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Vitamin D Supplementation during Pregnancy: An Evidence Analysis Center Systematic Review and Meta-Analysis

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ABSTRACT

Background Given the high rates of vitamin D deficiency among pregnant women and possible effects on offspring health, a systematic review on this topic was conducted to help inform future practice guidelines.

Objective To evaluate associations between maternal vitamin D supplementation, maternal 25-hydroxyvitamin D (25(OH)D) concentrations, and health outcomes.

Methods A PubMed literature search was conducted to identify studies that examined the health effects of vitamin D supplementation during pregnancy on maternal and infant health outcomes published from 2000 to 2016. Among 976 identified publications, 20 randomized clinical trials met the inclusion criteria. The initial search was extended to include five studies published between July 2016 and September 2018.

Main outcome measures Maternal and infant 25(OH)D concentrations, gestational diabetes, preeclampsia or gestational hypertension, cesarean section, maternal parathyroid hormone and calcium concentrations, and infant gestational age, birth weight, and birth length.

Statistical analyses Mean differences, odds ratios, and 95% CIs were calculated, only for the initial search, using separate random-effects meta-analyses for each outcome.

Results Evidence was good or strong that maternal vitamin D supplementation significantly increased maternal (13 studies, n=18, mean difference, 14.1 ng/mL [35.2 nmol/L]; 95% CI=9.6-18.6 ng/mL [24.0-46.4 nmol/L]) and infant (nine studies, n=12; 9.7, 5.2, 14.2 ng/mL [24.2, 12.9, 35.5 nmol/L]) 25(OH)D concentrations, although heterogeneity was significant (I^2=95.9% and I^2=97.4, respectively, $P<0.001$). Evidence was fair that vitamin D supplementation significantly decreases maternal homeostatic model assessment-insulin resistance (five studies, n=7; −1.1, −1.5, −0.7) and increases infant birth weight (nine studies, n=11, 114.2, 63.4, 165.1 g), both had insignificant heterogeneity. A null effect of maternal supplementation on other maternal (preeclampsia, cesarean section) and infant (gestational age, birth length) outcomes was found.

Conclusions Results show vitamin D supplementation during pregnancy improves maternal and infant 25(OH)D concentrations and may play a role in maternal insulin resistance and fetal growth. To further inform practice and policies on the amount of vitamin D, which supports a healthy pregnancy, high quality dose-response randomized clinical trials, which assess pregnancy-specific 25(OH)D thresholds, and appropriately powered clinical outcomes are needed.

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Supplementary materials: *Figures 4, 5, 7, 8, 10, and 12 are available at www.jandonline.org*

PREGNANT WOMEN AND NEWborns have been described as a population at increased risk for vitamin D deficiency.[1] According to a 2016 systematic review, the prevalence of vitamin D deficiency, defined by the authors as serum 25-hydroxyvitamin D (25(OH)D)<20 ng/mL (50 nmol/L), was reported as 64% of women from the Americas, 57% from Europe, 46% from the Eastern Mediterranean, 87% from Southeast Asia, and 83% from the Western Pacific.[1] The high prevalence of maternal vitamin D deficiency may be related to changes in lifestyle (sun exposure and dietary intake) rather than increased physiological requirements as the mother can provide calcium to the fetus without requiring vitamin D.[1-4] Furthermore, women who have greater skin melanin, immigrant (particularly if emigrated from more sunny climates) and veiled or covered are considered at particular high risk for deficiency as endogenous production of vitamin D from ultraviolet exposure is limited.[5,6] Because the fetus is dependent on maternal vitamin D, vitamin D deficiency may lead to consequences for maternal health as well as fetal and infant growth and development. Given the high rates throughout the world, vitamin D deficiency is a potential public health problem.

There is considerable ongoing discussion about the circulating 25(OH)D cut points, which are associated with deficiency, adequacy, and optimal health.[4] In older adults, the threshold has been defined as the concentration of 25(OH)D, which maximally suppresses parathyroid hormone (PTH) and minimizes bone loss.[7] The National

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Academy of Medicine defines 25(OH)D concentrations<12 ng/mL (30 nmol/L) as deficient, 12 to 20 ng/mL (30 to 50 nmol/L) as inadequate, and ≥20 ng/mL (50 nmol/L) as adequate for bone health, and concentrations>50 ng/mL (125 nmol/L) are associated with potential adverse effects.[4] The Endocrine Society recommends a higher cutoff of >30 ng/mL (75 nmol/L) and suggests pregnant women may require 1,500 to 2,000 IU daily to achieve these levels.[8] In North America, the current recommended dietary allowance (600 IU/day) is considered sufficient to achieve a vitamin D status of 20 ng/mL (50 nmol/L) for 97.5% of all pregnant and nonpregnant women.[4] When setting these current recommendations, there was insufficient evidence to increase amounts for pregnant women.[4] The unavailability of guidelines that increase dietary recommendations during pregnancy was based primarily on insufficient available evidence linking higher maternal 25(OH)D level with optimal maternal or fetal skeletal outcomes. Despite this, some observational studies have reported a beneficial effect of maternal vitamin D status on offspring skeletal development later in life.[9,10] As a result of the increased risk of vitamin D deficiency and absence of specific guidelines during pregnancy, there is a need for studies to address this gap to inform policy makers who establish nutrition guidelines, as well as nutrition or dietetics practitioners who provide nutrition counseling for women during pregnancy.

Defining the daily dose sufficient to ensure vitamin D adequacy is further complicated by the fact that vitamin D status is affected by a number of factors including maternal baseline vitamin D status, prepregnancy body weight, ultraviolet exposure, sunscreen use, skin pigmentation, seasonality, latitude, and genetics. As sunshine exposure is not considered a safe nor sustainable source of vitamin D, vitamin D should be supplied during pregnancy through exogenous sources.[11] Natural dietary sources of vitamin D are limited in many commonly consumed foods in the United States, and as such, most North American populations rely on vitamin D-fortified sources such as milk and dairy products to meet their needs.[12] However, mandatory vitamin D fortification is not universal practice in all countries including Europe.[12,13] As a result, many pregnant women rely on vitamin D supplementation predominately through prenatal supplementation as their main source of vitamin D. Although adherence with daily prenatal supplementation is high (reported as 72% to 80%), many commercially available supplements contain just 400 IU of vitamin D per day, which according to some experts may be lower than ideal.[14,15]

To facilitate the development of clinical practice guidelines, the question of the appropriate vitamin D requirement for a healthy pregnancy, encompassing perinatal outcomes, needs resolution. Research suggests an association between vitamin D status and pregnancy complications such as preeclampsia, gestational diabetes mellitus (GDM), and risk of cesarean section, which have also been the focus of previous reviews and meta-analyses.[16,17] In addition, low maternal vitamin D status may impact offspring length of gestation and potentially fetal growth.[18-20] The association between maternal vitamin D status and health outcomes is evolving, yet our understanding of the effect of vitamin D intake on 25(OH)D status is still unclear. Well-designed and executed randomized clinical trials (RCTs) are considered to provide the strongest evidence for the role of vitamin D supplementation during pregnancy. The purpose of this systematic review and meta-analysis of eligible RCTs was to evaluate associations between maternal vitamin D supplementation and maternal and infant health outcomes.

MATERIALS AND METHODS

Evidence Analysis Team and Process

This project was undertaken as part of the Academy of Nutrition and Dietetics Evidence Analysis Library (EAL) project, which uses a rigorous systematic review methodology to synthesis the research literature on topics of interest for Academy members.[21] The Malnutrition in Pregnancy project began in 2016 and included seven registered dietitians or registered dietitians or nutritionists with clinical, community, and research experience in the work group. A thorough recruitment procedure was undertaken with requests for participation posted on the American Academy of Nutrition and Dietetics' website and via e-mail correspondence, which targeted all Academy members, Academy Dietetic Practice Groups, and known experts in the field. The applicants were rubric scored using a set of quantitative and qualitative criteria and potential for conflict of interest. All work group members signed a conflict of interest disclosure form as well as declared verbally any conflicts of interest prior to the start of each work group meeting. A project manager facilitated these meetings with the assistance of a lead analyst. A complete description of the Evidence Analysis Process is available at the Academy's EAL website[21] and is also described by Handu and colleagues (2016).[22] Articles meeting the inclusion criteria were abstracted using the EAL Data Extraction Tool and reviewed for accuracy by EAL analysts. A summary evidence table was constructed for each question along with narrative summaries of evidence.

Literature Search and Application of Inclusion and Exclusion Criteria

A comprehensive literature search of PubMed was conducted to identify studies that examined the health effects of diet and supplementation of vitamin D during pregnancy on maternal and infant (defined as <1 year of age) health outcomes. Full-length studies meeting the eligibility criteria included human studies that were published in English from 2000 to July 2016. The following search terms were used to identify the vitamin D intervention: "dietary vitamin D," "diet/diet therapy," "25-hydroxy D3/calcidiol," "1,25 dihydroxyvit D," "cholecalciferol (D3)," "ergocalciferol (D2)," "sun exposure," and "endogenous production." To enable the interpretation of primary meta-analyses, outcomes were identified based on the number of studies with available outcome data, in combination with considerations for the outcomes' relative importance in the field. Due to a considerable number of RCTs included, only RCTs or clinical controlled studies were included in this review. Additional inclusion criteria were mean maternal age between 15 and 55 years of age, a minimum of 10 study participants and a dropout rate less than 30% compared with 20% used by previously reported reviews, with our higher rate

adopted due to longer follow-up period required to observe pregnancy and neonatal outcomes. Articles were excluded from consideration if it was unclear whether vitamin D supplementation was included in the study, if participants were above specified age range, or if the study was published in a non-peer-reviewed journal; and only full-length articles were considered. Studies with the same authors and reporting on a similar (or subset) population were excluded. The work group members and lead analysts assessed all studies identified in the PubMed search for relevance. As a quality check, analysts and lead analysts who worked on data extraction then reassessed these articles for eligibility. Twenty RCTs that examined the relationship between vitamin D supplementation during pregnancy and maternal or infant health outcomes met the inclusion criteria (Figure 1). Food-based

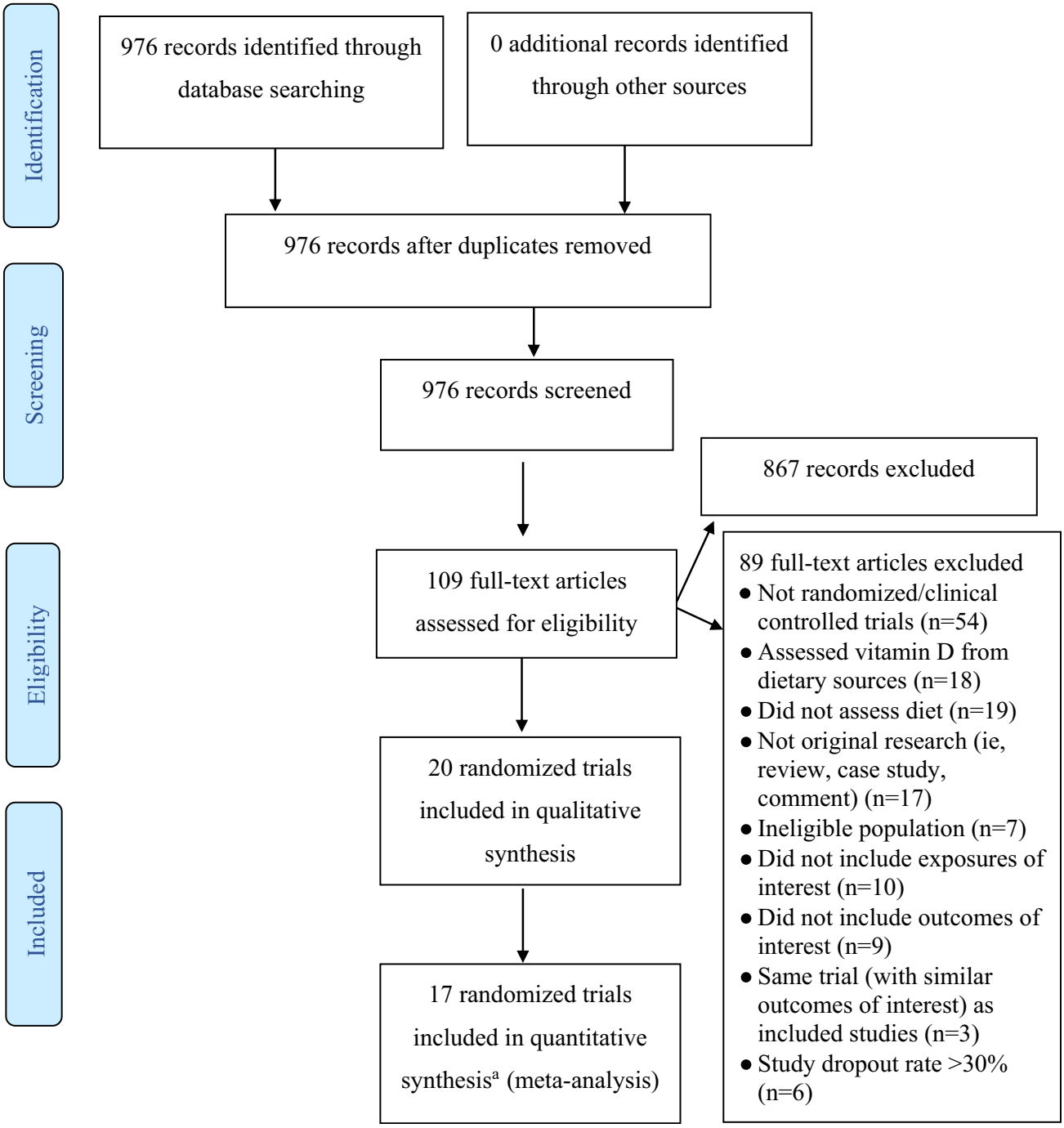

Figure 1. Search strategy flow diagram. Based on Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6(7):e1000097.[23] [a]Included in one or more separate meta-analysis for outcome of interest.

interventions were sought yet, none met the inclusion criteria. The Academy's online data extraction tool was used to extract and store data from the research articles. Trained analysts or methodology experts extracted the following data from each eligible research article: title, year and journal of publication, study design, intervention and control groups, details of interventions (study location, population, duration and dose of intervention, baseline vitamin D status, and quantification method for vitamin D) if applicable, confounding variables considered in the analysis, and outcomes of interest (ie, other nutrients). A second reviewer (lead analyst) verified the accuracy of data entered into the data extraction tool. Positive, negative, or neutral ratings reflect the risk of bias rating for each study. The Academy uses Quality Criteria Checklist as a risk of bias tool to assess the quality of each study, which includes 10 domains on scientific soundness (see Handu and colleagues[22] for explanation of rating system). Positive rating means risk of bias in that study is very low, negative rating means that the study has high risk of bias, and neutral rating means that the study has moderate risk of bias. Any discrepancies in ratings were resolved by a third analyst. A detailed description of each trial is shown in Table 1.

