No conflict of interest is declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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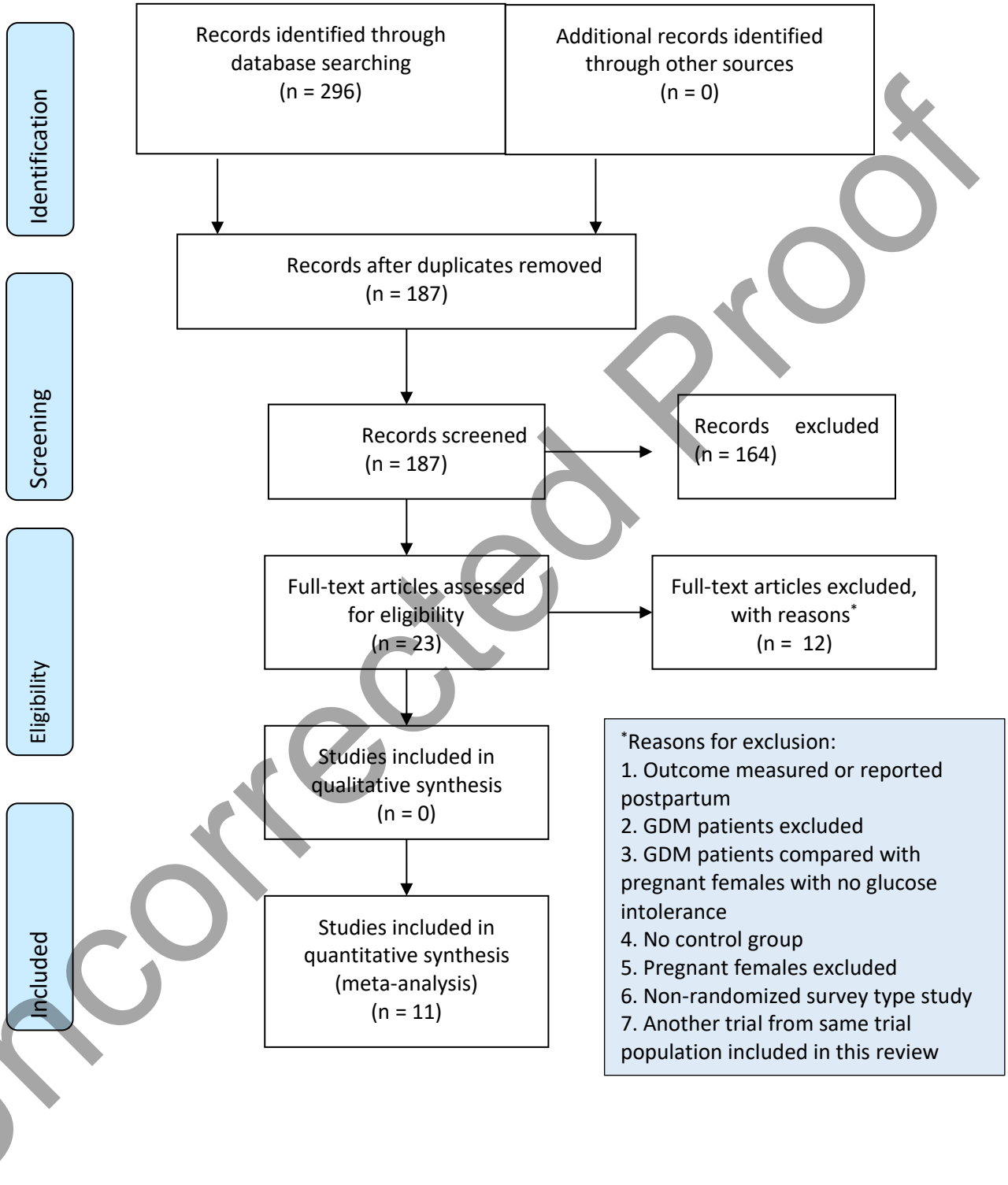
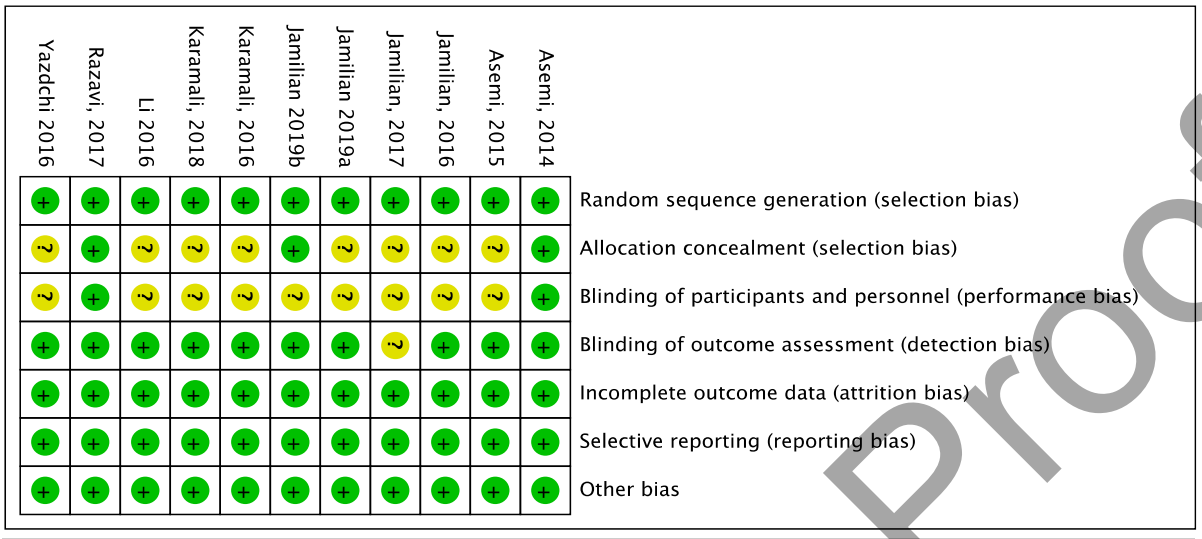
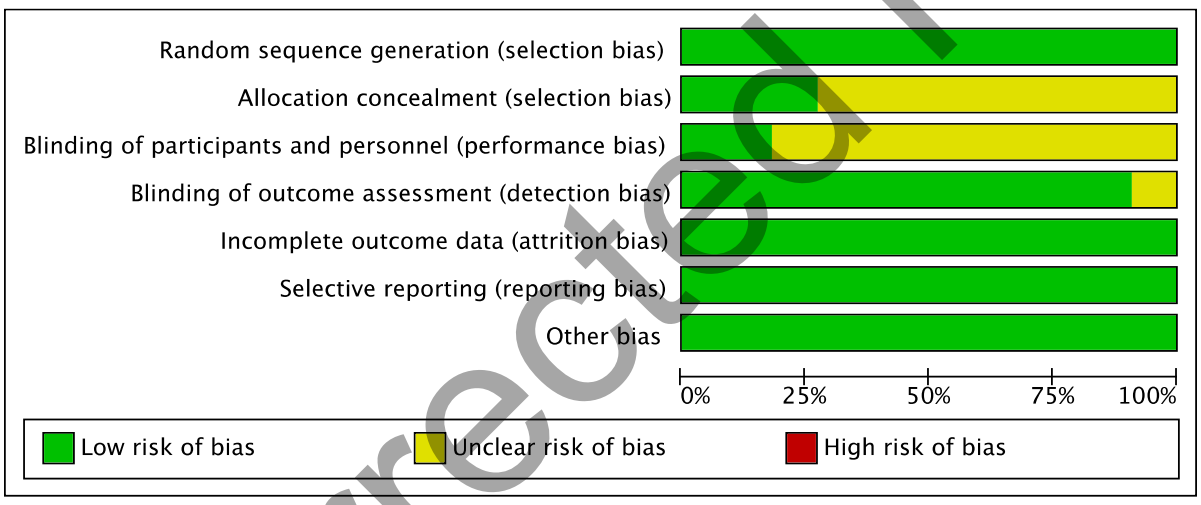


