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The Effects of Vitamin D Supplementation on Glycemic Control and Maternal-Neonatal Outcomes in Women with Established Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

Mengmeng Wang[1#], Zhaojing Chen[1#], Yan Hu[1], Yin Wang[1], Yinyin Wu[1], Fuzhi Lian[1], Hongjuan Li[2], Jun Yang[1,3]*, and Xianrong Xu[1]*

[1]Departmemnt of Preventive Medicine, Hangzhou Normal University School of Medicine, Hangzhou, 311121; [2]Department of Basic Medicine, Hangzhou Normal University School of Medicine, Hangzhou, 311121; and [3]Zhejiang Provincial Center for Uterine Cancer Diagnosis and Therapy Research, The Affiliated Women's Hospital, Zhejiang University, Hangzhou, 310006, China

[#]These two authors contributed equally to this work.

*Correspondence should be addressed to:

Jun Yang, Ph.D., Department of Preventive Medicine, Hangzhou Normal University School of Medicine, Hangzhou, 311121, China

E-mail: gastate@zju.edu.cn

Or

Xianrong Xu, Ph.D., Department of Preventive Medicine, Hangzhou Normal University School of Medicine, Hangzhou, 311121, China

E-mail: xuxianrong@hznu.edu.cn

Abstract

Background &aims: Gestational Diabetes Mellitus (GDM) is associated with a well-documented range of adverse pregnancy outcomes. The present meta-analysis was conducted to evaluate the effects of vitamin D supplementation on glycemic control and maternal-neonatal outcomes in women with established GDM.

Methods: Published literature was retrieved and screened from PubMed, Embase, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang, and Cochrane Center Register of Controlled Trails up to May 2020. RCTs of vitamin D supplementation on pregnant women with GDM were included.

Results: 19 RCTs (1550 participants) were eligible for meta-analyses. Overall, vitamin D supplementation significantly reduced serum fasting plasma glucose (FPG) (MD: -10.20 mg/dl, 95%CI:-13.43 to -6.96), insulin concentration (MD: -5.02 μIU/mL, 95%CI: -6.83 to -3.20) and the homeostasis model assessment of insulin resistance (HOMA-IR) (MD:-1.06, 95%CI: -1.40 to -0.72) in women with GDM. In addition, vitamin D supplementation in pregnant women with GDM significantly reduced adverse maternal outcomes including cesarean section (RR: 0.75, 95%CI: 0.63 to 0.89), maternal hospitalization (RR: 0.13, 95%CI: 0.02 to 0.98) and postpartum hemorrhage (RR: 0.47, 95%CI: 0.22 to 1.00). Several adverse neonatal complications including neonatal hyperbilirubinemia (RR:0.47, 95%CI: 0.33 to 0.67), giant children (RR:0.58, 95%CI: 0.38 to 0.89), polyhydramnios (RR:0.42, 95% CI: 0.24 to 0.72), fetal distress (RR:0.46, 95%CI: 0.24 to 0.90) and premature delivery (RR:0.43, 95% CI: 0.26 to 0.72) were also significantly reduced.

Conclusions: This meta-analysis suggested that supplementation of GDM women with vitamin D may lead to an improvement in glycemic control and reduction of adverse maternal-neonatal outcomes.

Keywords: Vitamin D; Gestational diabetes mellitus; Fasting plasma glucose; Maternal-neonatal outcome; Meta-analysis;

1. Introduction

Gestational diabetes mellitus (GDM) is a common medical complication of pregnancy which is defined as "diabetes diagnosed in the second or third trimester of pregnancy that is not overt diabetes"[1]. It is estimated that approximately 15% of live births were affected by GDM globally[2], and the overall prevalence of GDM was around 5.4% (95%CI: 3.8%-7.8%) in Europe[3], 11.5% (95%CI: 10.9%-12.1%) in Asia[4] and 13.6% in Africa[5], respectively. GDM is regarded as a significant risk factor to both mother and developing fetus, which is associated with preeclampsia, cesarean section, polyhydramnios, fetal distress, malformation, macrosomia, premature infants, as well as long-term consequences on the health of the pregnant women and their offspring[6-8]. Moreover, GDM puts a disproportionate economic burden on the patients[9], and it is estimated that the overall cost of care for an individual with GDM is 34% greater than the cost for a woman without the disease[10]. In light of this finding, along with the rising prevalence of obesity epidemic, physical inactivity, and advanced childbearing age among women of childbearing age[11, 12], measures that could prevent or reduce the adverse outcomes of GDM need to be identified.

Accumulating evidences have indicated that vitamin D, a lipid-soluble nutrient, plays an important role in the development of GDM[13]. The possible mechanisms for the modulation of glucose homeostasis by vitamin D may include driving the recovery of physiological insulin secretion[14], interacting with insulin-like growth factor (IGF)[15], enhancing duodenal absorption and renal resorption of calcium and

then facilitating the intracellular signaling transduction of insulin[16]. To date, there have been a number of published systematic reviews and meta-analyses which evaluated the relationship between vitamin D and GDM[17-27]. However, some of the studies only focused on association of vitamin D deficiency with the development of GDM rather than the therapeutic effect of vitamin D supplement on GDM[20, 23, 26]. For those studies evaluating the therapeutic potential of vitamin D supplementation, some mixed observational studies with randomized controlled trials (RCTs) together[21, 22] . Additionally, some of the studies did not separate patients taking vitamin D for GDM prevention from those taking vitamin D for GDM treatment[21]. Even for the studies investigating the therapeutic effects of vitamin D supplementation on glucose metabolism and lipid profiles in patients with GDM, only six[24, 27] or five[18] RCTs were included, and the sample size was relatively small with high heterogeneity. Partial of the reason might be due to the fact that some of the studies were published in Chinese, which are not indexed in PubMed or other international databases and thus were missed by researchers outside China. Moreover, the effects of vitamin D supplementation on glucose homeostasis and maternal-neonatal outcomes of women with established GDM had not been carefully evaluated. Therefore, here we conducted a meta-analysis to examine the therapeutic effects of vitamin D supplementation versus placebo on glycemic control, pregnancy complications, and newborn outcomes in pregnant women diagnosed with GDM.