Statistical Analyses

For continuous outcomes, mean difference (MD) and 95% CI were calculated as summary statistics for the statistical analysis. The dichotomous variables were presented as odds ratio (OR) (95% CI). Random-effects models were used to account for variations both within and between studies.[44] Each arm of a multi-arm study was presented separately and (each intervention was compared with the same comparison or control group). The denominator for each outcome was the total number of participants in each arm of the trial that were analyzed. A subgroup meta-analyses was performed for maternal and infant 25(OH)D concentrations to control for maternal baseline 25(OH)D status. As there is inconsistency in vitamin D status cutoff points, the following were established based on previous research[4,8]: deficient (<12 ng/mL [<30 nmol/L]), insufficient (12 to 20 ng/mL [30 to 50 nmol/L]), and sufficient (20 to 30 ng/mL [50 to 75 nmol/L]). No studies included maternal baseline 25(OH)D≥30 ng/mL (75 nmol/L). Cochran's Q and I^2 tests of heterogeneity were performed to identify heterogeneity among studies. Significant heterogeneity was noted with P values<0.10 in Cochran's Q statistic. I^2 values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively.[45] Funnel plots and Egger tests were used to evaluate publication bias.[46] All the meta-analyses were performed using R software (version 3.4.2). Results from studies excluded from meta-analyses because data were presented in a manner not consistent for comparison can be found in Figure 2.

Development of Conclusion Statements

Evidence summaries and conclusion statements on the effects of vitamin D supplementation in pregnancy and maternal and infant health outcomes were drafted by the workgroup and lead analyst based on evidence analysis after completion of the data extraction process. The EAL Manual for Grading the Strength of the Evidence[47] was used for grading the conclusion statements according to the following grades: grade I (good or strong), grade II (fair), grade III (limited or weak), grade IV (expert opinion only), or grade V (grade not assignable).

RESULTS

Research Reviewed

Among the 20 studies meeting inclusion criteria, there were 16 positive-quality RCTs[25-31,33-37,40-43] and four neutral-quality randomized controlled trials.[24,32,38,39] Trials were conducted in North America,[32,35] Europe,[42,43] Oceania,[30,41] and Asia.[24-29,31,33,34,36-40] Studies did not consistently report on ethnicity or skin pigmentation as well as season and body mass index—all variables known to affect vitamin D status. Sample size ranged from 21[36] to 169[32] per group. The majority (14 studies) included women without comorbidity, although four[26-28,36] included women with GDM and two[24,34] included women at risk for preeclampsia. Two studies[38,39] supplemented participants based on maternal baseline status and included a mixture of baseline vitamin D status. Overall, seven studies included women with mean baseline 25(OH)D in the deficient (<12 ng/mL [<30 nmol/L]) range,[29,33,36,39,40,42,43] seven insufficient (12 to 20 ng/mL [30 to 50 nmol/L]),[25,27,28,31,34,37,41] four sufficient (20 to 50 ng/mL[50 to 75 nmol/L]) range,[26,30,32,35] and one not reported.[24] Eight[26-29,31,32,35,40] studies used a placebo as a comparison group, one used 200 IU/d,[40] five used 400 IU/d,[31,32,35,41] one used 600 IU/d,[42] four used routine care (no vitamin D),[33,36,38,43] and two[29,39] compared two or more high-dose vitamin D regimens. Intervention dosages varied considerably from 200 IU daily[24] to four doses of 120,000 IU.[38] Only one study[42] tested an ergocalciferol (vitamin D-2) supplement. Three studies[24,27,31] compared oral vitamin D plus calcium supplementation. In all studies, women were recruited and started supplementation at 12 weeks' gestation. Supplementation periods ranged from a minimum of 40 days[34] to 12 weeks[31,36,42] with some following mothers until delivery[32,33,37-42] or up to 8 weeks postpartum.[35] Only two studies[30,37] used chromatography-tandem mass spectrometry techniques (gold standard method) to measure circulating 25(OH)D concentrations.

Maternal Outcomes

Vitamin D Status: Circulating 25(OH)D Concentrations. Eighteen studies examined the effects of maternal dietary supplements of vitamin D on maternal 25(OH)D—sixteen positive[25-31,33-37,40-43] and two neutral quality.[32,38] The effects of maternal dietary supplements of vitamin D on maternal 25(OH)D concentrations were consistent. Maternal dietary supplements of vitamin D were associated with a significant (P<0.001) increase in maternal 25(OH)D concentrations. The pooled mean increase in maternal 25(OH)D concentration was 14.1 ng/mL (35.2 nmol/L) (95% CI=9.6-18.6 ng/mL [24.0-46.4 nmol/L]) with significant heterogeneity (I^2=95.9%, P<0.001) (Figure 3). Overall, the increase in 25(OH)D ranged from 0.1 ng/mL to 37.8 ng/mL (0.3 nmol/L[42] to 94.6 nmol/L).[37]

Subgroup analysis, based on maternal baseline vitamin D status (Figure 3), found mothers in the insufficient range (12 to 20 ng/mL [30 to 50 nmol/L]) experienced the highest increase in circulating 25(OH)D (20.2 [50.4], 95% CI=12.5 to 27.8 ng/mL [31.2 to 69.6 nmol/

Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a]

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Asemi and colleagues, 2012[24]	Kashan, Iran (34°N)	n=54; 18-35 y old; pregnant women at risk for preeclampsia, primigravida; singleton pregnancy	Calcium-vitamin D group (n=27): 500 mg carbonate calcium and 200 IU vitamin D-3/day Placebo group (n=27): identical coded tablets (lactose) Duration: 9 wk (25 wk gestation at baseline)	N/A[b]	N/A
Asemi and colleagues, 2013[25]	Kashan, Iran (34°N)	n=54; 18-40 y old; pregnant women without major comorbidity (eg, gestational diabetes); primigravida; singleton pregnancy	Vitamin D group (n=27): 400 IU vitamin D-3/day Placebo group (n=27): identical coded tablets Duration: 9 wk (25 wk gestation at baseline)	Vitamin D group: 44.5±3.3 nmol/L; 5 (21%) <30 nmol/L; 12 (50%) <50 nmol/L Placebo group: 36.25±3 nmol/L; 11 (46%) <30 nmol/L; 20 (83%) <50 nmol/L	Enzyme-linked immunosorbent assay
Asemi and colleagues, 2013[26]	Kashan, Iran (34°N)	n=54; 18-40 y old; pregnant women with GDM[c]	Vitamin D group (n=27): 50,000 IU vitamin D-3 two times (baseline and at day 21 of intervention) Placebo group (n=27): two placebos (same times as vitamin D group) Duration: 6 wk (24-28 wk gestation at baseline)	Vitamin D group: 51.1±35.8 nmol/L Placebo group: 51.0±33.6 nmol/L	Enzyme-linked immunosorbent assay
Asemi and colleagues, 2014[27]	Kashan, Iran (34°N)	n=56; 18-40 y old; pregnant women with GDM	Calcium-vitamin D group (n=28): 1,000 mg calcium carbonate/day and 50,000 IU vitamin D-3 two times (baseline and at day 21 of intervention) Placebo group (n=28): placebos for calcium (daily) and vitamin D (same times as calcium-vitamin D group) Duration: 6 wk (24-28 wk gestation at baseline)	Calcium-vitamin D group: 43.1±28.2 nmol/L Placebo group: 49.1±34.3 nmol/L	Enzyme-linked immunosorbent assay

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Asemi and colleagues, 2015[28]	Kashan, Iran (34°N)	n=50; 18-40 y old; pregnant women with GDM; primigravida	Vitamin D group (n=25): 50,000 IU vitamin D-3 two times (baseline and at day 21 of intervention) Placebo group (n=25): two placebos (same times as vitamin D group) Duration: 6 wk (24-28 wk gestation at baseline)	Vitamin D group: 47.3±36.3 nmol/L Placebo group: 52.3±35.8 nmol/L	Enzyme-linked immunosorbent assay
Dawodu and colleagues, 2013[29]	Al Ain, United Arab Emirates (24°N)	n=192; 26.8±5.3 y old; pregnant women without major comorbidity (eg, disease that may affect calcium and vitamin D levels); singleton pregnancy	4,000 IU vitamin D group (n=63): 3,600 IU vitamin D-3/day (40-day supply) and 400 IU vitamin D-3/day (90-day supply) 2,000 IU vitamin D group (n=65): 1,600 IU vitamin D-3/day (40-day supply) and 400 IU vitamin D-3/day (90-day supply) 400 IU vitamin D group (n=64): placebo/day (40-day supply) and 400 IU vitamin D-3/day (90-day supply) Duration: 40 days (intervention) + additional 50 days (on 400 IU vitamin D-3/day—existing recommended intake) (12-16 wk gestation at baseline)	4,000 IU vitamin D group: 19.5 nmol/L 2,000 IU vitamin D group: 20.5 nmol/L 400 IU vitamin D group: 21.5 nmol/L Overall: 75% <25 nmol/L, 23% 25-<50 nmol/L	Radioimmunoassay
Grant and colleagues, 2014[30]	Auckland, New Zealand (37°S)	n=260; 28±6, 27±6, and 26±7 y old (in the three groups); pregnant women without major comorbidity (eg, disease that may affect calcium and vitamin D levels); singleton pregnancy	Higher-dose vitamin D group (n=86): mother 2,000 IU vitamin D-3/day and infant 800 IU vitamin D-3/day Lower-dose vitamin D group (n=87): mother 1,000 IU vitamin D-3/day and infant 400 IU vitamin D-3/day Placebo group (n=87): mother placebo and infant placebo Duration: mother: enrollment until delivery; Infant: birth until 6 mo (26-30 wk gestation at baseline) Only maternal supplementation (until delivery) was reported for this study	Higher-dose vitamin D group (median, 25th, 75th centile): 55 (32.5, 87.5) nmol/L; 45% ≤50 nmol/L; 64% ≤75 nmol/L Lower-dose vitamin D group: 57.5 (40, 90) nmol/L; 36% ≤50 nmol/L; 63% ≤75 nmol/L Placebo group: 55 (32.5, 80) nmol/L; 46% ≤50 nmol/L; 70% ≤75 nmol/L	Isotope-dilution liquid chromatography-tandem mass spectrometry