Figure 1. Study selection process [PRISMA flow chart (58)]

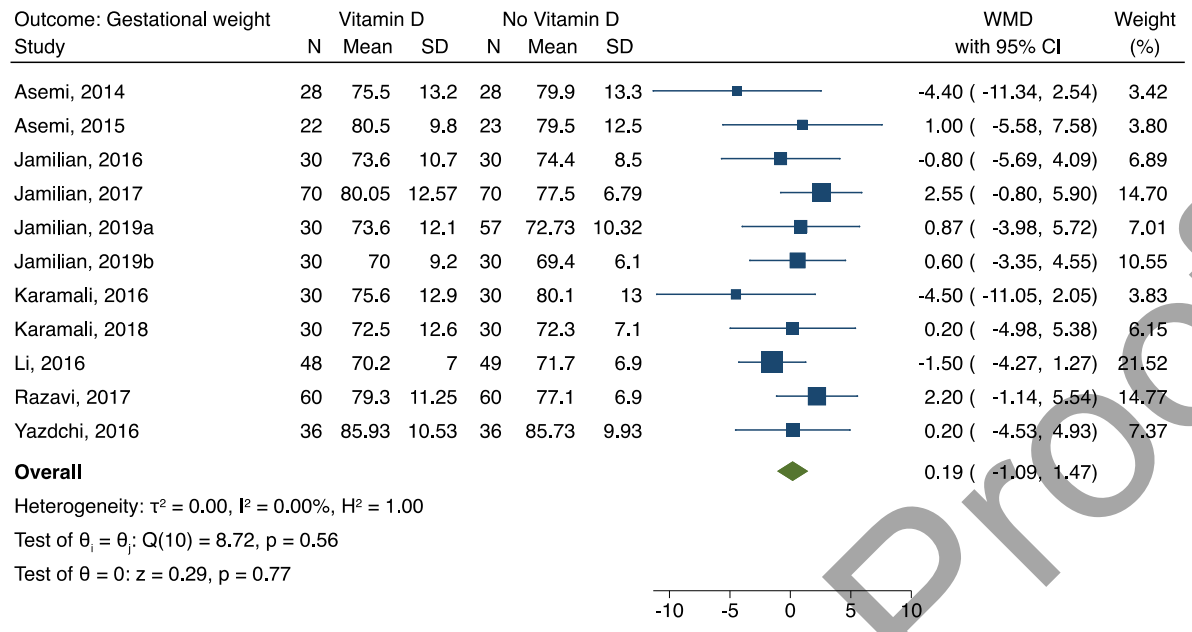


2a.