2. Material and Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[28].

2.1. Search strategy

A comprehensive literature search was carried out in PubMed, EMBASE, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang Data (a database for Chinese publications), and Cochrane Center Register of Controlled Trials from inception to May 1, 2020. The literature search was conducted using the following medical subject heading terms and Boolean operators: “vitamin D” OR “25(OH)-D” OR “25-hydroxy vitamin D” OR “vitamin D deficiency” AND “GDM” OR “gestational diabetes” OR “diabetes pregnancy” AND “randomized controlled trial” (see Supplement material 1). Searching was restricted to articles in English and Chinese, and we also screened the references of the articles retrieved. Three authors independently screened the title, abstract, and full-text of the retrieved articles. Any discrepancy between the findings of the three reviewers was resolved through discussion.

2.2. Study Eligibility criteria

Studies included in this meta-analysis should meet the following criteria: (a) RCTs; (b) pregnant women diagnosed with GDM; (c) vitamin D was administered during pregnancy; (d) control group was supplemented with placebo or without any supplementation. Vitamin D could be given in either form (vitamin D2 or D3),

administered at any dose, by any route (oral or intramuscular), and at any frequency—"regular" dosing in which supplementation was offered at least three times in a regular/recurrent manner (such as daily, weekly, or monthly) and "bolus" dose regimens in which the supplement was administered only once or twice. The studies should be published in English or Chinese. Trials involving those women with a history of high dose vitamin D consumption during the previous 3 months, women with diagnosis of GDM class A2 which require insulin therapy are excluded. Also, the studies that did not report the mean and standard deviation of glucose metabolism for intervention and control groups, conference abstracts without full text, case reports, observational cohorts rather than RCTs, and studies in which the intervention was administered only before conception or after delivery were excluded from the study. Three independent reviewers screened abstracts and full text articles for inclusion, and any disagreements were resolved through consensus of at least two reviewers.

2.3. Quality assessment

The Cochrane Collaboration tool was used to assess the quality of all included studies[29]. Three authors assessed each study independently against the six criteria, including selection bias, performance bias, personal bias, detection bias, attrition bias, and reporting bias[30]. Each criterion was assessed with 3 potential outcomes: low risk of bias, high risk of bias, or unclear risk of bias.

2.4. Data Extraction

Data were independently extracted from each article by three authors using a data

collection form. Data items collected included: first author, journal name, year of publication, the country in which the trial was conducted, number of trial participants, diagnosis criteria of GDM, mean age of mother, intervention, control measures, length of study, sample size, outcome measures of interest, and risk of bias.

2.4. Outcome measures

The studies that met inclusion criteria were reviewed by three authors, and the outcomes of these RCTs that could be retained for meta-analysis were considered the primary outcome in this review. Therefore, the primary outcome measures included in this review were mean changes in fasting plasma glucose (FPG), insulin, plasma insulin resistance index (HOMA-IR), GDM pregnant outcomes (cesarean section, maternal hospitalization, and postpartum hemorrhage), and newborn complications (hyperbilirubinemia, giant children, hypoglycemia, polyhydramnios, fetal distress, and premature delivery). Data from different studies were converted to the same unit, with mg/dL for FPG and μIU/mL for insulin concentration, respectively. The units of the data were transformed by the following equation: for FPG, 1 mmol/L=18 mg/dL; for insulin, 1 pmol/L=6.965 μIU/mL (https://www.thebloodcode.com/calculators/).

2.5. Statistical analysis

Data analysis was performed by using the Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK) and STATA 14.0. The relative risk (RR) and weighted mean difference (WMD) were used for measuring the association between vitamin D supplementation and GDM. Forest plots were used to

visually assess pooled estimates and corresponding 95% CIs. The homogeneity across studies was examined by the Higgins inconsistency test (I^2)[31]. In the presence of significant heterogeneity (I^2>50% or P≤0.05), a random-effects model was used to calculate the pooled effect size; otherwise (I^2<50% or P≥0.05), a fixed-effects model was applied. We further conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each run. We also conducted a subgroup analysis to explore the possible explanations for heterogeneity. Potent publication bias was assessed by using the Egger's test and funnel plots.

3. Results

3.1. Literature Search

Figure 1 shows the search details of the study selection process and the reasons for the exclusion of studies for this systematic review and meta-analysis of vitamin D supplementation in GDM. In detail, by searching the databases, 759 articles were identified in our initial search; of these, 496 were excluded as duplicates, and 263 were further screened for inclusion. Then, 213 were excluded by title and abstract based on not being RCTs or quasi-experimental studies or using vitamin D supplementation for preventing GDM, or not human studies. Finally, 19 articles[32-50] were included for the final pooled analysis.

A summary of the included studies is presented in Table 1. The earliest study was published in 2011 and the latest in 2019, but more than half of the studies were published within the past 5 years. The sample size of the participants in each study ranged from 45 to 213, and the total number of participants included in this systematic review was 1550. Among the 19 studies, 12 were conducted in Iran, and the other 7 were conducted in China.