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Hashemipour and colleagues, 2014[31]	Qazvin, Iran (36°N)	n=130; 27.6±4.6 and 27.0±4.6 y old (in the two groups); pregnant women with vitamin D deficiency or insufficiency (25(OH) D<50 and 50-75 nmol/L, respectively) but without major comorbidity (eg, disease that may affect calcium and vitamin D levels); singleton pregnancy	Vitamin D group (n=65): 200 mg calcium/day, multivitamin (including 400 IU vitamin D-3)/day, and 50,000 IU vitamin D-3/wk Control group (n=65): 200 mg calcium/day and multivitamin (including 400 IU vitamin D-3)/day Duration: 8 wk (24-26 wk gestation at baseline)	Vitamin D group: 39.8±14.0 nmol/L; 68% <50 nmol/L; 33% 50-75 nmol/L Control group: 44.0±12.0 nmol/L; 66% <50 nmol/L; 34% 50-75 nmol/L	Enzyme-linked immunosorbent assay
Hollis and colleagues, 2011[32]	South Carolina, USA (34°N)	n=502; 17-44 y old; pregnant women; singleton pregnancy without major comorbidities	4,000 IU vitamin D group (n=169): 3,600 IU vitamin D-3/day and 400 IU vitamin D-3/day 2,000 IU vitamin D group (n=167): 1,600 IU vitamin D-3/day and 400 IU vitamin D-3/day 400 IU vitamin D group (n=166): placebo/day and 400 IU vitamin D-3/day Duration: enrollment until delivery (12-16 wk gestation at baseline)	4,000 IU vitamin D group: 58.2±21.8 nmol/L 2,000 IU vitamin D group: 58.3±22.3 nmol/L 400 IU vitamin D group: 61.6±27.1 mol/L	Radioimmunoassay
Hossain and colleagues, 2014[33]	Karachi, Pakistan (25°N)	25.2±4.4 and 26.0±3.1 y old (in the two groups); pregnant women without major comorbidity (eg, gestational diabetes); singleton pregnancy	Vitamin D group (n=100): 4,000 IU vitamin D-3/day Routine care group (n= 100): 200 mg ferrous sulfate/day and 600 mg calcium/day Duration: 20 wk gestation until delivery (≤20 wk gestation at baseline)	Vitamin D group: 22.1±29.6 nmol/L Routine care group: 15.8±9.93 nmol/L	Chemiluminescence assay

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n=randomized n based on mothers)	Intervention (n=randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Karamali and colleagues, 2015[34]	Arak, Iran (34°N)	n=60; 18-40 y old; pregnant at risk for preeclampsia	Vitamin D group (n=30): 50,000 IU vitamin D-3 every 2 wk from 20 wk gestation Placebo group (n=30): placebo every 2 wk from 20 wk gestation Duration: 12 wk (20 wk gestation at baseline)	Vitamin D group: 42.5±3.5 nmol/L Placebo group: 42.8±5.53 nmol/L	Enzyme-linked immunosorbent assay
March and colleagues, 2015[35]	Vancouver, British Columbia, Canada (49°N)	n=226; 18-45 y old; pregnant women without major comorbidity (eg, diabetics) and not taking vitamin D supplements (>400 IU)	2,000 IU vitamin D group (n=74): 2,000 IU vitamin D-3/day 1,000 IU vitamin D group (n=76): 1,000 IU vitamin D-3/day 400 IU vitamin D group (n=76): 400 IU μg vitamin D-3/day All groups received a standard supplement that included multiple vitamins and minerals Duration: Enrollment until 8 wk postpartum (13-24 wk gestation at baseline)	2,000 IU vitamin D group: mean (95% CI) 68 (63-73) nmol/L; 0 <30 nmol/L; 5 (7%) <40 nmol/L; 18 (24%) <50 nmol/L; 47 (62%) <75 nmol/L 1,000 IU vitamin D group: 64 (59, 68) nmol/L; 0 <30 nmol/L; 6 (8%) <40 nmol/L; 21 (28%) <50 nmol/L; 58 (76%) <75 nmol/L 400 IU vitamin D group: 67 (63, 71) nmol/L; 0 <30 nmol/L; 4 (5%) <40 nmol/L; 9 (12%) <50 nmol/L; 52 (70%) <75 nmol/L	Chemiluminescence assay
Mozaffari-Khosravi and colleagues, 2012[36]	Yazd, Iran (32°N)	n=45; 30.7±6.2 and 29.5±4.0 y old (in the two groups); pregnant women with gestational diabetes	Vitamin D group (n=24): 300,000 IU vitamin D-3×1 intramuscular injection Control group (n=21): standard of care Duration: 12 wk (24-28 wk gestation at baseline)	Vitamin D group: 25th, 50th, 75th percentiles: 17.05, 24.25, 28.2 nmol/L Control group: 20.00, 25.30, 32.35 nmol/L Overall: 80% <35 nmol/L	Enzyme-linked immunosorbent assay

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Roth and colleagues, 2013[37]	Dhaka, Bangladesh (24°N)	n=160; 18 - <35 y old; pregnant women who had not been using dietary supplement with >400 IU vitamin D/day or with major comorbidities Antenatal vitamin D in Dhaka (aViDD) trial	Vitamin D group (n=80): 35,000 IU vitamin D-3/wk Placebo group (n=80): placebo/wk Duration: enrollment until delivery (26 - <30 wk gestation at baseline)	Vitamin D group: 45.4±18.4 nmol/L; 18 (23%) <30; nmol/L; 32 (40%) 30-49 nmol/L; 25 (31%) 50-79 nmol/L; 5 (6%) ≥80 nmol/L Placebo group: 44.0±20.9 nmol/L; 21 (26%) <30 nmol/L; 32 (40%) 30-49 nmol/L; 21 (26%) 50-79 nmol/L; 6 (8%) ≥80 nmol/L	High-performance liquid chromatography tandem mass spectroscopy
Sablok and colleagues, 2015[38]	New Delhi, India (29°N)	n=180; age: not reported; pregnant women without major comorbidity (eg, osteomalacia, liver dysfunction); singleton pregnancy	Vitamin D group (n=120): vitamin D supplement based on baseline 25(OH)D: *>50 nmol/L (sufficient)*: one dose of 60,000 IU vitamin D-3 at 20 wk *25-50 nmol/L (insufficient)*: two doses of 120,000 IU D_3 at 20 and 24 wk *<25 nmol/L (deficient)*: four doses of 120,000 IU vitamin D-3 at 20, 24, 28, and 32 wk Nonintervention group (n=60): did not receive any supplementation Duration: enrollment until delivery (14-20 wk gestation at baseline)	Vitamin D group: 53 (49%) <25 nmol/L; 27 (25%) 25-50 nmol/L; 28 (26%) >50 nmol/L	Enzyme-linked immunosorbent assay

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Shakiba and colleagues, 2013[39]	Yazd, Iran (32°N)	n=51; 25±3 y; pregnant women	200,000/50,000 IU vitamin D group (n=17): initially treated with 200,000 IU of vitamin D-3 (50,000 IU vitamin D-3/wk) followed by 50,000 IU vitamin D-3/mo (women in this group had serum 25(OH)D levels<75 nmol/L) 100,000 IU vitamin D group (n=17): 100,000 IU vitamin D-3/mo 50,000 IU vitamin D group (n=17): 50,000 IU vitamin D-3/mo Duration: enrollment until delivery (second trimester of pregnancy at baseline)	200,000/50,000 IU vitamin D group: 17.5±7.5 nmol/L; 17 (100%) <50 nmol/L 100,000 IU vitamin D group: 45.0±19.5 nmol/L; 11 (65%) <50 nmol/L 50,000 IU vitamin D group: 40.0±18.5 nmol/L; 9 (53%) <50 nmol/L Overall: 51 (100%) <75 nmol/L	Chemiluminescence assay
Soheilykhah and colleagues, 2013[40]	Yazd, Iran (32°N)	n=120 randomized; (200 IU/d) 25±4.3, (50,000 IU/mo) 26.5±4.5, and (50,000 IU/2 wk) 26.3±4.8 y old; pregnant women without diabetes or gestational diabetes treated with insulin, thyroid or parathyroid disorders, polycystic ovary disease before pregnancy, body mass index before pregnancy >30 kg/m^2, received vitamin D supplementation in prior 6 mo	50,000 IU/2 wk vitamin D group (n=40): 50,000 IU vitamin D-3/2 wk 50,000 IU/mo vitamin D group (n=40): 50,000 IU vitamin D-3/mo 200 IU/day vitamin D group (n=40): 200 IU vitamin D-3/day Duration: enrollment until delivery (12 wk gestation at baseline)	50,000 IU/2 wk vitamin D group: 18.3±14.8 nmol/L 50,000 IU/mo vitamin D group: 18.3±13.3 nmol/L 200 IU/day vitamin D group: 20.8±19.5 nmol/L Overall: mean 25(OH)D: 19.0±15.8 nmol/L (94.7% <50 nmol/L, 4% 50-75 nmol/L, and 0.9% >75 nmol/L)	Chemiluminescence assay

(*continued on next page*)

Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Yap and colleagues, 2014[41]	Sydney, Australia (34°S)	n=179 randomized; 400 IU=28.8±4.9 and 5,000 IU=29.5±4.7 y old (for the two groups at randomization); women not taking ≥1,000 IU vitamin D/day and without major comorbidity (eg, diabetes/history of glucose intolerance in current pregnancy, calcium or vitamin D metabolic disorders, hypercalcemia, renal impairment) and with plasma 25(OH)D levels <80 nmol/L before 20 wk gestation; singleton pregnancy	5,000 IU vitamin D group (n=89): 5,000 IU vitamin D-3/day 400 IU vitamin D group (n=90): 400 IU vitamin D-3/day Duration: enrollment at median gestation of 15.6 (400 IU) and 15.1 (5,000 IU) wk at randomization until delivery	5,000 IU vitamin D group: 50.0±17.5 nmol/L 400 IU vitamin D group: 45.0±17.5 nmol/L	Chemiluminescence assay
Yesiltepe Mutlu and colleagues, 2014[42]	Kocaeli, Turkey (41°N)	n=91; 16-42 y old; pregnant women without calcium metabolism or untreated thyroid disorders; singleton pregnancy	2,000 IU vitamin D group (n=32): 2,000 IU vitamin D-3/day 1,200 IU vitamin D group (n=31): 1,200 IU vitamin D-3/day Control 600 IU vitamin D group (n=28): 600 IU vitamin D-3/day Duration: 3 mo (13-32 wk gestation at baseline)	2,000 IU vitamin D group: 25.0±7.3 nmol/L 1,200 IU vitamin D group: 28.3±10.3 nmol/L Control 600 IU vitamin D group: 24.8±7.3 nmol/L Overall: 98% of women had serum 25(OH)D<50 nmol/L	Enzyme immunoassay

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Table 1. Characteristics of included studies that evaluated the effects of maternal dietary or supplemental vitamin D on maternal and offspring health outcomes, 2000-2016[a] *(continued)*

Author(s), year	Location (latitude)	Population (n=randomized n based on mothers)	Intervention (n=randomized n based on mothers) and duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D
Yu and colleagues, 2009[43]	London, UK (52°N)	n=180 randomized; 18-45 y old; pregnancy women without major comorbidity (eg, preexisting sarcoidosis, osteomalacia, renal dysfunction, tuberculosis)	200,000 IU vitamin D group (n=60): 200,000 IU vitamin D-3—single dose 800 IU/d vitamin D group (n=60): 800 IU vitamin D-2/day No treatment group (n=60): no treatment Duration: enrollment until delivery (27 wk gestation at baseline)	200,000 IU vitamin D group: median (intraquartile range): 26 (21-41) nmol/L; 25 (42%) <25 nmol/L 800 IU/d vitamin D group: 26 (20-37) nmol/L; 27 (45%) <25 nmol/L No treatment group: 25 (21-38) nmol/L; 30 (50%) <25 nmol/L	Not reported

[a]To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.4. To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.5. 25(OH)D of 1 nmol/L=0.4 ng/mL.
[b]N/A=not available.
[c]GDM=gestational diabetes mellitus.

L]) vs mothers in the deficient (<12 ng/mL [<30 nmol/L]) (8.7 [21.8], 95% CI=3.7 to 13.7 ng/mL [9.3 to 34.2 nmol/L]) or sufficient (20 to 30 ng/mL [50 to 75 nmol/L]) ranges (8.8 [22.1], 95% CI=5.4 to 12.3 ng/mL [13.6 to 30.7 nmol/L]). Heterogeneity was significant ($P<0.05$) and ranged from I^2=87.2%, 96.8%, and 67.3% for the deficient, insufficient, and sufficient groups, respectively. The overall strength of the available evidence was scored as grade I (good or strong). The evidence reviewed supports maternal vitamin D supplementation (ranging from a daily dose of 400 IU to up to four doses of 120,000 IU) during pregnancy in women with mixed nutritional status increases maternal circulating 25(OH)D concentrations.

Proportion of Women with Preeclampsia or Gestational Hypertension. Five studies examined the effects of dietary supplements of vitamin D on the development of preeclampsia or gestational hypertension—four positive[28,33,34,41] and one neutral quality.[38] Maternal dietary supplements of vitamin D did not have significant effects on the development of preeclampsia (or related conditions—eg, gestational hypertension). No significant MDs were noted between vitamin D supplementation and placebo or control groups in all included studies. Results indicate a pooled OR of 0.7 (95% CI=0.4 to 1.4) for the proportion of participants who developed preeclampsia without evidence of heterogeneity (I^2=15.6%, P=0.31) and a pooled OR of 0.8 (95% CI=0.3 to 2.2) for the proportion of participants with gestational hypertension without heterogeneity (I^2=47.6%, P=0.15) (Figure 4, available at www.jandonline.org). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed does not support a role for maternal vitamin D supplementation (ranging from a daily dose of 4,000 IU to up to four doses of 120,000 IU) during pregnancy in women with mixed nutritional status on the development of preeclampsia or gestational hypertension.