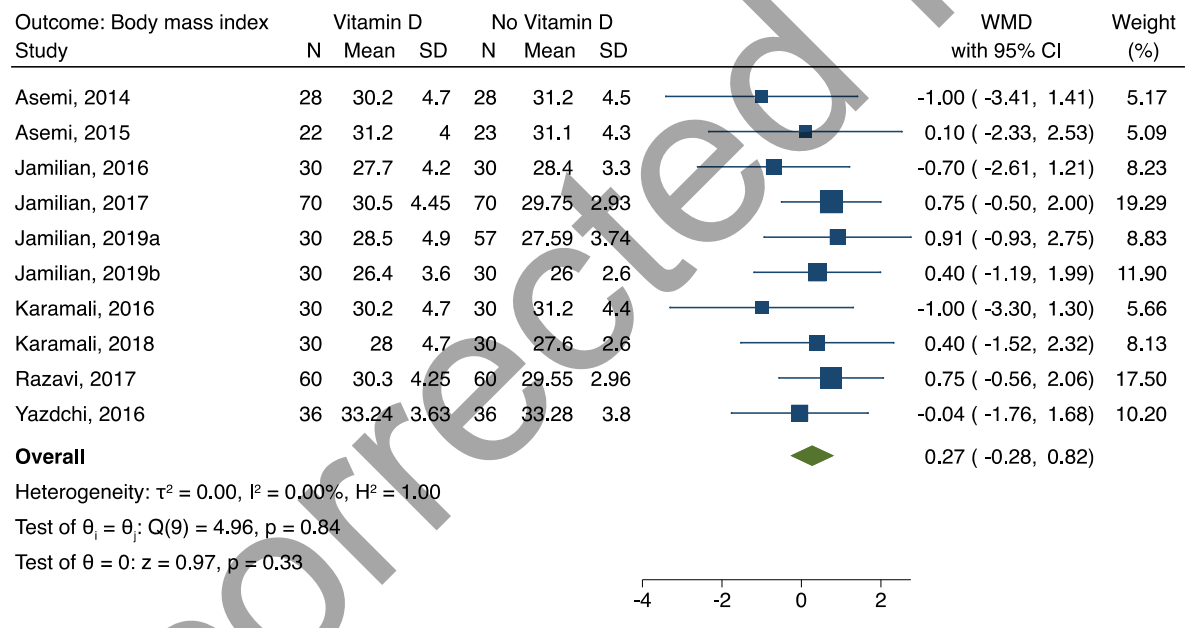


2b.

Figure 2. a) Risk of bias graph: review authors' evaluation of respective risk of bias items presented across all studies included in the review. b) Risk of bias summary: review authors' evaluation of respective risk of bias item for each included study



3a.