3.2. Assessment of The Risk of Bias

The methodological quality according to the researchers' decisions on each risk of bias point for each included study is shown in Figures 2 and 3. Results of the Cochrane risk of bias assessments (Fig. 2 and Fig. 3) present an overall low risk of bias, especially concerning random sequence generation. A slightly higher risk was

reported for detection bias and attrition bias. Unclear risks were related to selection bias and detection bias.

3.3. Effect of Vitamin D Supplementation on FPG, Insulin, and HOMA-IR

Eleven RCTs with 717 participants[32, 34, 35, 38, 40, 42-44, 46, 48, 49], seven RCTs with 479 participants[32, 37, 38, 40, 43, 46, 48], and eight RCTs with 514 participants[32, 34, 37, 38, 40, 43, 46, 49] studied the effects of vitamin D supplementation versus placebo on FPG serum level, fasting plasma insulin level and HOMA-IR, respectively. As the I^2 statistic indicated significant heterogeneity among the studies (I^2= 80%, 78% and 74%, respectively, all with p<0.001), random effect model was used to pool the data. The estimated overall effect demonstrated vitamin D supplementation in women with GDM led to a significant lower FPG serum level (MD: -10.20 mg/dL, 95%CI: -13.43 mg/dL to-6.96 mg/dL, p<0.001; Fig. 4a), fasting plasma insulin level (MD: MD: -5.02 µIU/mL, 95%CI: -6.83 µIU/mL to -3.20 µIU/mL, p<0.001; Fig. 4b), and HOMA-IR (MD: -1.06 mmol/L, 95%CI: -1.40 mmol/L to - 0.72 mmol/L, p<0.001; Fig 4c).

3.5. The effect of Vitamin D Supplementation During Pregnancy on GDM pregnant outcomes: cesarean section, maternal hospitalization, and postpartum hemorrhage

Nine RCTs with 765 participants[33, 35, 36, 39, 41-43, 47, 50], two RCTs with 105 participants[33, 47] and two RCTs with 328 participants[36, 45] studied the effects of vitamin D supplementation on cesarean section rate, maternal hospitalization, and postpartum hemorrhage, respectively. As the I^2 statistic suggested

low heterogeneity among the studies for these three pregnant outcomes (I^2 = 43%, 0%, and 0%, respectively, all with p>0.05), the fixed-effect model was used to pool the data. The results showed that vitamin D supplementation during pregnancy could significantly reduce maternal cesarean section rate (RR:0.75, 95%CI: 0.63 to 0.89, p=0.0001, Fig. 5a), maternal hospitalization rate (RR: 0.13, 95%CI: 0.02 to 0.98, p=0.05, Fig. 5b), and postpartum hemorrhage (RR: 0.47, 95%CI: 0.22 to 1.00, p=0.05, Fig. 5c) in women with GDM.

3.6. Effect of Vitamin D supplementation during pregnancy on neonatal outcomes: newborn hyperbilirubinemia, newborn hypoglycemia, polyhydramnios, fetal distress, premature delivery, and occurrence of giant children

Seven RCTs with 522 participants[33, 41-43, 47, 49 , 50], six RCTs with 615 participants[36, 41-43, 47, 50], four RCTs with 596 participants[33, 36, 47, 49, 50], five RCTs with 461 participants[33, 36, 42, 43, 47], two RCTs with 383 participants[36, 45], and eight RCTs with 765 participants[33, 36, 41-43, 45, 47, 50] investigated the effects of vitamin D supplementation on newborns hyperbilirubinemia, occurrence of giant children, hypoglycemia, polyhydramnios, fetal distress, premature delivery, respectively. As the I^2 statistic indicated no heterogeneity among the studies (I^2 = 0%, all with p > 0.10), a fixed effect model was used to pool the data. The estimated total effect implicated that vitamin D supplementation during pregnancy significantly reduced the risk of new hyperbilirubinemia (RR: 0.47, 95%CI: 0.33 to 0.67, p<0.0001; Fig. 6a), giant children (RR: 0.58, 95%CI: 0.38 to 0.89, p=0.01; Fig. 6b), polyhydramnios (RR: 0.42, 95%CI:

0.24 to 0.72, p=0.002; Fig. 6d), fetal distress (RR: 0.46, 95%CI: 0.24 to 0.90, p=0.02; Fig. 6e) and premature delivery (RR: 0.43, 95%CI: 0.26 to 0.73, p=0.002; Fig. 6f), while no significant effect on the risk of newborns' hypoglycemia was observed (RR: 0.82, 95%CI: 0.52 to 1.29, p=0.39; Fig. 6c).

3.7. Publication Bias

No significant publication bias was observed when funnel plots were examined (Supplementary data 2). The results of Egger's tests also did not indicate the presence of publication bias (Supplementary data 3).

4. Discussion

There has been a rapidly growing interest in the protective effects of vitamin D on the risk of GDM and pregnancy outcomes. Results from several meta-analyses have found that there is a significant inverse relationship between serum 25(OH)D concentration and the risk of GDM[26, 51, 52]. Also, vitamin D supplementation has beneficial effects on maternal and neonatal outcomes in normoglycemic pregnant women[53]. However, the therapeutic effects of vitamin D supplements on women with established GDM are still unclear. Jahanjoo *et al* conducted a meta-analysis to evaluate the impact of vitamin D supplementation on maternal and neonatal health outcomes in GDM patients, but the relatively short intervention duration, small sample size, and high degree of heterogeneity among included studies may restrict the application of the finding[18]. Therefore, we performed this systematic review and meta-analysis in pregnant women with established GDM to evaluate the therapeutic effects of vitamin D supplementation on glycemic control and maternal-neonatal outcomes.