Markers of Gestational Diabetes: Plasma Glucose Level and Homeostatic Model Assessment Insulin Resistance in Fasting Subjects. Eight studies examined the effects of maternal supplements of vitamin D

Outcomes	Results
Maternal	
Vitamin D status	
Circulating 25(OH)D concentrations	Five studies[29,30,36,38,43] were excluded from the pooled results because data were presented in a manner inconsistent for comparison although their findings were in agreement with the pooled results.
Proportion vitamin D deficient or insufficient	One study[38] (excluded from subgroup analysis) supplemented participants based on maternal baseline status (49% <25 nmol/L, 25% 25-50 nmol/L, and 26% >50 nmol/L) and found that compared with a nonintervention group (46.1±74.2 nmol/L), the vitamin D intervention group (80±51.5 nmol/L) had greater adjusted serum 25(OH)D level (*P* value unreported).
Proportion of women with gestational diabetes (or related values—eg, plasma glucose level in fasting subjects, HOMA-IR[a], hemoglobin A1C, glucose challenge test)	One[41] and two studies[36,41] for glucose and HOMA-IR, respectively, were excluded from the pooled results. Although Yap et al (2014)[41] found no effect on either glucose in fasting subjects or HOMA-IR, Mozaffari-Khosravi et al (2012)[36] found the vitamin D group (25th, 50th, 75th percentile values: 0.4, 0.5, 0.8) had significantly lower HOMA-IR at the end of the intervention compared with the placebo group (0.7, 0.9, 1.0; *P*=0.004).
Parathyroid hormone concentrations and total or albumin-adjusted calcium concentrations	Three studies[29,32,35] were excluded from the pooled results—two studies[29,35] found no significant differences in serum calcium between groups and the other only presented results graphically.[32]
Infant	
Vitamin D status: circulating 25(OH)D concentrations	Three studies[29,30,43] were excluded from the pooled results because data were presented in a manner inconsistent for comparison. Two studies[38,39] supplemented participants based on maternal baseline status (both excluded from subgroup analysis). Sablok et al (2015)[38] supplemented participants based on maternal baseline status (49% <25 nmol/L, 25% 25-50 nmol/L, and 26% >50 nmol/L) and found that compared with a nonintervention group (43.1±81.3 nmol/L), the vitamin D group (56.8±47.5 nmol/L) had greater infant serum 25(OH)D levels (*P* value unreported). Shabika and Iranmanesh (2013)[39] supplemented women with baseline 25(OH)D <75 nmol/L with 200,000 IU followed by 50,000 IU/mo and found compared with both the 50,000 IU/mo (62.5±17.5 nmol/L) and 100,000 IU/mo (80.0±30.0 nmol/L) vitamin D groups, the 200,000/50,000 IU vitamin D group had significantly greater cord blood 25(OH)D concentrations (87.5±20.0 nmol/L, *P*=0.003).
Proportion preterm birth infants (or related values—eg, gestational age, proportion preterm labor)	One study[38] was excluded from the pooled results although preterm labor was less common in the vitamin D (8.3%) compared with nonintervention group (21.1%, *P*=0.02).
Birth weight and sex- or age-specific weight percentile	Two studies[29,39] were excluded from the pooled results although both found no differences among groups.
Birth length and sex- or age-specific length percentile	Two studies[29,39] were excluded from the pooled results although both found no difference among groups.

Figure 2. Results from studies excluded from meta-analyses. Data from these studies were presented in a manner inconsistent for comparison. To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.4. To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.5. 25(OH)D of 1 nmol/L=0.4 ng/mL. [a]HOMA-IR=homeostatic model assessment insulin resistance.

on GDM (or related values—ie, glucose and homeostatic model assessment insulin resistance [HOMA-IR] in fasting subjects), seven positive[25-27,34,36,40,41] and one neutral quality.[24] The effects of maternal dietary supplements of vitamin D on GDM (or related values—eg, glucose level, HOMA-IR) were mixed. Maternal dietary supplements of vitamin D had no significant effects on plasma glucose in fasting subjects (Figure 5, available at

www.jandonline.org) but were associated with a significant decrease in HOMA-IR. The pooled MD in plasma glucose in fasting subjects was −3.8 (95% CI= −8.6 to 1.1 mg/dL) with significant heterogeneity (I^2=77.2%, P<0.001) and −1.1 (95% CI= −1.5 to −0.7) in HOMA-IR with insignificant heterogeneity (I^2=40.0%, P=0.14) (Figure 6). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed suggests maternal vitamin D supplementation (ranging from a daily dose of 200 IU to a one-time dose of 300,000 IU) during pregnancy in women with mixed nutritional status decreases HOMA-IR, but not plasma glucose in fasting subjects.

Proportion of Women with a Cesarean Section. Six studies examined the effects of maternal dietary supplements of vitamin D on proportion of women with a cesarean section—five positive[28,33,34,37,41] and one neutral quality.[32] Maternal dietary supplements of vitamin D did not have significant effects on the percentage of women with cesarean section deliveries. No significant differences were noted between vitamin D and placebo or control group in all included studies, with a pooled OR of 0.9 (95% CI=0.7 to 1.2) and insignificant heterogeneity (I^2=0%, P=0.62) (Figure 7, available at www.jandonline.org). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed does not support a role for maternal vitamin D supplementation (ranging from a daily dose of 2,000 IU to two doses of 50,000 IU) during pregnancy in women with mixed nutritional status on cesarean section delivery.

PTH Concentrations. Four studies examined the effects of maternal dietary supplements of vitamin D on PTH—three positive[29,37,43] and one neutral quality.[32] Meta-analysis was not presented for this outcome because three of the four studies were presented in a manner not consistent for comparison. Overall, the effects of maternal dietary supplements of vitamin D on maternal PTH were mixed. Although three studies[29,37,43] concluded that maternal dietary supplements of vitamin D significantly decreased PTH, Hollis and colleagues did not.[32] Although PTH concentrations were lower across pregnancy time points, this was not significantly different at the final time point (ie, 1 month prior to delivery).[32] The overall strength of the available evidence was scored as grade III (limited). The evidence reviewed does not support a role for maternal vitamin D supplementation (ranging from a daily dosage of 800 IU to one dose of 200,000 IU) during pregnancy in women with mixed nutritional status on maternal PTH concentrations.

Circulating Calcium Concentrations. Eight positive studies[25-27,28,35-37,40] and one neutral-quality study[32] examined the effects of maternal dietary supplements of vitamin D on circulating calcium. The effects of maternal dietary supplements of vitamin D on calcium were mixed. Although one study[25] concluded that maternal dietary supplements of vitamin D were associated with increased calcium concentrations, seven studies[26,27,29,35-37,40] did not observe this. The pooled mean increase was 0.16 mg/dL [0.04 nmol/L] (95% CI=0.04-0.28 mg/dL [0.01 to 0.07 nmol/L]) with insignificant heterogeneity (I^2=19.3%, P=0.28) (Figure 8, available at www.jandonline.org). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed does not support a role for maternal vitamin D supplementation (ranging from a daily dose of 400 IU to a one-time dose of 300,000 IU) during pregnancy in women with mixed nutritional status on circulating calcium.

Infant Outcomes

Vitamin D Status: Circulating 25(OH)D Concentrations. Twelve studies examined the effects of maternal dietary supplements of vitamin D on infant 25(OH)D—nine positive[29-31,33,35,37,41-43] and three neutral quality.[32,38,39] The effects of maternal dietary vitamin D supplements on infant 25(OH)D concentrations were consistent. In general, maternal dietary supplements of vitamin D were associated with a significant (P<0.001) increase in infant 25(OH)D concentrations. The pooled mean increase in infant 25(OH)D concentrations was 9.7 [24.2] (95% CI=5.2 to 14.2 ng/mL [12.9 to 35.5 nmol/L]) with a significant heterogeneity (I^2=97.4%, P<0.001) (Figure 9). Three studies[29,30,43] were not included in the pooled results. Overall, the increase in 25(OH)D ranged from −1.2 ng/mL (−3.0 nmol/L)[35] (1,000 IU) to 25.5 ng/mL (63.8 nmol/L).[37]

Subgroup analysis (Figure 9), based on maternal baseline vitamin D status, found mothers in the insufficient (12 to 20 ng/mL [30 to 50 nmol/L]) or sufficient ranges (20 to 30 ng/mL [50 to 75 nmol/L]) had a significant (P<0.01) increase in infant's circulating 25(OH)D. The increase was higher for infants of mothers with insufficient (17.1 [42.7], 95% CI=11.0 to 23.1 ng/mL [27.6 to 57.7 nmol/L]) compared with sufficient (2.7 [6.8], 95% CI=0.9 to 4.6 ng/mL [2.2 to 11.4 nmol/L]) maternal baseline 25(OH)D status. Infants of mother's in the deficient range (12 ng/mL [<30 nmol/L]) group also showed an increase in 25(OH)D (10.6, 4.5, 16.7 ng/mL [26.5, 11.3, 41.8 nmol/L]). Heterogeneity ranged from I^2=65.8%, 90.8%, and 73.4% for the deficient, insufficient, and sufficient groups, respectively, and was significant for the insufficient (P<0.001) and sufficient (P=0.01) groups. The overall strength of the available evidence was scored as grade I (good or strong). The evidence reviewed supports maternal vitamin D supplementation (ranging from a daily dosage of 2,000 IU to up to four doses of 120,000 IU) during pregnancy in women with mixed nutritional status increases cord or infant circulating 25(OH)D concentrations.

Gestational Age. Seven studies examined the effects of maternal dietary supplements of vitamin D on gestational age—five positive[28,33,34,37,41] and two neutral quality.[32,38] The effects of maternal dietary supplements of vitamin D on gestational age were mixed and the overall MD in gestational age in the pooled studies was not significant. Results found a pooled MD of 0.1 weeks (95% CI=−0.2 to 0.3 weeks) with insignificant heterogeneity (I^2=15.6%, P=0.31) (Figure 10, available at www.jandonline.org). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed does not support a role for maternal vitamin D supplementation (ranging from a daily dosage of 2,000 IU to up to four doses of 120,000 IU) during pregnancy in women with mixed nutritional status on gestational age.

Birth Weight. Eleven studies examined the effects of maternal dietary supplements of vitamin D on birth weight—eight positive[28,29,31,33,34,37,41,42]

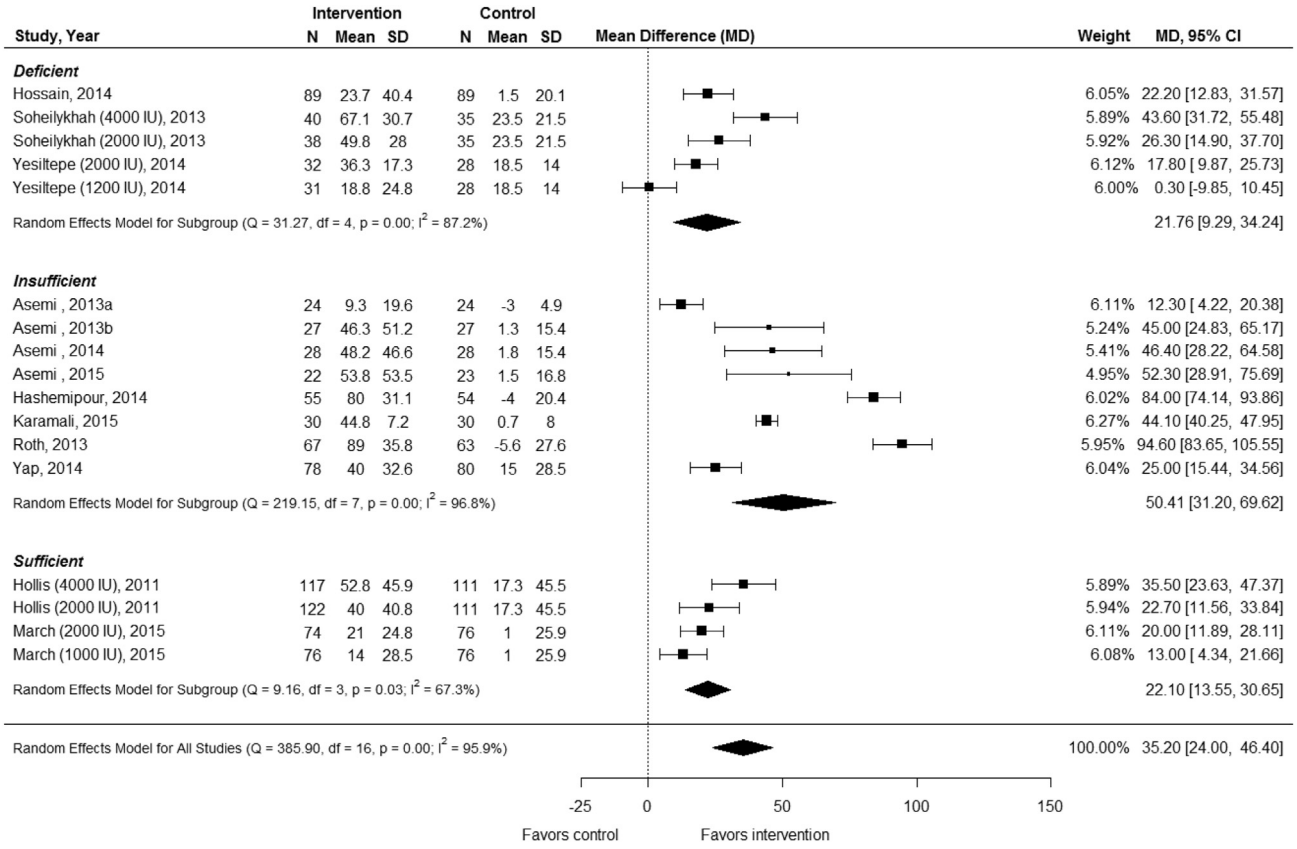

Figure 3. Forest plot of the effects of maternal vitamin D supplementation on maternal circulating 25(OH)D concentrations by maternal baseline vitamin D status. Maternal baseline vitamin D status categorized as deficient (25(OH)D≤30 nmol/L), insufficient (30 nmol/L<25(OH)D≤50 nmol/L), and sufficient (50 nmol/L<25(OH)D≤75 nmol/L). Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) are presented for intervention and control groups. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data presented in nmol/L. To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.4. To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.5. 25(OH)D of 1 nmol/L=0.4 ng/mL. The overall summary effect sizes of the meta-analysis as well as subgroup analyses are noted as a diamond.

and three neutral quality.[32,38,39] The effects of maternal dietary supplements of vitamin D on birth weight were mixed, and the overall MD in birth weight in the pooled studies was significant. Only two studies[31,38] found a significant increase in birth weight between the vitamin D and nonintervention group. The pooled MD was +114.2 g (95% CI=63.4 to 165.1 g) with insignificant heterogeneity (I^2=0%, P=0.66) (Figure 11). The overall strength of the available evidence was scored as grade II (fair). The evidence reviewed supports maternal vitamin D supplementation (ranging from a daily dosage of 1,200 IU to up to four doses of 120,000 IU) during pregnancy in women with mixed nutritional status increases infant birth weight.