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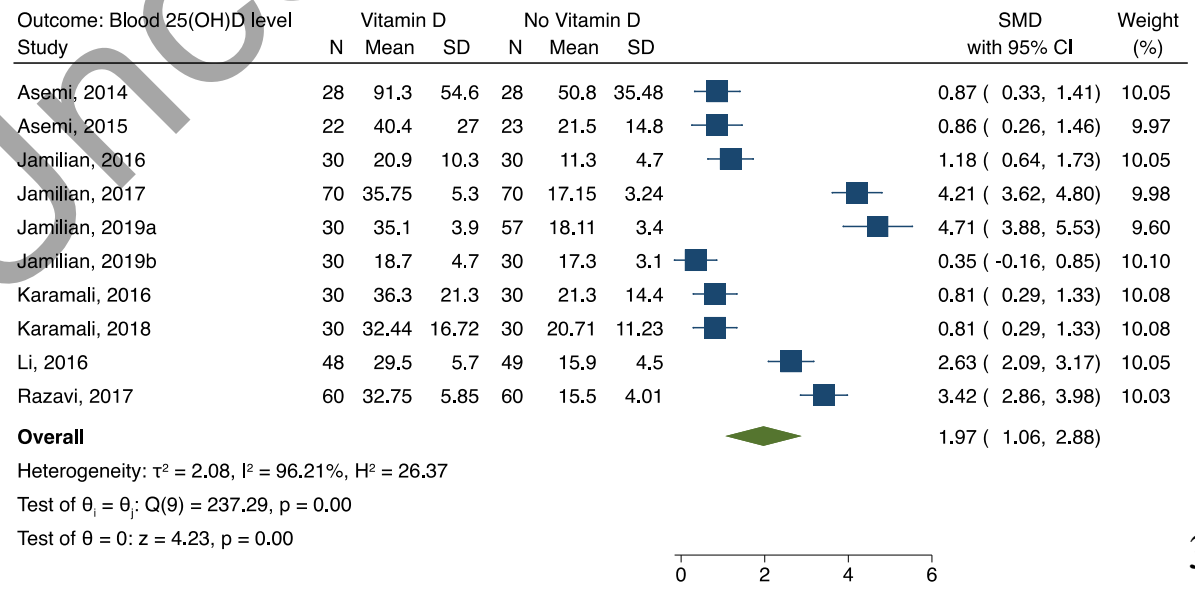
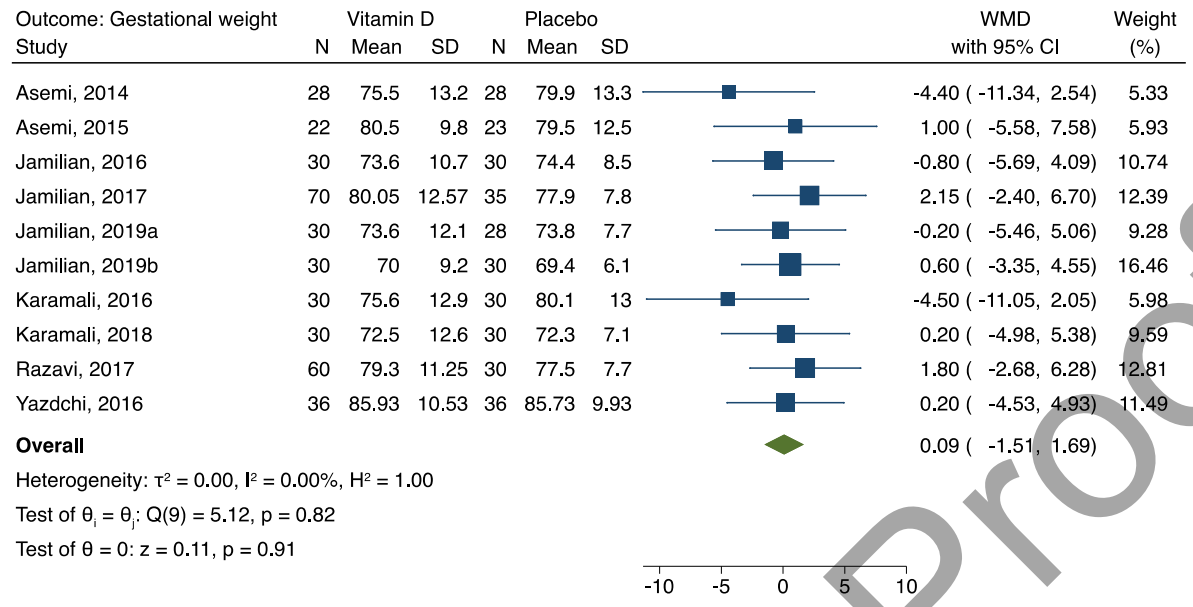
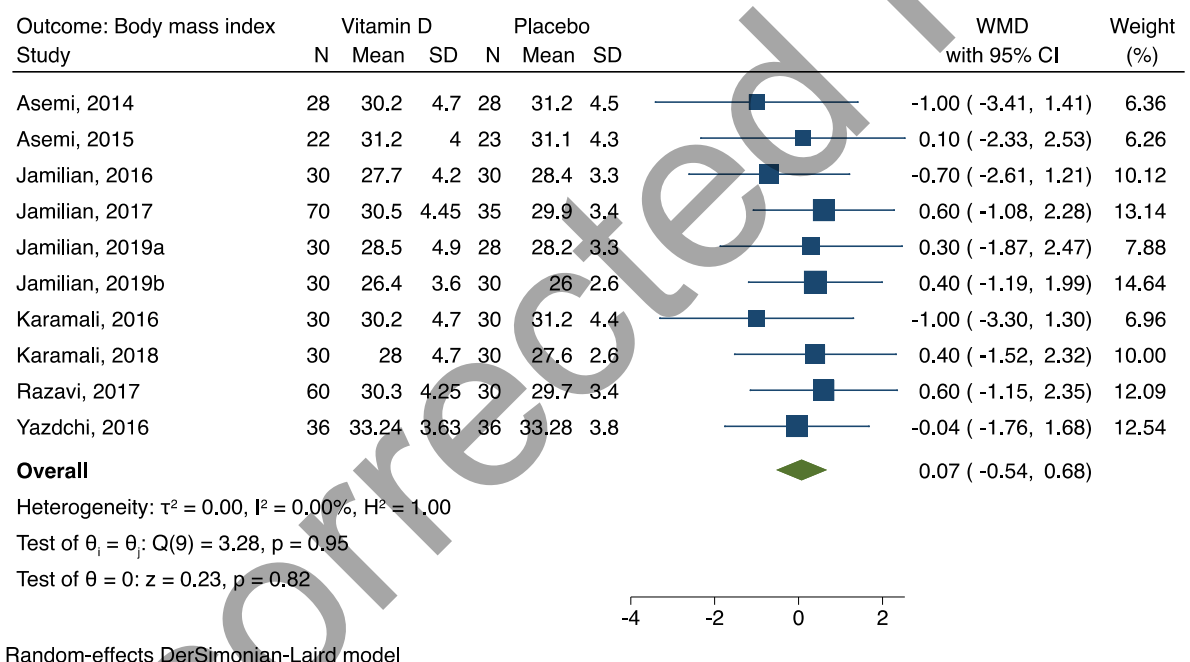


3c.