Nineteen RCTs fulfilled our eligibility criteria and were included in this review. In our meta-analysis of RCTs, vitamin D supplementation elicited a statistically significant decrease in FPG, insulin concentration, and HOMA-IR. These findings were consistent with the results from previous studies[18, 21], which suggested that vitamin D might help glycemic control in pregnant women through increasing the absorption of glucose by cells directly or through the enhancement of insulin sensitivity[54]. On the other hand, there were also reports showing no favorable effect

of vitamin D administration on FPG[27, 55]. One possible reason for the contradicting results may be due to the inclusion of non-GDM patients who had higher baseline levels of vitamin D[55]. Besides, the heterogeneity among the studies included in the meta-analysis conducted by Akbari *et al* was high, which would likely lead to a negative result[27]. Furthermore, the dosage of vitamin D and study duration varied among these studies, which could be important confounding factors that contributed to the contradicting results.

GDM is associated with a well-documented range of adverse pregnancy outcomes for both mother and fetus, including macrosomia, cesarean section, induction of labor, large for gestational age, and shoulder dystocia[56-58]. In our study, vitamin D supplementation was associated with reduced risk of maternal cesarean section, maternal hospitalization, and postpartum hemorrhage. Moreover, vitamin D supplementation during pregnancy significantly reduced the risk of newborn hyperbilirubinemia, giant children, polyhydramnios, fetal distress, and premature delivery. These findings were partially consistent with the results of Jahanjoo *et al*, in which it was shown that supplementation of GDM women with vitamin D may lead to an improvement in FPG, serum lipids, and newborns hyperbilirubinemia[18]. Palacios *et al* also found that supplementation with vitamin D alone or vitamin D plus calcium reduced the risk of pre-eclampsia[59]. However, the results from a study conducted by Perez-Lopez *et al*[17] suggested that vitamin D supplementation did not influence the maternal and neonatal outcomes in women with GDM. Although there is a biological rationale for the beneficial effects of vitamin D

on the maternal and neonatal adverse outcomes[60], evidence was still limited. For example, there were only two RCTs reported the effects of vitamin D supplementation on maternal hospitalization[33, 47], postpartum hemorrhage[36, 45], and fetus distress[36, 45], respectively, even the results were statistically significant. Therefore, larger and better-designed RCTs are warranted to confirm the findings of our study.

The strengths of this study include the large sample size (19 RCTs with 1550 GDM women), relatively high quality, and low heterogeneity among the studies included, which may increase the reliability of the results. Besides, we comprehensively evaluate the effects of vitamin D supplementation on glycemic control, maternal and neonatal outcomes, to gain a better understanding of the benefits of vitamin D supplementation in women with established GDM. However, our study still has some limitations. First, both studies used vitamin D supplement only and vitamin D plus other supplements were enrolled and analyzed together in our study. Thus, whether there were interfering effects of the other supplements on the outcomes in the participants were unclear. To answer this question, we re-analyzed the data, and the results indicated that both vitamin D supplement alone and vitamin D plus other supplements could significantly reduce FPG and insulin concentrations in women with GDM, and there was no significant difference between the two groups (supplementary data 4, Fig. S1 and Fig.S3). However, vitamin D plus other supplements could significantly reduce the HOM-IR, while vitamin D supplement alone did not have such effects (Fig. S2). Thus, it is necessary to identify what is the

interfering component(s) from other supplements.

Second, the doses, route, and intervention duration of vitamin D supplementation varied among the included studies. To address this issue, we also re-analyzed the data, and it was found that that oral but not intramuscular administration of vitamin D could significantly improve FPG in the participants (Fig. S4). This discrepancy can be explained in part by the limited number of the studies (only two studies) in the intramuscular administration group. Besides, in the intramuscular administration group, obese participants (BMI:28.9±4.8) were enrolled in one study[35], which may also influence the pooled effect of vitamin D supplement on glucose-insulin homeostasis in this group[61] . Moreover, we found that the length of intervention did not influence the beneficial effects of vitamin D supplementation on FPG (Fig. S5), insulin concentration (Fig. S6), HOMA-IR (Fig. S7) and neonatal hypoglycemia (Fig. S8). Finally, we examined the effects of different doses on the final outcomes. The studies were arbitrarily divided into two classes: <800 IU/d and ≥800 IU/d. The results indicated that, vitamin D supplements could significantly improve FPG (Fig.S9), HOMA-IR (Fig. S11), cesarean section (Fig. S12), and premature delivery (Fig. S16) in GDM patients at both doses. However, when the dose was less than 800 IU/d, vitamin D supplements had no significant effects on neonatal hypoglycemia (Fig.S13) and giant children (Fig. S14). Still, more studies were required to confirm these findings.

Besides, all of these studies are single-center trials, which tend to exhibit greater therapeutic effects compared to multi-center RCTs, and hence, the results should be

used with caution in decision-making[62]. Additionally, no trial evaluated the adverse events of vitamin D supplementation. Therefore, whether a linear correlation exists between vitamin D supplementation and maternal-neonatal outcomes is not clear. And finally, tolerable upper intake level (UL) of vitamin D supplementation in women with GDM remains to be determined.