Birth Length. Eight studies examined the effects of maternal dietary supplements of vitamin D on birth length—seven positive[28,29,31,33,34,37,41] and one neutral quality.[39] The effects of maternal dietary supplements of vitamin D on birth length were mixed (eight studies); the overall MD in birth length in the pooled studies was not significant. Only one study[31] found a significant increase in birth length between the vitamin D and nonintervention group. The pooled MD was 0.3 (95% CI= −0.1 to 0.7 cm) with insignificant heterogeneity (I^2=12.1%, P=0.34) (Figure 12, available at www.jandonline.org). The overall strength of the available evidence was scored as grade II (fair). The evidence does not support a role for maternal vitamin D supplementation (ranging from a daily dose of 2,000 IU to a monthly dose of 100,000 IU) during pregnancy in women with mixed nutritional status on infant birth length.

Publication Bias. No indications of publication bias were observed for all outcomes (Egger's test, P>0.05 for all), except for maternal HOMA-IR (Egger's test, P=0.02).

Research Published after Completion of the Initial Review. To determine whether the results of the initial review were consistent with literature published after 2016, an additional systematic review was conducted for literature published between July 2016 and September 2018 using the same procedures as the initial search. The results from this search are presented qualitatively and not included in the meta-analysis, similar to previous work.[48] A total of 277 abstracts were reviewed for relevance with five studies[49-53] retrieved for detailed evaluation and included for in this updated

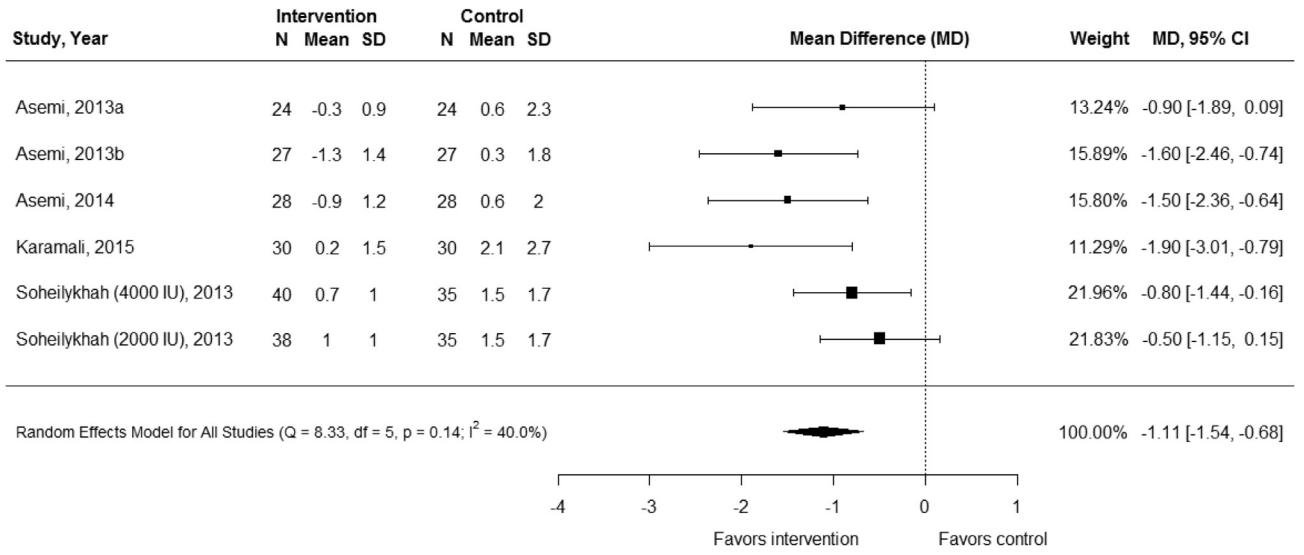

Figure 6. Forest plot of the effects of maternal vitamin D supplementation on homeostatic model assessment insulin resistance (HOMA-IR). Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. The overall summary effect sizes of the meta-analysis are noted as a diamond.

review. Detailed description and results for each trial are shown in Table 2. All studies included generally healthy pregnant women, and one study[52] supplemented participants based on maternal baseline status. Four studies[49-51,53] used a placebo as a comparison group, and one[52] used usual care (no vitamin D). The latter[52] explored several vitamin D regimens as part of a prenatal vitamin D screening program. Intervention dosages varied from daily dosing ranging from 400 IU[51] to 2,000 IU[50] to weekly dosing ranging from 4,200 IU[53] to 50,000 IU.[52] Overall, findings were consistent with the initial review as maternal vitamin D supplementation increased maternal 25(OH)D concentrations[49-53] as well as infant concentrations,[51,53] although O'Callaghan and colleagues[51] found no difference between the 400 IU/day compared with both the 800 IU/day and placebo control groups. Similarly, there was no effect of supplementation on cesarean section deliveries[53] and infant birth length.[50,53] There was no effect of supplementation on infant birth weight,[50,53] in contrast to previous findings,[31,38] as well as on gestational age or preterm birth.[53] This latter finding conflicts with Rostami and colleagues,[52] who found supplementation, provided through a screening program, decreased preterm birth as well as preeclampsia and GDM compared with a nonscreening (no supplementation) group.

DISCUSSION

This review provides supportive evidence that prenatal vitamin D supplementation significantly increases both maternal and infant 25(OH)D concentrations, yet the effects of supplementation on perinatal health outcomes is unsupported by strong evidence. To inform practice guidelines and policy makers on the required amount of vitamin D for a healthy pregnancy, two questions need resolution. The first includes the amount of vitamin D, which is associated with positive health outcomes. Our review found evidence (grade of "fair") on the favorable effect of supplementation on gestational diabetes; in particular, a significant decrease in HOMA-IR was observed (−1.1, 95% CI= −1.5 to −0.7). This is in line with a previous meta-analyses[54] but not others,[16,17] which may be attributed to the different outcomes assessed (HOMA-IR was assessed in our review and[55] vs percent GDM in others).[16,17] Postulated biological mechanism of vitamin D's actions on metabolism include stimulation of insulin secretion or sensitivity directly or via suppression of PTH, which may decrease the effect on β-cell dysfunction and dysglycemia,[55,56] thus supporting a causal relationship between vitamin D and insulin resistance. In addition, there was fair evidence to suggest maternal vitamin D supplementation increases infant birth weight; a clinically significant pooled birth weight increase of 114.2 g was noted with low heterogeneity (I^2=0%). This suggests vitamin D may play a role in fetal growth and is in line with previous meta-analyses,[17,57] although a recent large RCT by Roth and colleagues found otherwise.[53] This latter trial initiated supplementation in the second half of pregnancy in women who had severe vitamin D deficiency and were at high risk for fetal-infant growth restriction.[53] Supplementation dosages in the range provided (4,200 to 28,000 IU weekly) may have been insufficient to resolve vitamin D deficiency and have positive effects for offspring in this population. In contrast, the two studies reported in this current review[31,38] that found a significant increase in birth weight provided high-dose supplementation, which ranged from 50,000 IU weekly to four doses of 120,000 IU. Adding the study by Roth and colleagues to our meta-analysis (data not presented) did not change the results (MD=49.2 g, 95% CI=5.2 to 93.1 g). Fetal growth is, however, affected by a number of factors beyond maternal diet including genetics and fetal,

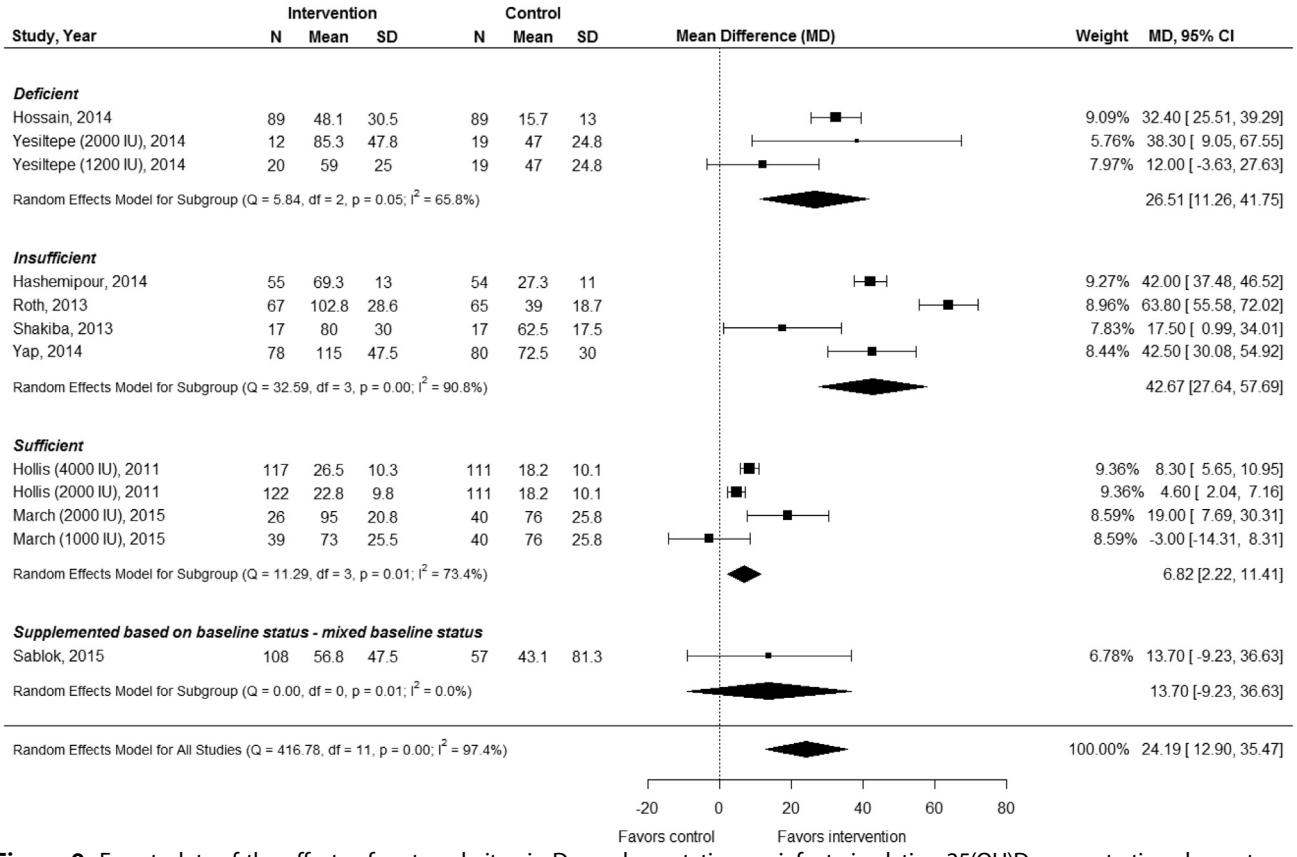

Figure 9. Forest plots of the effects of maternal vitamin D supplementation on infant circulating 25(OH)D concentrations by maternal baseline vitamin D status. Maternal baseline vitamin D status categorized as: deficient (25(OH)D≤30 nmol/L), insufficient (30 nmol/L<25(OH)D≤50 nmol/L), and sufficient (50 nmol/L<25(OH)D≤75 nmol/L). Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) are presented for intervention and control groups. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data presented in nmol/L. To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.4. To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.5. 25(OH)D of 1 nmol/L=0.4 ng/mL. The overall summary effect sizes of the meta-analysis as well as subgroup analyses are noted as a diamond. The study by Shakiba and Iranmanesh (2013) was classified in the insufficient group; however, one of three groups supplemented was included based on maternal baseline status.

placental, and maternal hormones and growth factors. Other maternal and infant outcomes (preeclampsia or gestational hypertension, cesarean section, maternal circulating calcium concentrations, gestational age, infant birth length) were found to have fair evidence and did not find an association with maternal vitamin D supplementation. Future trials should be designed beyond the assessment of vitamin D status and should be sufficiently powered to test clinical outcomes related to pregnancy.[57] Furthermore, our results suggest baseline vitamin D status may be an important consideration. Significant positive effects on preeclampsia, GDM, and preterm birth were found among studies that supplemented women based on baseline status,[38,52] suggesting deficient women may benefit more from supplementation and hence supporting screening of at risk women.