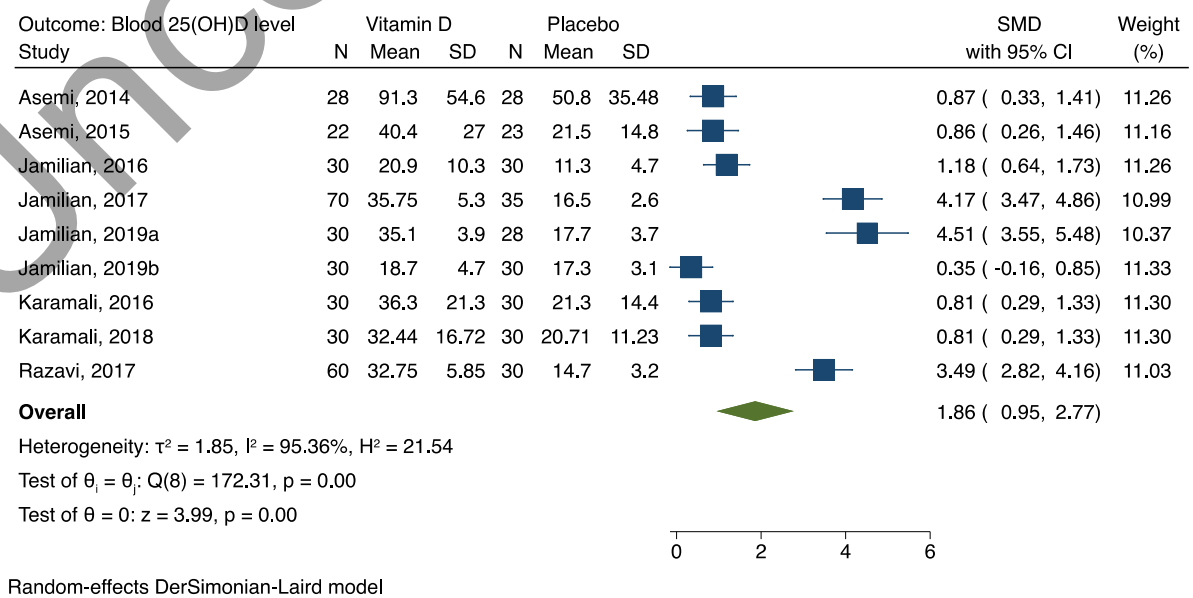
Figure 3. Forest plots depicting meta-analysis findings (random-effect model). Outcome: gestational weight a), body mass index b), and 25(OH)D level in blood c). A comparison between antenatal vitamin D supplementation (as the only or co-supplement with other supplements) and non-vitamin D based supplementation; Two trials had with identical trial author name and year have been suffixed with alphabet ‘a’(50) and ‘b’(18) after the study name and year



4a.



4b.



4c.

Figure 4. Forest plots depicting meta-analysis findings (random-effect model). Outcome: gestational weight a), body mass index b), and 25(OH)D level in blood c). A comparison between antenatal vitamin D supplementation (as a sole or co-supplement with other supplements) and placebo; Two trials had with identical trial author name and year have been suffixed with alphabet ‘a’(50) and ‘b’(18) after the study name and year

Table 1. Summary table				
Trial	**Design**	**Population**	**Intervention arms**	**Outcomes reported**
1. Karamali, 2016 (16)	Randomized, placebo-controlled trial Blinding: double blinded Number of intervention arms: two Multi-center or single-center trial: multi-centric Study duration: six weeks Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201407115623N23	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 60 Calcium and vitamin D armarm(n): 30 Placebo group (n): 30 Average age of Calcium and vitamin D arm: 28.7 (6.1) years Average age of placebo group: 31.6 (6.3) years Missing outcome data: 0 Baseline mean BMI (SD): Placebo group: 30.5 (4.5) kg/m^2; Calcium and vitamin D arm: 29.4 (4.7) kg/m^2 Baseline mean GW (SD): Placebo group: 78.1 (13.4) kg; Calcium and vitamin D arm: 73.7 (12.8) kg Baseline mean (SD) vitamin D levels: Placebo group: 20.8 (14.4) ng/ml; Calcium and vitamin D arm: 17.3 (10.9) ng/ml	Calcium and vitamin D arm: calcium carbonate 1000 mg/day (six weeks) and 50,000 IU D3 (at trial initiation and 21st day). Placebo arm. Intervention given between 24 and 28 weeks of pregnancy. Total vitamin D received in six weeks: 100,000 IU.	1. GW 2. BMI 3. 25(OH)D
2. Karamali, 2018 (17)	Randomizedplacebo-controlled trial Blinding: double blinded Number of intervention arms: two Multi-center or single-center trial: single-centric Study duration: six weeks	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 60 Magnesium, zinc, calcium and vitamin D supplements arm(n): 30 Placebo group (n): 30 Average age of Magnesium, zinc, calcium and vitamin D supplements arm: 30 (4.5) years Average age of placebo group: 31.1 (4.2) years Missing outcome data: 0	Magnesium, calcium, zinc and vitamin D arm: 100 mg magnesium, 400 mg calcium, 4 mg zinc, and 200IU vitamin D 2x/d (six weeks). Placebo arm. Total vitamin D received in six weeks: 16,800IU	1. GW 2. BMI 3. 25(OH)D

	Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: not clear Information regarding funding: provided Clinical trial registration number: not available	Baseline mean BMI (SD): Placebo group: 27 (2.6) kg/m^2; Magnesium, zinc, calcium and vitamin D supplements arm: 27.4 (4.8) kg/m^2 Baseline mean GW (SD): Placebo group: 70.7 (7.2) kg; Magnesium, zinc, calcium and vitamin D supplements arm: 70.9 (12.8) kg Baseline mean (SD) vitamin D levels: Placebo group: 20.21 (10.73) ng/ml; Magnesium, zinc, calcium and vitamin D supplements arm: 18.96 (11.23) ng/ml		
3. Asemi, 2015 (49)	Randomized, placebo-controlled trial Blinding: double blinded Number of intervention arms: two Multi-center or single-center trial: multi-centric Study duration: six weeks Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201305115623N7	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 50 Vitamin D arm(n): 25 Placebo group (n): 25 Average age of vitamin D arm: 31.1 (5.5) years Average age of placebo group: 30.8 (6.2) years Missing outcome data: 5 (three in vitamin D armand two in placebo arm); Causes of missingness: intra-uterine fetal death (n=1), placenta abruption (n=1), completed bed rest (n=1), insulin therapy (n=1), pre-eclampsia (n=1) Baseline mean BMI (SD): Placebo group: 30.5 (4.5) kg/m^2; Vitamin D arm: 30.7 (3.9) kg/m^2 Baseline mean GW (SD): Placebo group: 77.8 (12.9) kg; Vitamin D arm: 79.0 (9.7) kg Baseline mean (SD) vitamin D levels: Placebo group: 20.9 (14.3) ng/ml; Vitamin D arm: 18.9 (14.5) ng/ml	Vitamin D arm: 50 000 IU D3 (at trial initiation and 21st day). Placebo arm. Total vitamin D received in six weeks: 100,000 IU.	1. GW 2. BMI 3. 25(OH)D

4. Jamilian 2019a (50)	Randomized, placebo-controlled trial Blinding: double blinded No. of treatment arms: two Single centered trial Study duration: six weeks Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding fundingInformation regarding funding: provided Clinical trial registration number: IRCT201706075623N119	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 90 Probiotic and vitamin D arm(n): 30 Probiotic arm(n): 30 Placebo group (n): 30 Average age of probiotic and vitamin D arm: 28.9 (6.1) years Average age of probiotic group: 31.2 (5.9) years Average age of placebo group: 29.9 (3.7) years Missing outcome data: 3; Causes of missingness: insulin therapy (n=1) and hospitalization (n=1) Baseline mean BMI (SD): Placebo group: 27.5 (3.3) kg/m^2; Probiotic and vitamin D arm: 27.8 (4.9) kg/m^2; Probiotic group: 26.4 (4.2) kg/m^2 Baseline mean GW (SD): Placebo group: 72.0 (7.7) kg; Probiotic and vitamin D arm: 71.9 (12.1) kg; Probiotic group: 70.0 (12.5) kg Baseline mean (SD) vitamin D levels: Placebo group: 14.3 (4.1) ng/ml; Probiotic and vitamin D arm: 13.4 (4.1) ng/ml; Probiotic group: 12.9 (3.2 ng/ml	Probiotic and vitamin D arm: 50,000 IU D3 (every 2 weeks) and $8*10^9$ CFU/g probiotic Probiotic arm: $8*10^9$ CFU/g probiotic Placebo arm. Total vitamin D received in six weeks: 150,000IU	1. GW 2. BMI 3. 25(OH)D
5. Jamilian 2019b (18)	Randomized, placebo-controlled trial Blinding: double blinded No. of treatment arms: two Single centered trial Study duration: six weeks Country where trial was conducted: Iran	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 60 Magnesium, zinc, calcium plus vitamin D arm(n): 30 Placebo group (n): 30 Average age of magnesium, zinc, calcium plus vitamin D arm: 27.7 (4.0) years Average age of placebo group: 29.1 (4.1) years Missing outcome data: 0	Magnesium, calcium, zinc, and vitamin D arm: 100 mg magnesium, 400 mg calcium, 4 mg zinc, and 200 IU D3: two times daily for six weeks. Placebo arm. Total vitamin D received in six weeks: 16800 IU	1. GW 2. BMI 3. 25(OH)D

	Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201704225623N109	Baseline mean BMI (SD): Placebo group: 25.3 (2.5) kg/m^2; magnesium, zinc, calcium plus vitamin D arm: 25.8 (3.7) kg/m^2 Baseline mean GW (SD): Placebo group: 67.6 (6.1) kg; Magnesium, zinc, calcium plus vitamin D arm: 68.2 (9.4) kg Baseline mean (SD) vitamin D levels: Placebo group: 13.5±3.6 ng/ml; Magnesium, zinc, calcium plus vitamin D arm: 12.6 ± 4.2 ng/ml		
6. Li 2016 (37)	Randomized, clinical trial Blinding: double blinded No. of treatment arms: two Multricentric trial Study duration: 16 weeks Country where trial was conducted: China Ethical permission: obtained Consent from participants: obtained Information regarding funding: not clear Clinical trial registration number: not clear	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 103 Yoghurt supplemented with vitamin D arm(n): 52 Plain yoghurt group (n): 51 Average age of yoghurt supplemented with vitamin D arm: 29.0±5.3 years Average age of plain yoghurt group: 28.3±4.1 years Missing outcome data: 6 (non-compliance (3) and personal reasons (3)) Baseline mean GW (SD): Plain yoghurt group 69.3±6.7) kg; Yoghurt supplemented with vitamin D arm: 67.9±7.1) kg Baseline mean (SD) vitamin D levels: Plain yoghurt group: 16.2 (3.4) ng/ml; Yoghurt supplemented with vitamin D arm: 16.8±4.6) ng/ml	Yoghurt and vitamin D arm: plain yoghurt and 500 IU D3 (twice daily for 16 weeks) Plain yoghurt arm: twice daily for 16 weeks. Total vitamin D received in six weeks: 112,000IU	1. GW 2. 25(OH)D level
7. Razavi, 2017(51)	Randomizedclinical trial Blinding: double blinded No. of treatment arms: two Single centered trial	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 120 Vitamin D arm(n): 30 Omega-3 arm(n): 30 Vitamin D and Omega-3 arm(n): 30	Vitamin D arm: 50000 IU **(two weekly)** Omega-3 arm: 1000 mg omega-3 fatty acids two times a day	1. GW 2. BMI 3. 25(OH)D