In conclusion, the results of this study demonstrate that vitamin D supplementation could improve glycemic control in women with established GDM. This review also shows that vitamin D supplementation can reduce the adverse maternal and neonatal outcomes related to GDM. However, due to the limited number of studies included, the conclusions should be interpreted with caution. Further studies are warranted to confirm the findings from our study and to fully understand the underlying mechanisms by which vitamin D affects glucose metabolism and maternal-neonatal outcomes.

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Author contribution

All authors contributed to the design of the research (project conception, development of the overall research plan) and approved the final manuscript; M.W., Z.C., X.X, and J. Y. designed and conducted the research (conducted the systematic search, screened the literature, and extracted the data); M. W. completed the first draft of the manuscript; Y. H., Y.W., Y.W., F.L., and H.L. analyzed the data and performed the statistical analyses; X.X. had primary responsibility for final content; J. Y. critically reviewed the manuscript.

Conflict of Interest

None of the other authors reported a conflict of interest related to the study.

Figure legends

Figure 1. Diagram for the search and selection process of articles included in this review.

Figure 2. Risk of bias graph per type of bias assessed.

Figure 3. Diagram of bias in the included studies.

Figure 4. Forest plot of glucose parameter. (a) effect of vitamin D supplementation on FPG; (b) effect of vitamin D supplementation on Insulin; (c) effect of vitamin D supplementation on HOMA-IR.

Figure 5. Forest plot of maternal outcomes. (a) effect of vitamin D supplementation on cesarean section; (b) effect of vitamin D supplementation on maternal hospitalization; (c) effect of vitamin D supplementation on postpartum hemorrhage.

Figure 6. Forest plot of neonatal outcomes. (a) effect of vitamin D supplementation on newborns' hyperbilirubinemia; (b) effect of vitamin D supplementation on giant children; (c) effect of vitamin D supplementation on newborns' hypoglycemia; (d) effect of vitamin D supplementation on polyhydramnios; (e) effect of vitamin D supplementation on fetal distress; (f) effect of vitamin D supplementation on premature delivery.

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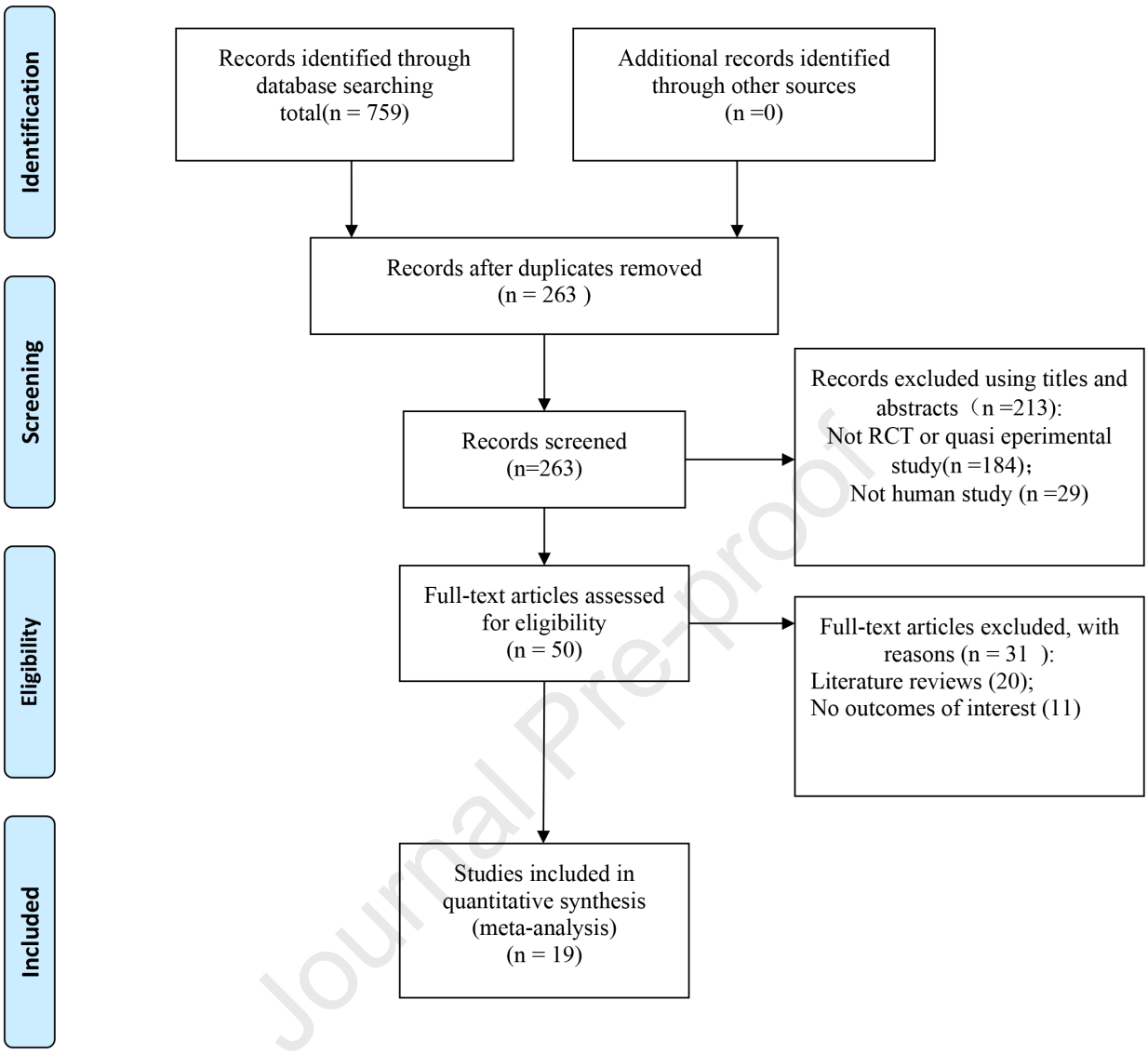
Table 1. Data extraction table for all included studies