In the absence of evidence on the appropriate amount of vitamin D associated with positive perinatal outcomes, a related second question remains: what is the appropriate amount of vitamin D to achieve optimal vitamin D status? This question is complicated by the fact that only ~20% of exogenous vitamin D contributes to vitamin D supply[58] (the remaining 80% is through endogenous sources), and this varies considerably by factors such as season, latitude, skin color, and adipose tissue. Furthermore, there is a lack of consensus on 25(OH)D cut points to define optimal status.[4,8] In our subgroup analysis, we found the increase in maternal and infant 25(OH)D concentrations was affected by maternal baseline status. Studies among women who had a mean 25(OH)D in the insufficient range reported higher increase in their 25(OH)D, as well as their infant's 25(OH)D concentrations, compared with those with women in the deficient or sufficient range at baseline. Although lower basal vitamin D status has been consistently shown to improve 25(OH)D response to supplementation,[59] in this review maternal supplementation regimens ranged significantly within these groups and the majority of studies among women who had a mean 25(OH)D in the insufficient range included a much higher loading dose in the amount of 50,000 IU[25,27,28,31,34,37] compared with those in the deficient range, which were limited to daily dosages of 1,200 to 4,000 IU.[33,40,42] Thus, the dosages provided to women

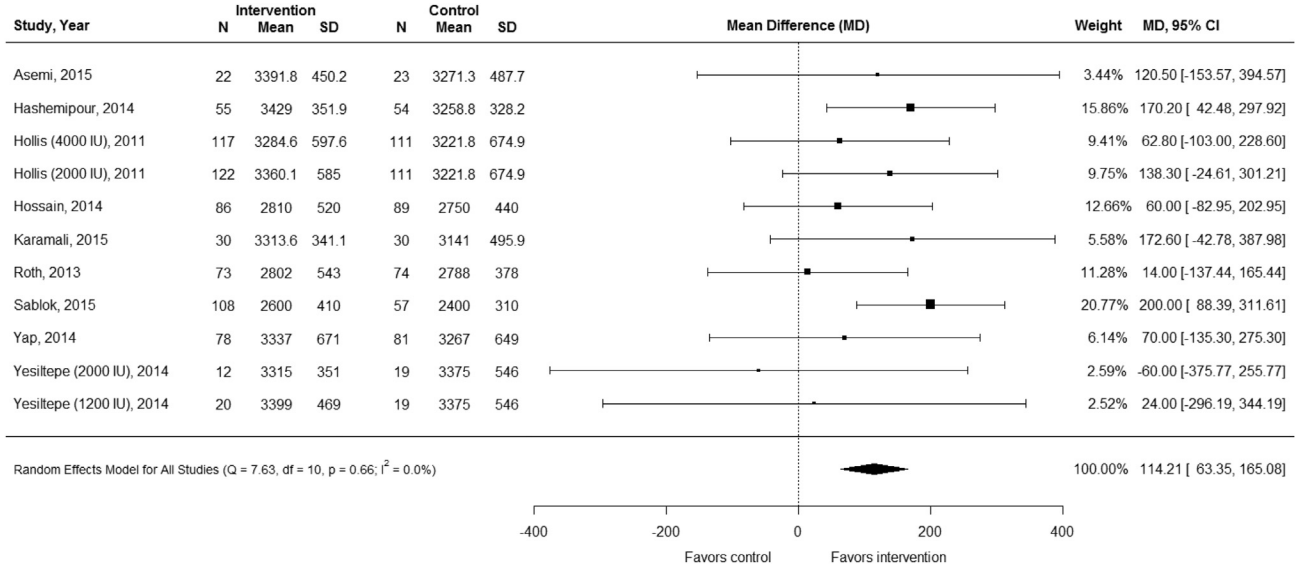

Figure 11. Forest plot of the effects of maternal vitamin D supplementation on infant birth weight. Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data for infant birth weight presented as grams. The overall summary effect sizes of the meta-analysis are noted as a diamond.

in the deficient range may have been likely too low to improve their status. Of all trials reviewed, only three studies[39,48,53] supplemented participants based on baseline vitamin D status, albeit expert opinion supports studies incorporating baseline status in future supplementation trials.[59,60] The recent dose-response trial by O'Callaghan and colleagues[51] aims to resolve the question on the appropriate dosage for adequate maternal and infant 25(OH)D status. Researchers found 1,200 IU was required for white-skinned mothers to achieve a 25(OH)D concentration of 20 ng/mL (50 nmol/L), which in turn prevented neonatal 25(OH)D concentrations <50 to 125 ng/mL (<25 to 30 nmol/L), a level thought sufficient to prevent nutritional rickets. Most experts agree that dosages up to 2,000 IU of vitamin D daily is safe to treat deficiency during pregnancy[60] and dosages as high as 4,000 IU daily was found to be safe and most effective at achieving sufficiency (32 ng/mL [>80 nmol/L]) among neonates in a diverse group of women (68% black) living in a southern latitude. Yet, in both these trials,[32,51] women had baseline status in the sufficient range; hence, lower doses of supplementation may be necessary to illicit a 25(OH)D response. In addition to a need for clearer pregnancy-specific 25(OH)D thresholds, additional dose-response trials with varying baseline vitamin D status are needed to advance our understanding of optimal amounts and hence establish public health guidelines.

Over the past decade, there have been a number of reviews on the topic of maternal vitamin D supplementation during pregnancy.[16,17,54,57,61] This present review provides a comprehensive assessment, including both maternal and infant clinical health outcomes, utilizing the Academy's rigorous methodology and including only RCTs—the majority deemed positive quality, which provide the highest quality and strongest evidence for causality. To show consistency with the literature published after our initial review in 2016, our search was extended and included two recent large-scale studies,[52,53] which have contributed significantly to the discussion. All trials including those that compared different dosages of vitamin D supplementation were included in this review. In addition, an extensive literature search was completed at all stages using an evidence-based approach.[22] The majority of trials were limited to Asia (11 of 20 included in the meta-analysis were from Iran), and although these were among the smallest studies, this makes for a very homogeneous grouping. Different supplementation regimes, comparison groups, timing of intervention, and use of other supplements (ie, calcium) were used in these studies introducing heterogeneity and may explain our high to moderate I^2 for some outcomes. Circulating calcium concentrations were not corrected for albumin, nor was a time-by-treatment interaction explored as suggested by others,[62] and studies did not assess vitamin D binding protein, which may have affected results. In addition, we did not exclude studies that combined calcium supplementation or multivitamins with vitamin D. This review was not listed at the PROSPERO international prospective register of systematic reviews. Lastly, the low number of studies for some outcomes may limit our ability to draw conclusive regarding publication bias and heterogeneity of studies.

Implications

This review supports a role for vitamin D supplementation on maternal and infant status as well as on potential health effects. Supplementation dosages varied considerably in the studies reviewed with 14 of the 25 studies providing dosages well above the upper level intake for pregnant women of 4,000 IU daily.[4] The initial search

Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a]

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH) D)	Quantification method for 25(OH) D	Major findings
Moon and colleagues, 2016[49]	Southampton (50.9°N), Oxford (51.8°N), Sheffield (53.4°N), UK	n=829; 18 y old or older; healthy pregnant women, not taking >400 IU/day vitamin D supplementation and 25(OH)D between 25 to 100 nmol/L and serum calcium<2.75 nmol/L MAVIDOS (Maternal Vitamin D Osteoporosis Study)	Vitamin D group (n=407): 1,000 IU vitamin D-3/day Control group (n=422): matched placebo Duration: 20 wk, enrollment (14 wk gestation at baseline) until 34 wk	Vitamin D group: median (IQR[b]) 45.7 (34.3-57.8) nmol/L Control group: 44.4 (33.2-57.0) nmol/L	Radioimmunoassay	Maternal serum 25(OH)D: compared with control group (43.1±22.5 nmol/L), vitamin D group (67.7±21.3 nmol/L) had greater increase in serum 25(OH)D level at 34 wk gestation ($P<0.0001$). Compared with control group (35.6%), participants in the vitamin D group (83.3%) achieved vitamin D replete status (>50 nmol/L 25(OH)D) at 34 wk gestation ($P<0.001$).
Vaziri and colleagues, 2016[50]	Shiraz, Iran (29.6°N)	n=127; 18 y old or older; healthy pregnant women, no mental illness or pregnancy complications	Vitamin D group (n=62): two1,000 IU pills (total 2,000 IU/day) vitamin D-3 Control group (n=65): matched placebo Duration: 8 wk (enrollment, 26-28 wk gestation, until delivery)	Vitamin D group: 29.1±14.0 nmol/L Control group: 31.8±20.9 nmol/L	Chemiluminescence assay	Maternal serum 25(OH)D: compared with placebo group (−1.73±24.3 nmol/L), vitamin D group (16.1±27.6 nmol/L) had greater increase in serum 25(OH)D level at end of the intervention ($P<0.001$). Infant's birth weight: there were no significant differences in birth weight between the groups ($P=0.43$). Infant's birth length: there were no significant differences in birth weight between the groups ($P=0.75$).

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Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D	Major findings
O'Callaghan and colleagues, 2018[51]	Cork, Ireland (51.9°N)	n=142; 18 y old or older; healthy white-skinned, pregnant women, no pregnancy complications, not taking >400 IU vitamin D or >650 mg calcium supplementation daily	800 IU vitamin D group (n=46): 800 IU pill vitamin D-3 400 IU vitamin D group (n=48): 400 IU pill vitamin D-3 Control group (n=48): matched placebo Duration: 22 wk (enrollment, ≤18 wk until 36 wk gestation)	800 IU vitamin D group: 58.0±22.9 nmol/L 400 IU vitamin D group: 49.6±19.6 nmol/L Control group: 57.2±24.5 nmol/L	Liquid chromatography-tandem mass spectrometry	Maternal serum 25(OH)D: compared with placebo, the 400 IU (24.3±5.8 nmol/L) and 800 IU (29.2±5.6 nmol/L) vitamin D groups had greater mean increase in serum 25(OH)D level at end of the intervention ($P<0.001$). Compared with control group (23%), participants in the 400 IU (5%) and 800 IU (2%) vitamin D groups achieved 25(OH)D concentrations <50 nmol/L at completion of the intervention ($P=0.004$). Infant cord 25(OH)D: compared with placebo, infants in the 800 IU vitamin D (11.3±3.83 nmol/L) had greater mean increase in serum 25(OH)D level ($P=0.011$), with no significant differences between the 400 IU group and other two groups. There were no significant differences in prevalence of 25(OH)D concentrations <50 nmol/L among groups ($P=0.41$).

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Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH) D)	Quantification method for 25(OH) D	Major findings
Rostami and colleagues, 2018[52]	Khuzestan province, Iran (31.4°N)	n=1,600; 18-40 y old; healthy pregnant women, not taking >400 IU vitamin D supplementation daily	Screening group (n=1,600)[c]: Supplementation based on baseline 25(OH)D: severely deficient (<25 nmol/L) and moderately deficient (25 to 50 nmol/L) randomly allocated to one of eight interventions as per below, women in normal >50 nmol/L (n=200) did not receive any supplementation Severe deficiency <25 nmol/L (n=400): one dose of 50,000 IU vitamin D-3 weekly for 12 wk (A1), one dose of 50,000 IU vitamin D-3 weekly for 12 wk plus monthly maintenance dose of 50,000 IU until delivery (A2), intramuscular 300,000 IU each 6 wk for two doses (A3), intra-muscular 300,000 IU each 6 wk for two doses plus monthly maintenance of 50,000 IU until delivery (A4) Moderate deficiency 25-50 nmol/L (n=400): one dose of 50,000 IU vitamin D-3 weekly for 6 wk (B1), one dose of 50,000 IU vitamin D-3 weekly for 6 wk plus monthly maintenance dose of 50,000 IU until delivery (B2), one intramuscular 300,000 IU dose (B3), one intramuscular 300,000 IU plus monthly maintenance of 50,000 IU until delivery (B4) Nonscreening group: (n=900): did not receive any supplementation Duration: enrollment until delivery (14-20 wk gestation at baseline)	Screening group (n=900): median and IQR 27.5 (17.5-40) nmol/L Nonscreening groups (n=900): 27.5 (17.5-40) nmol/L	ELISA[d]	Maternal serum 25(OH)D: compared with nonscreening (median; IQR: 27.5; 17.5-45 nmol/L), screening group (52.5; 45-62.5 nmol/L) had greater increase in serum 25(OH)D level at delivery ($P<0.001$). Compared with nonscreening (0.02%), 53% of women in the screening group achieved vitamin D replete status (>50 nmol/L 25(OH)D) at end of the study (*P* value unspecified). Maternal preeclampsia: compared with nonscreening (17%), preeclampsia was lower than the screening group (8%) (OR[e], 95% CI: 0.4, 0.3-0.6; $P<0.001$). Maternal GDM[f]: compared with nonscreening (6%), GDM was lower than the screening group (4%) (OR, 95% CI: 0.5, 0.3-0.9; $P=0.01$). Preterm birth: compared with nonscreening (15%), preterm birth was lower than the screening group (8%) (OR, 95% CI: 0.6, 0.4-0.8; $P<0.001$).