	(59) Study duration: six weeks. Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201701305623N106	Placebo arm(n): 30 Average age of Vitamin D arm: 29.9 ± 5.0 years Average age of Omega-3 arm: 29.7 ± 3.6 years Average age of vitamin D and Omega-3 arm: 29.9 ± 4.0 years Average age of placebo arm: 29.2 ± 3.4 years Missing outcome data: 0 Baseline mean GW (SD): Vitamin D arm: 76.1 ± 12.7 kg; Omega-3 arm: 74.3 ± 5.8 kg; Vitamin D and Omega-3 arm: 77.4 ± 10.2 kg; Placebo arm: 75.1 ± 7.7 kg Baseline mean (SD) BMI: Vitamin D arm: 29.2 ± 5.0 kg/m^2; Omega-3 arm: 28.5 ± 2.4 kg/m^2; Vitamin D and Omega-3 arm: 29.5 ± 3.8 kg/m^2; Placebo arm: 28.8 ± 3.4 kg/m^2 Baseline mean (SD) vitamin D levels: Vitamin D arm: 13.6 ± 3.7 ng/mL; Omega-3 arm: 15.6 ± 4.0 ng/mL; Vitamin D and Omega-3 arm: 14.2 ± 2.9 ng/mL; Placebo arm: 14.9 ± 3.2 ng/mL	Vitamin D and Omega-3 arm: 50,000 IU Vitamin D (two weekly) and 1000 mg omega-3 fatty acids: two times a day for six weeks. Placebo arm. Total vitamin D received in six weeks: 150,000 IU	
8. Yazdchi 2016(33)	Randomizedcontrolled clinical trial Blinding: double blinded No. of treatment arms: two Single centered trial Study duration: 8 weeks. Country where trial was conducted: Iran Ethical permission: obtained	Diagnosis: GDM (using International Association of Diabetes and Pregnancy Study Groups criteria) Number of participants randomized: 76 Vitamin D arm(n): 38 Placebo arm(n): 38 Average age of Vitamin D arm: 31.64±4.40 years Average age of placebo arm: 32.11±3.61 years Missing outcome data: 4 (severe preeclampsia (1), early childbirth (1), unwilling to continue (1), and hospitalization (1)) Baseline mean GW (SD): Vitamin D arm: 81.48 ± 10.79 kg; Placebo arm: 81.09 ± 9.80 kg	Vitamin D arm: 50,000 IU D3 (two weeklies) Placebo arm. Total vitamin D received in eight weeks: 200,000 IU	1. GW 2. BMI 3. 25(OH)D

	Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201306253140N11	Baseline mean (SD) BMI: Vitamin D arm: 31.51 ± 3.74 kg/m^2; Placebo arm: 31.47 ± 3.71 kg/m^2 Vitamin D levels data was reported in median (25th and 75th percentiles) due to nonparametric distribution: Baseline: Vitamin D arm: 9.54 (6.12-15.94) ng/mL; Placebo arm: 9.02 (7.29-14.70) ng/mL		
9. Asemi, 2014(34)	Randomized clinical trial Blinding: double blinded No. of treatment arms: two Multicentric trial Study duration: six weeks. Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201311205623N11	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 56 Vitamin D and calcium arm(n): 28 Placebo arm(n): 28 Average age of vitamin D and calcium arm: 28.7±6.0 years Average age of placebo arm: 30.8±6.6 years Missing outcome data: 5 Baseline mean (SD) GW: Vitamin D and calcium arm: 73.6±13.0 kg; Placebo arm: 78.2±13.6 kg Baseline mean (SD) BMI: Vitamin D and calcium arm: 29.4±4.6 kg/m^2; Placebo arm: 30.5±4.6 kg/m^2 Baseline mean (SD) 25(OH)D: Vitamin D and calcium arm: 43.11±28.17 nmol/l; Placebo arm: 49.05±34.30 nmol/l	Vitamin D and calcium arm: 1,000 mg calcium carbonate (daily) and 50,000 U D3 (at trial initiation and on 21st day) Placebo arm. Total vitamin D received in six weeks: 100,000 IU	1. GW 2. BMI 3. 25(OH)D
10. Jamilian, 2016(15)	Randomizedplacebo-controlled clinical trial Blinding: double blinded No. of treatment arms: two	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 60 Vitamin D3 and EPO arm(n): 30 Placebo arm(n): 30	Vitamin D3 and EPO arm: 1000 IU of vitamin D and 1000 mg of EPO: daily(60) Placebo arm.	1. GW 2. BMI 3. 25(OH)D