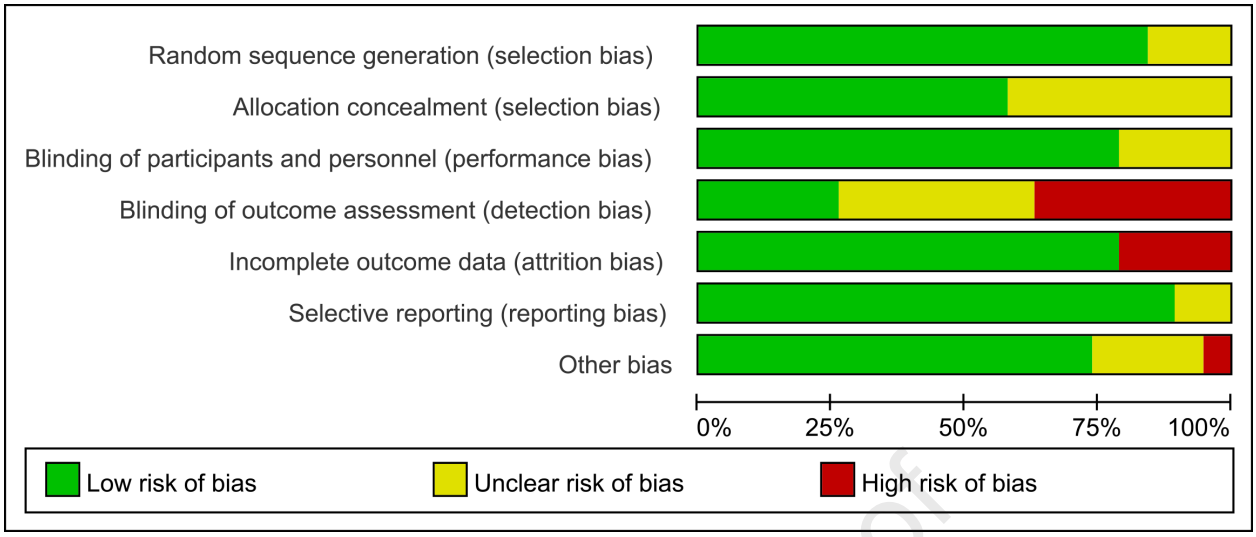
Study	GDM Diagnostic criteria	Country	Journal	Maternal age, year	Gestational age, weeks	Intervention	Control	Approach	Length of study	Sample Size (Intervention, Control)
Jamilian 2017[32]	ADA	Iran	J Clin Lipidol	18～40	24–28	50000 IU VD every 2 weeks + 1000 mg omega-3 fatty acids twice a day	Placebo	oral	6 weeks	70 (35,35)
Karamali 2016[33]	ADA	Iran	Public Health Nutr	18～40	24–28	1000 mg Ca/d + 50 000 IU VD3 twice	Placebo	oral	6 weeks	60 (30,30)
Karamali 2018[34]	ADA	Iran	Appl Physiol Nutr Metab	18～40	24–28	100 mg Mg + 4 mg Zn + 400 mg Ca + 200 IU VD twice a day	Placebo	oral	6 weeks	60 (30,30)
Mozaffari-Khosravi M 2012[35]	Carpenter and Coustan criteria	Iran	Diabet Med	30.7±6.2	24–28	300 000 IU VD3	Nothing	Intramuscular injection	12 weeks	45 (24,21)
Yue 2019[36]	ADA	China	Chinese Contemporary Medicine	18-35	24–28	1200 IU VD3, Once a day	Placebo	oral	12 weeks	238 (116,122)
Zhang Y 2019[37]	Gynecology (8th Edition)	China	Chinese Medicine		24–28	500 IU VD3, twice a day	Placebo	oral	12 weeks	84 (42,42)
Asemi 2014[38]	ADA	Iran	Diabetologia	18-40	24–28	Ca plus VD 50,000 IU VD3 2 times during the study (at baseline and at day 21 of the intervention)	Placebo	oral	6 weeks	56 (28,28)
Hosseinzadeh-Shamsi-Anar 2012[39]	ADA	Iran	Iran J Med Sci	30.7±6.2	24–28	300,000 IU of VD	Nothing	Intramuscular injection	12 weeks	45 (24,21)
Jamilian 2016[40]	ADA	Iran	Lipids	28.4 ± 6.2	24–28	1000IU VD+1000mg evening primrose oil	Placebo	oral	6 weeks	60 (30,30)