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Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH)D)	Quantification method for 25(OH)D	Major findings
Roth and colleagues, 2018[53]	Dhaka, Bangladesh (24°N)	n=1,300; 18-<35 y old; generally pregnant women Maternal Vitamin D for Infant Growth (MDIG) trial	Prenatal 4,200 IU vitamin D group (n=260): 4,200 IU per wk Prenatal 16,800 IU vitamin D group (n=259): 16,800 IU per wk Prenatal 28,000 IU vitamin D group (n=260): 28,000 IU per wk Prenatal and postpartum 28,000 IU vitamin D group (n=260): 28,000 IU per wk plus 26 wk of postpartum supplementation Control group (n=259) Placebo throughout the prenatal period and 26 wk postpartum Duration: enrollment (17 to 24 wk gestation at baseline) until 26 wk postpartum	Prenatal 4,200 IU vitamin D group: 27.4 ±14.3 nmol/L Prenatal 16,800 IU vitamin D group: 28.7±14.0 nmol/L Prenatal 28,000 IU vitamin D group: 27.0±14.7 nmol/L Prenatal and postpartum 28,000 IU vitamin D group: 26.6±13.2 nmol/L Control group: 27.7 ±13.8 nmol/L	High-performance liquid chromatography tandem mass spectroscopy	Maternal serum 25(OH)D: compared with placebo group (23.8±13.9 nmol/L), vitamin D groups achieved significantly greater serum 25(OH)D concentrations (69.7±19.5, 100.9±23.6, 110.7±28.0, and 113.6±25.7 nmol/L, by increasing dose group) at or near delivery ($P<0.001$). Compared with placebo group (76%), vitamin D groups achieved significantly lower proportion of participants with 25(OH)D concentrations ≤30 nmol/L (1.6%, 0%, 0.85%, 0%, by increasing dose group) ($P<0.001$). Maternal PTH: compared with placebo group (median [IQR], 4.96 IQR [3.27, 7.30 pmol/L]), vitamin D groups achieved significantly lower PTH concentrations (3.49 [2.42, 4.80], 2.91 (1.48, 4.44], 2.90 [1.71, 4.55], 2.40 [1.82, 3.97]) by increasing dose group) at or near delivery ($P<0.001$). Caesarean section (mode of delivery): there was no significant difference in Cesarean section deliveries among groups ($P=0.54$).

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Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH) D)	Quantification method for 25(OH) D	Major findings
						Infant serum 25(OH)D: compared with placebo group (11.9±7.4 nmol/L), vitamin D groups achieved significantly greater cord 25(OH)D concentrations (37.2±10.4, 59.9±13.0, 71.7±16.2, and 70.0±16.4 nmol/L, by increasing dose group) ($P<0.001$). Compared with placebo group (98%), vitamins D groups achieved significantly lower proportion of participants with 25(OH)D concentrations ≤30 nmol/L (22%, 0%, 0%, 0%, by increasing dose group) ($P<0.001$). Gestational age: there was no significant difference in gestational age or prevalence of preterm births among groups at birth ($P=0.62$ and 0.60, respectively). Infant's birth weight: there was no significant difference in infant birth weight among groups ($P=0.25$). Infant's weight at 1 y of age: there was no significant difference in infant weight-for-age *z* scores among groups ($P=0.34$). Infant's birth length: there was no significant difference in

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Table 2. Characteristics and main findings of studies published after completion of initial review, 2016-2018[a] (*continued*)

Author(s), year	Location (latitude)	Population (n = randomized n based on mothers)	Intervention (n = randomized n based on mothers);duration (gestational age at study initiation)	Baseline 25-hydroxyvitamin D status (25(OH) D)	Quantification method for 25(OH) D	Major findings
						infant birth length among groups (P=0.74). Infant's length at 1 y of age: there was no significant difference in infant length-for-age z scores among groups (P=0.23).

[a]To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.4. To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.5. 25(OH)D of 1 nmol/L=0.4 ng/mL.
[b]IQR=interquartile range.
[c]Due to sample adequacy, n=600 screened and then excluded from the trial (vitamin D–deficient women were referred to specialists).
[d]ELISA=enzyme-linked immunosorbent assay.
[e]OR=odds ratio.
[f]GDM=gestational diabetes mellitus.

sought food-based interventions, yet no studies met the inclusion criteria for this review. Hence this highlights a gap in our understanding of the effectiveness for food-based vitamin D interventions, which may act synergistically with other nutrients found in food and be better tolerated than supplementation. Women at risk for vitamin D deficiency should be screened and vitamin D status should be corrected, in addition to providing advice on appropriate dietary and supplemental sources of vitamin D to reach nutritional adequacy. This review highlights that if improvement in maternal or infant 25-hydroxyvitamin D status is the goal, maternal supplementation is well supported. However, if the goal is to modify maternal or infant health outcomes, maternal vitamin D supplementation is unsupported by strong evidence. This is aligned with current World Health Organization practice guidelines.[63] To better inform policies and practice guidelines on vitamin D that support healthy pregnancies, high-quality dose-response vitamin D supplementation trials that address pregnancy-specific 25(OH)D thresholds among diverse population groups and that are also appropriately powered to assess clinical outcomes are needed. Many outcomes were unable to be explored in the current review because these were either not reported or unavailable including infant health outcomes (ie, bone health, acute respiratory infections). Many prenatal vitamin D supplementation trials are currently unpublished, ongoing, or in intermediate status (35 were identified by Roth and colleagues[57]). Researchers are encouraged to incorporate maternal baseline status as an inclusion criterion or enroll a study group sample with vitamin D status across a broad range.

CONCLUSION

There was good or strong evidence that supports maternal vitamin D supplementation during pregnancy increases maternal and infant circulating 25(OH)D concentrations. The evidence was fair to suggest a favorable effect of supplementation on HOMA-IR and increasing infant birth weight. Future dose response trials that address both the amount of vitamin D and 25(OH)D thresholds associated with appropriately powered clinical outcomes are needed.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

R. Hakeem is the principal investigator on a research project on the genomic and lifestyle predictors of fetal outcome relevant to diabetes and obesity and their relevance to prevent strategies in South Asia. J. M. McDermid is a co-investigator on the Bill and Melinda Gates Foundation Grant on Early Life Interventions for Childhood Growth and Development in Tanzania. M. Pari-Keener is the past chair (2013) of the Women's Health Dietetic Practice Group. No potential conflict of interest was reported by the other authors.

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AUTHOR CONTRIBUTIONS

All authors were involved in the data collection, analyses, and interpretation of findings. S. Gallo wrote first draft with contributions from J. M. McDermid and F. W. Cheng. All authors reviewed and commented on subsequent drafts of the manuscript.

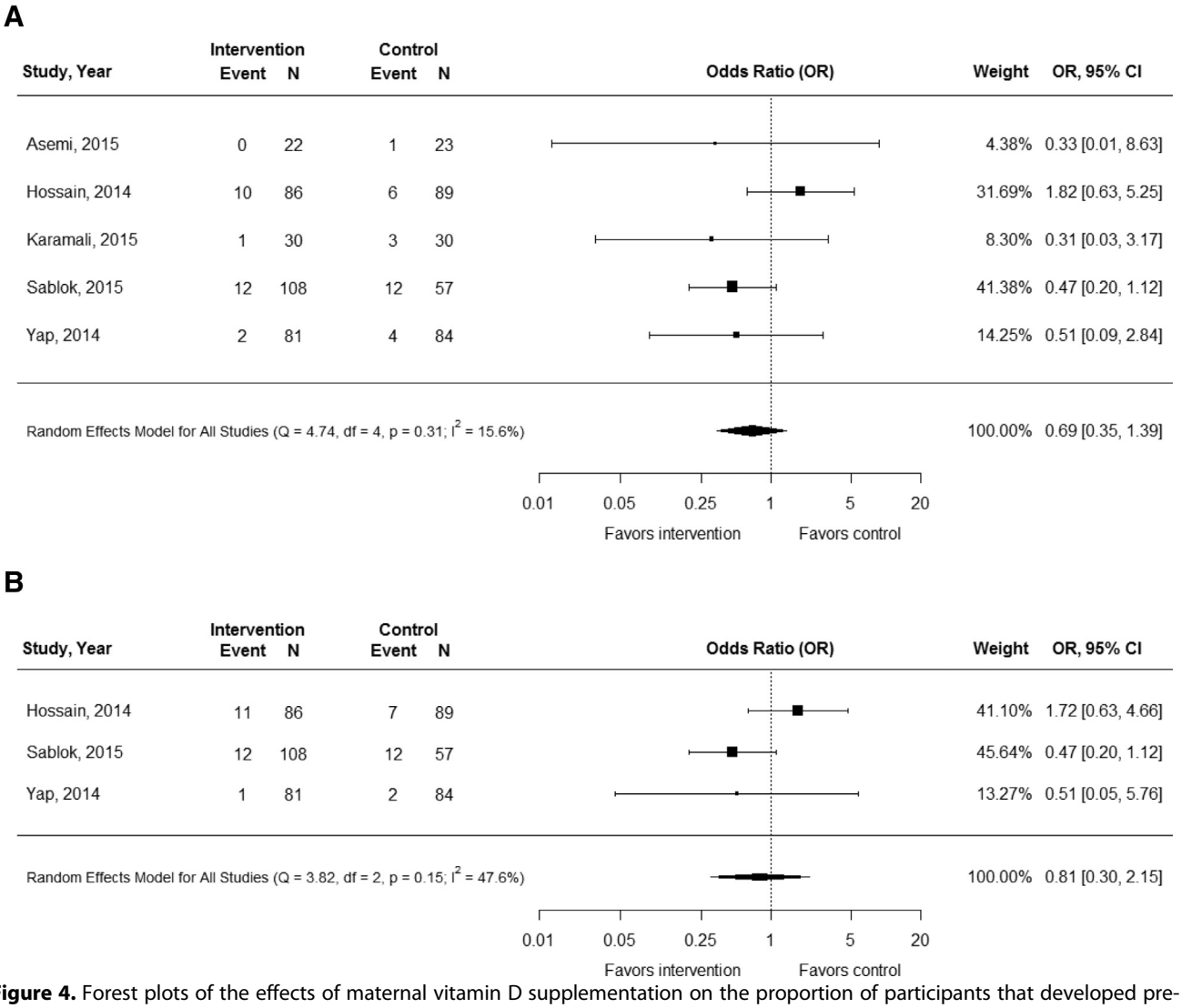

Figure 4. Forest plots of the effects of maternal vitamin D supplementation on the proportion of participants that developed pre-eclampsia (A) and gestational hypertension (B). Each study is identified by first author and year. Proportion of participants (event) and sample size (N) per intervention and control group. The individual effect sizes are identified as odds ratio (OR) with lower and upper limits (95% CIs) for each study. The overall summary effect sizes of the meta-analysis are noted as a square.

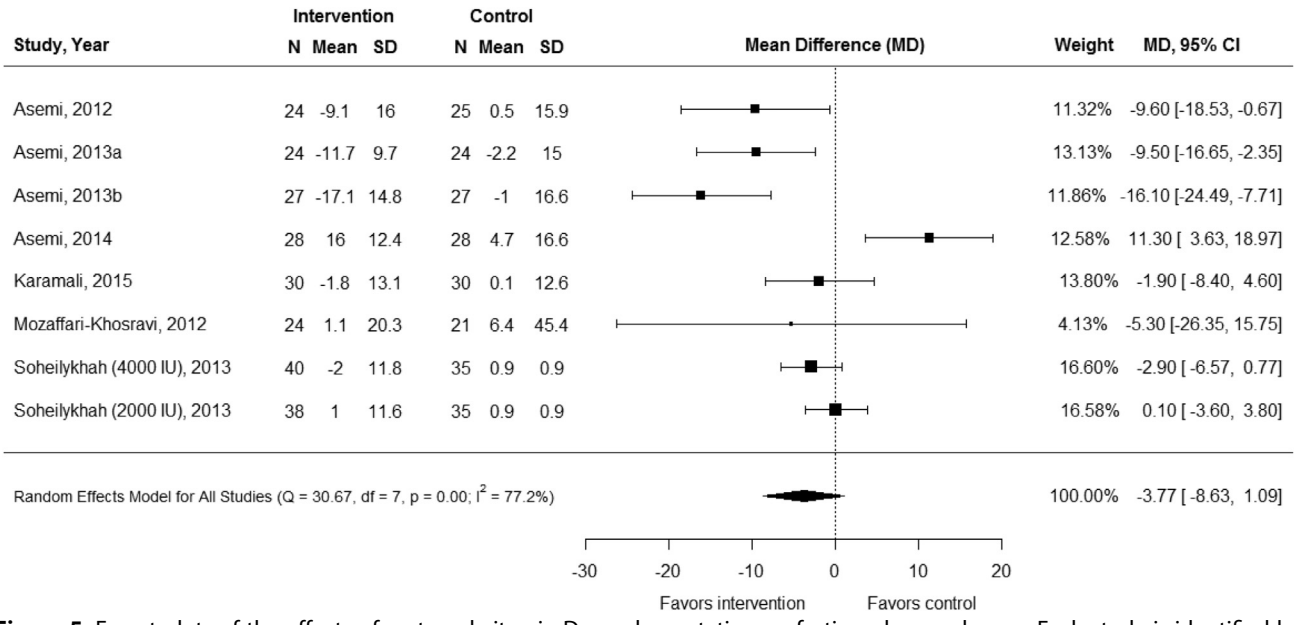

Figure 5. Forest plots of the effects of maternal vitamin D supplementation on fasting plasma glucose. Each study is identified by first author and year. Sample size (N), Mean and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data for fasting plasma glucose presented as mg/dL. To convert mg/dL to mmol/L glucose, multiply mg/dL by 0.0555. To convert mmol/L to mg/dL, multiply mmol/L by 18. Plasma glucose of 1 mmol/L=18 mg/dL. The overall summary effect sizes of the meta-analysis are noted as a diamond.