	Single centered trial Study duration: six weeks. Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided Clinical trial registration number: IRCT201509115623N52	Average age of vitamin D3 and EPO arm: 28.4 ± 6.2 years Average age of placebo arm: 29.6 ± 4.3 years Missing outcome data: 6 (all withdrawn from the trial due to personal reasons) Baseline mean (SD) GW: Vitamin D3 and EPO arm: 71.5 ± 10.8 kg; Placebo arm: 72.3 ± 8.5 kg Baseline mean (SD) BMI: Vitamin D3 and EPO arm: 27.0 ± 4.2 kg/m^2; Placebo arm: 27.6 ± 3.5 kg/m^2 Baseline mean (SD) 25(OH)D: Vitamin D3 and EPO arm: 14.0 ± 10.1 ng/mL; Placebo arm: 11.4 ± 4.3 ng/mL	Total vitamin D received in six weeks: 42,000 IU.	
11. Jamilian, 2017(35)	Randomized, placebo-controlled clinical trial Blinding: double blinded No. of treatment arms: four Single centered trial Study duration: six weeks. Country where trial was conducted: Iran Ethical permission: obtained Consent from participants: obtained Information regarding funding: provided	Diagnosis: GDM (using ADA criteria) Number of participants randomized: 140 Vitamin D and omega-3 fatty acid arm(n): 35 Vitamin D arm(n): 35 Omeag-3 fatty acid arm(n): 35 Placebo arm(n): 35 Average age of vitamin D and omega-3 fatty acid arm: 31.2 ± 4.3 years Average age of vitamin D arm: 31.5 $\pm$ 7.0 years Average age of omega-3 arm: 30.7 $\pm$ 3.5 years Average age of placebo arm: 30.7 $\pm$ 4.1years Missing outcome data: 6 (all withdrawn from the trial due to personal reasons) Baseline mean (SD) GW: Vitamin D and omega-3 fatty acid arm: 77.3$\pm$9.9 kg Vitamin D arm: 78.4 $\pm$ 15.2 kg	Vitamin D and omega-3 fatty acid arm: 50,000 IU of vitamin D (two weeklies) and 1000 mg omega-3 fatty acid (twice daily) Vitamin D arm: 50000 IU vitamin D (two weeklies) Omega-3 fatty acid arm: 1000 mg omega-3 fatty acids Placebo arm. Total vitamin D received in six weeks:150,000 IU	1. GW 2. BMI 3. 25(OH)D

	Clinical trial registration number: IRCT201605135623N78	Omeag-3 fatty acid arm: 75.0 ± 5.8 kg Placebo arm: 75.9 ± 7.1 kg Baseline mean (SD) BMI: Vitamin D and omega-3 fatty acid arm: 29.7 ± 3.9 kg/m^2 Vitamin D arm: 29.7 ± 5.1 kg/m^2 Omeag-3 fatty acid arm: 28.8 ± 2.4 kg/m^2 Placebo arm: 29.2 ± 3.4 kg/ m^2 Baseline mean (SD) 25(OH)D: Vitamin D and omega-3 fatty acid arm: 15.5 ± 3.1 ng/mL; Vitamin D arm: 15.2 ± 3.8 ng/mL; Omeag-3 fatty acid arm: 16.9 ± 3.5 ng/mL; `Placebo arm: 16.6 ± 2.6 ng/mL		

Abbreviations: ADA: American Diabetes Association(52,53); EPO: evening primrose oil

Table 2. Risk of bias assessment							
Trial[#]	**Selection bias (Random sequence generation)**	**Selection bias (Allocation concealment)**	**Performance bias Outcome: BMI, GW, and 25(OH)2D**	**Detection bias Outcome: BMI, GW, and 25(OH)2D**	**Attrition bias**	**Reporting bias**	**Other bias**
1. Karamali, 2016 (16)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: Allocation concealment: it's not clear if the midwife who measured did the random allocation of participant (in an unblind manner) was related the study personnel or the outcome assessor; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
2. Karamali, 2018 (17)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
3. Asemi, 2015 (49)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
4. Jamilian 2019a (50)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
5. Jamilian 2019b (18)	Low	Low	Unclear	Low	Low	Low	Low
	Authors' comment: Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
6. Li 2016 (37)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: Participants were blinded by using coded labels on the interventions. However, it remains unclear if study personnel were adequately blinded or not.						
7. Razavi, 2017(51)	Low	Low	Low	Low	Low	Low	Low
	Low	Unclear	Unclear	Low	Low	Low	Low

8. Yazdchi 2016(33)	Authors' comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it's not clear if study personnel were adequately blinded or not.						
9. Asemi, 2014(34)	Low	Low	Low	Low	Low	Low	Low
10. Jamilian, 2016(15)	Low	Unclear	Unclear	Low	Low	Low	Low
	Authors' comment: It remains unclear if the midwife responsible for random sequence generation and its allocation concealment was also the study personnel or anyway could have broken the blinding of the study personnel.						
11. Jamilian, 2017(35)	Low	Unclear	Unclear	Unclear	Low	Low	Low
	Authors' comment: The precise mechanism used to keep the allocation sequence of the computer-generated random numbers concealed from the participants was not clear. It's not clear how were study personnel and participants blinded in this trial as we couldn't find a clear mention about it. It also remains unclear if the nutritionist and the midwife measuring weight and height of participants were part of the intervention providing team or anyway their blinding might have been broken about the interventions received by the participants.						

#1st author's last name and publication year