Mao 2019[41]	Gynecology (8th Edition)	China	Chinese Modern Doctor	18-35	16–20	400U VD/day	Placebo	oral		118 (59, 59)
Jamilian 2019[42]	ADA	Iran	BMC Pregnancy Childbirth	27.7-33	24–28	100 mg Mg+4 mg Zn+400 mg Ca + 200IU VD twice a day	Placebo	oral	6 weeks	60 (30,30)
Jamilian 2018[43]	ADA	Iran	Clin Nutr		24–28	50000IU VD, 8*10^9 CFU/g Probiotics	Nothing	oral	6 weeks	58 (30,28)
Liu Y 2015[44]	ADA	China	Chinese Modern Medicine Application	30-40	36±2.2	VD3,7.5mg	Nothing	Intramuscular injection	15 days	85 (44,41)
Li L 2019[45]	Gynecology	China	Clinical research	29.3±4.23	35.2±5.23	400IU VD3	Nothing	oral		90 (45,45)
Asemi 2013[46]	ADA	Iran	Am J Clin Nutr	31.5 ± 6.1	24–28	50,000 IU VD3 2 times during the study (at baseline and at day 21 of the intervention)	Placebo	oral	6 weeks	54 (27,27)
Asemi 2015[47]	ADA	Iran	Horm Metab Res	30.9±5.8		50,000 IU VD3 2 times during the study (at baseline and at day 21 of the intervention)	Placebo	oral	6 weeks	45 (22,23)
Li Q 2016[48]	ADA	China	Ann Nutr Metab	28±4	13-15	2 servings (200g) of supplemented yogurt per day (500 IU VD3 per serving)	Placebo	oral	16 weeks	97 (48,49)
Yazdchi 2016[49]	IADPSG	Iran	Nutr Res Pract	31.88±4.0	24–28	50,000 IU of VD3/every 2 weeks	Placebo	oral	8 weeks	72 (36,36)
Valizadeh 2016[50]	ADA	Iran	Int J Endocrinol Metab	32±5		VD3	Placebo	oral		96 (48,48)

Note：VD：Vitamin D； T: test group； C: Control group； IU: international unit；GDM: gestational diabetes mellitus; ADA：American Diabetes

Association; IADPSG：International Diabetes and Pregnancy Study Group；





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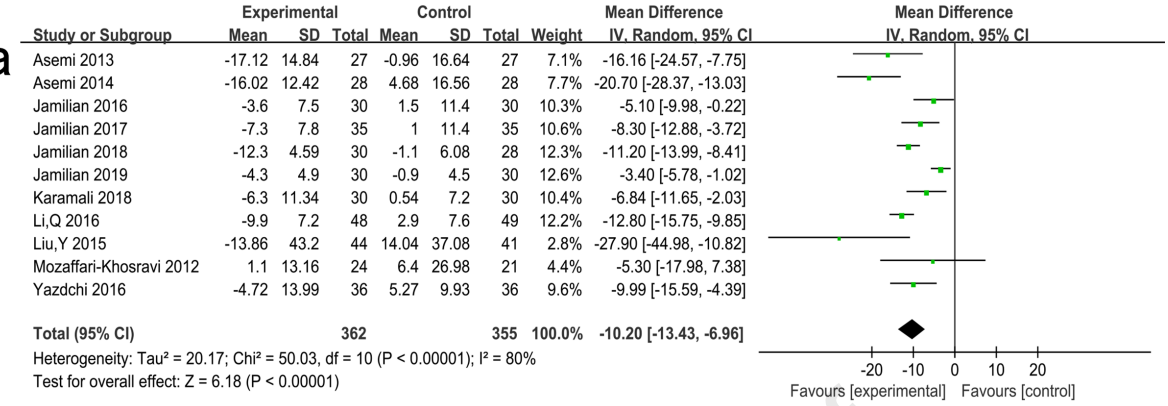

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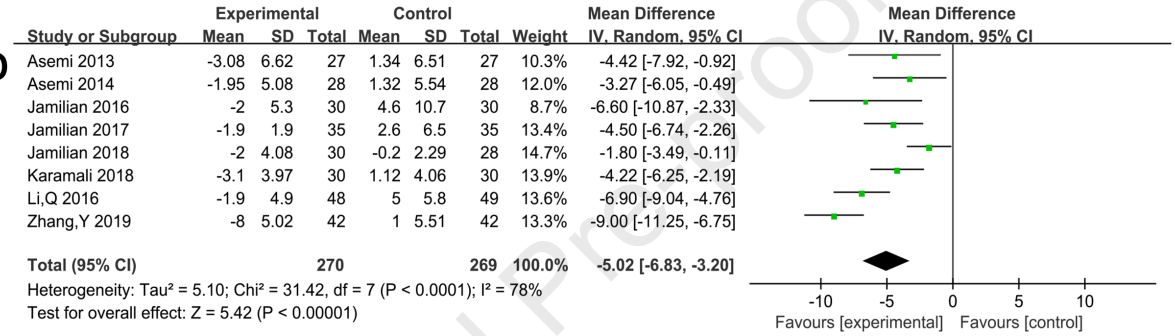

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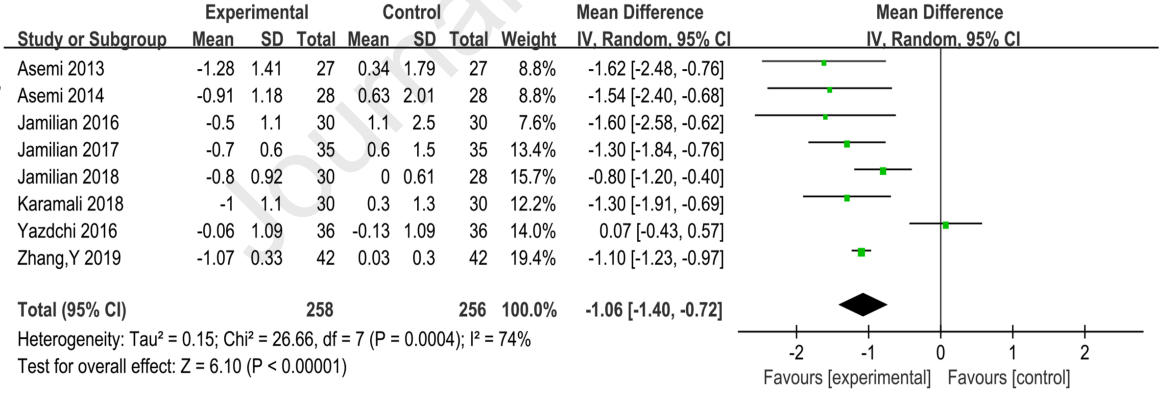