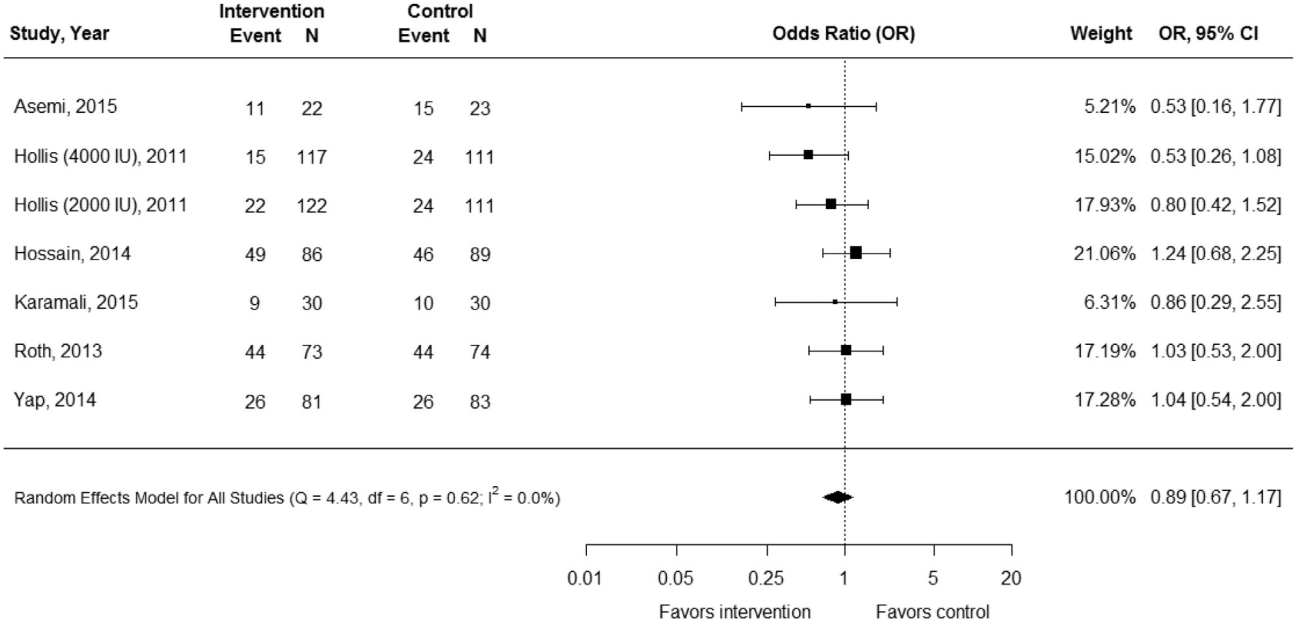

Figure 7. Forest plot of the effects of maternal vitamin D supplementation on the proportion of participants with cesarean section. Each study is identified by first author and year. Proportion of participants (event) and sample size (N) per intervention and control group. The individual effect sizes are identified as OR with lower and upper limits (95% CIs) for each study. The overall summary effect sizes of the meta-analysis are noted as a square.

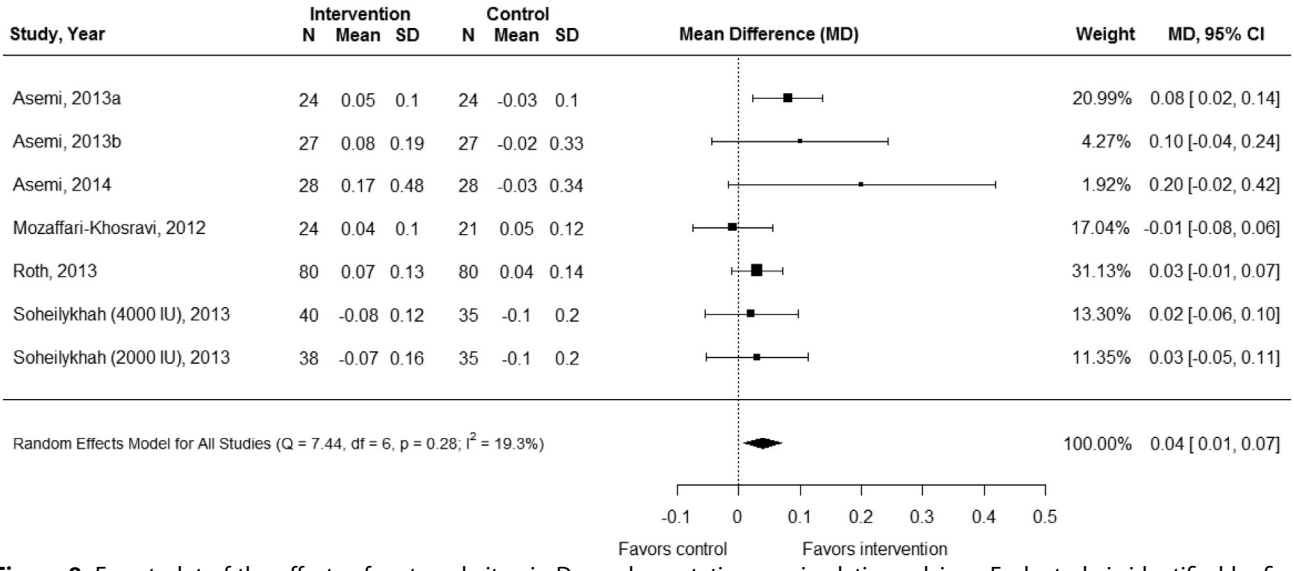

Figure 8. Forest plot of the effects of maternal vitamin D supplementation on circulating calcium. Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data for circulating calcium presented as mmol/L. To convert mg/dL to mmol/L calcium, multiply mg/dL by 0.25. To convert mmol/L to mg/dL, multiply mmol/L by 4. Circulating calcium of 1 mmol/L=4 mg/dL. The overall summary effect sizes of the meta-analysis are noted as a diamond.

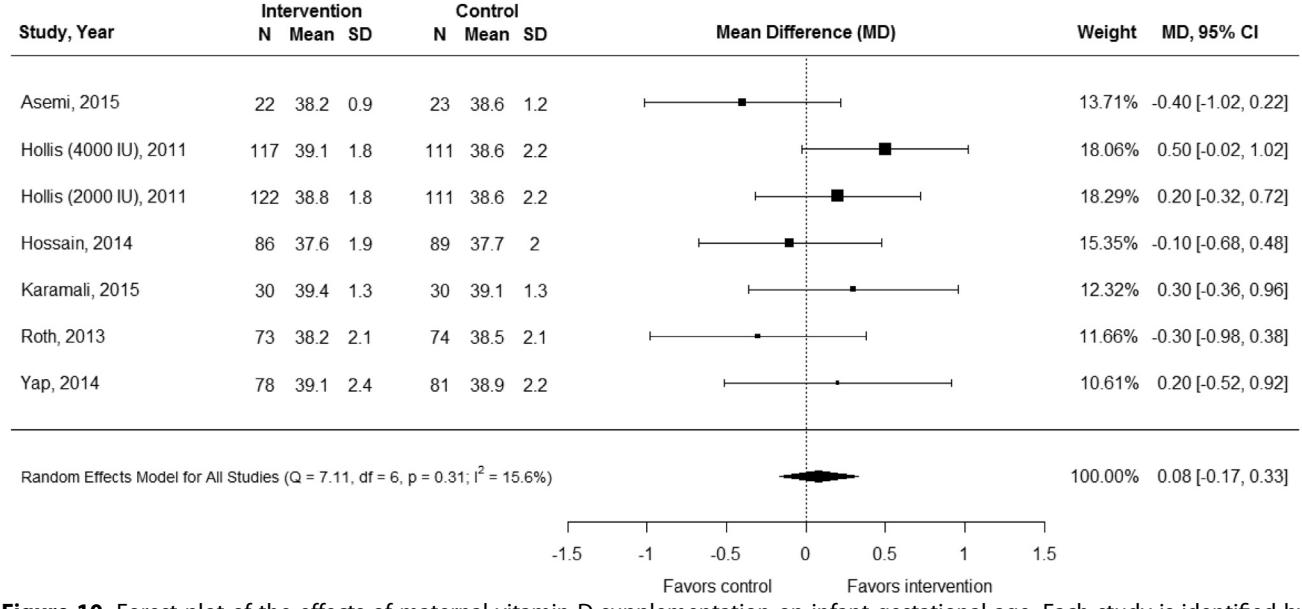

Figure 10. Forest plot of the effects of maternal vitamin D supplementation on infant gestational age. Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data for gestational age presented as weeks. The overall summary effect sizes of the meta-analysis are noted as a diamond.

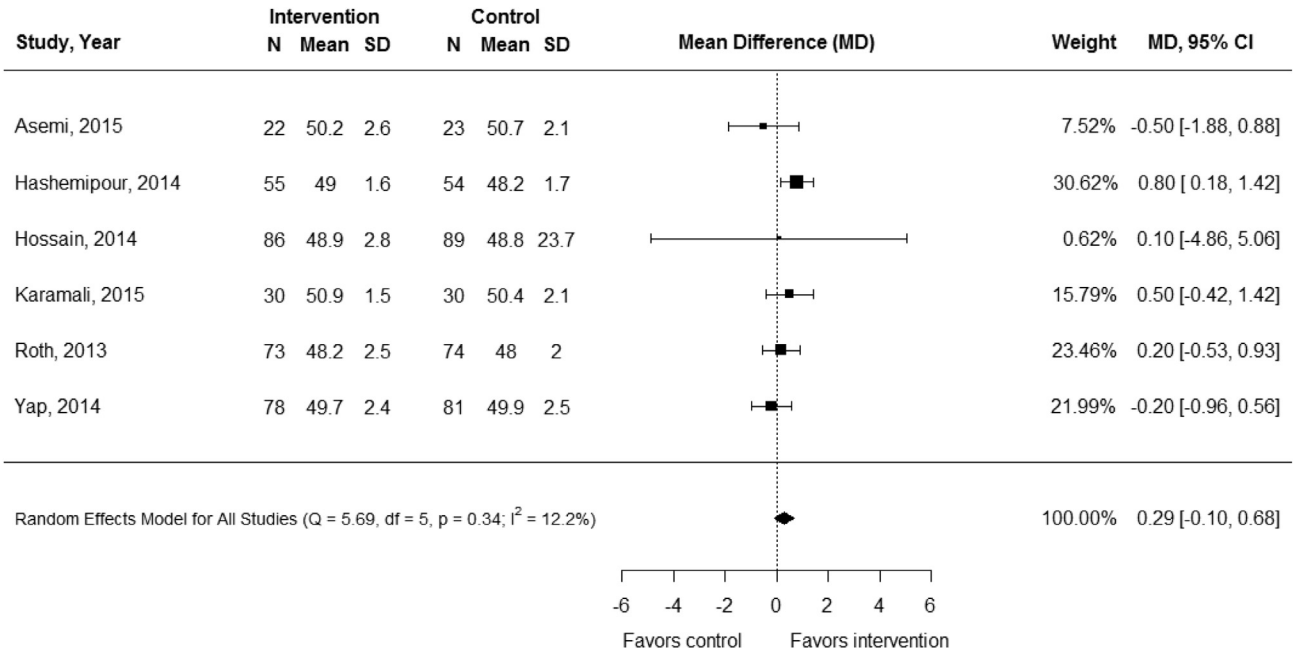

Figure 12. Forest plot of the effects of maternal vitamin D supplementation on infant birth length. Each study is identified by first author and year. Sample size (N), mean, and standard deviation (SD) per intervention and control group. The individual effect sizes are identified as mean difference (MD) with lower and upper limits (95% CIs) for each study. Data for infant birth length presented as centimeters. The overall summary effect sizes of the meta-analysis are noted as a diamond.