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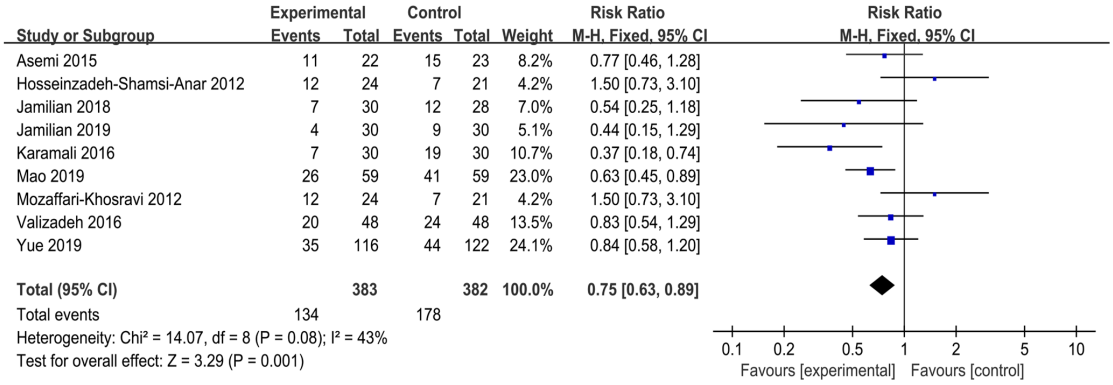

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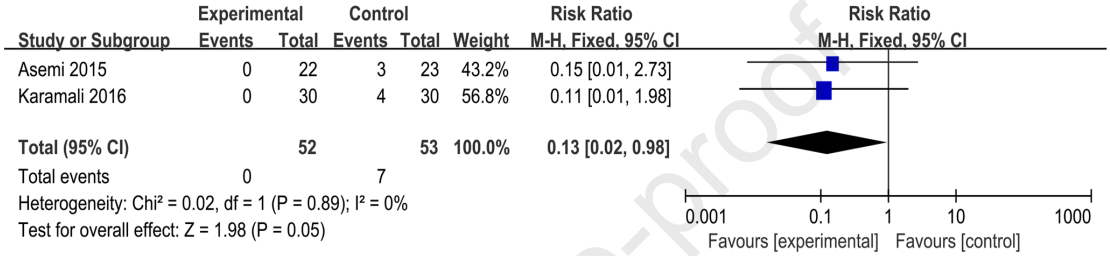

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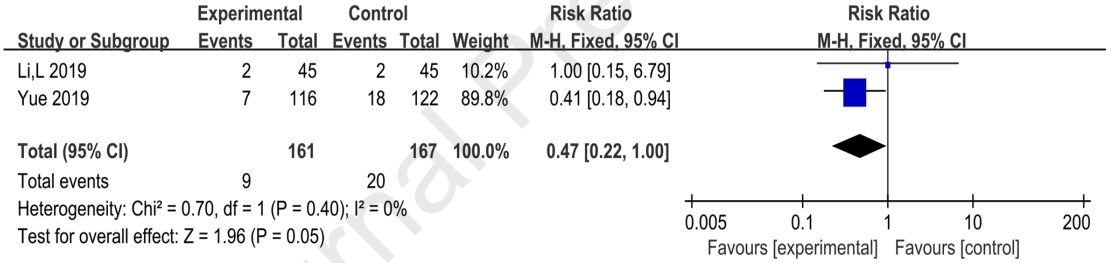

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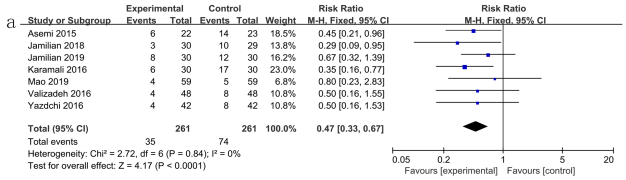

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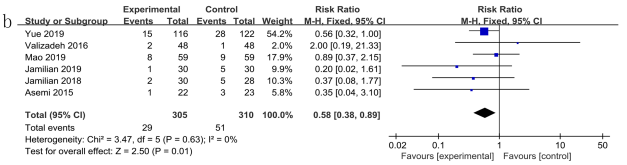

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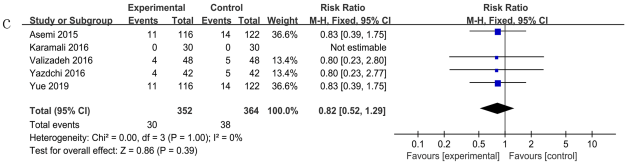

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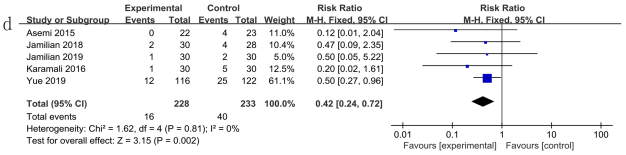

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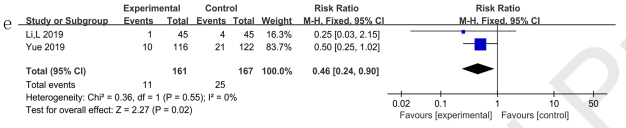

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