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Original Paper

Maternal Vitamin D Status and Risk of Gestational Diabetes: a Meta-Analysis

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Key Words
25-hydroxyvitamin D • Gestational diabetes • Meta-analysis

Abstract
Background/Aims: Whether maternal vitamin D deficiency is associated with gestational diabetes remains controversial. This meta-analysis aimed to systematically evaluate published evidence on the association between maternal vitamin D status and the risk of gestational diabetes. ***Methods:*** We retrieved relevant articles from the PubMed, Medline and Embase databases up to May 2017 for observational studies investigating the association between vitamin D status and the risk of gestational diabetes. Odds ratios (OR) or risk ratios (RR) from individual studies were pooled using the fixed and random effect models. ***Results:*** The meta-analysis of 29 observational studies included 28,982 participants, of which 4,634 were diagnosed with gestational diabetes, and showed that maternal vitamin D insufficiency was associated with a significantly increased risk of gestational diabetes by 39% (pooled OR = 1.39, 95%CI = 1.20-1.60) with moderate heterogeneity (I^2 = 50.2%; P = 0.001). Moreover, the 25(OH)D level was significantly lower in gestational diabetes cases than in controls with a pooled effect of -4.79 nmol/L (95% CI = -6.43, -3.15). Significant heterogeneity was also detected (I^2 = 65.0%, P < 0.001). Further subgroup analysis indicated that this association was also evident in most subpopulations. ***Conclusion:*** This meta-analysis indicated a significant association between vitamin D insufficiency and increased risk of gestational diabetes. Further well-designed large-scale clinical trials are essential to verify this association.

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Introduction

Gestational diabetes, defined by glucose intolerance with the onset or first recognition during pregnancy, is the leading cause of complications associated with childbirth. Its prevalence is increasing globally and has reached nearly 15%-20% [1]. Women with

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gestational diabetes had an increased risk of developing preeclampsia, dystocia and delivering macrosomia. It also has serious, long-term outcomes for both the mother and their offspring, including a predisposition to obesity, diabetes and metabolic syndrome later in life [2]. Research has shown that advanced maternal age, maternal obesity or overweight and a family history of diabetes could influence the development of gestational diabetes [2]. Whether maternal vitamin D deficiency is associated with gestational diabetes remains unclear. Due to foetal growth needs, inadequate vitamin D intake and limited sunlight exposure, vitamin D deficiency and insufficiency are very common in pregnant women [3]. Multiple studies have reported that maternal vitamin D deficiency during pregnancy appears to be associated with an increased risk of gestational diabetes [4-13]; vitamin D supplementation in gestational diabetes patients had beneficial effects on fasting plasma glucose and serum insulin levels [14, 15]. Moreover, some studies have shown that vitamin D is required for the normal production and secretion of insulin by the endocrine pancreas [16, 17]. However, controversial results are also abundant, suggesting no significant differences in vitamin D status between women with gestational diabetes and normal glucose tolerance [16-34]. Thus, to systematically evaluate published evidence on the association between maternal vitamin D status and the risk of gestational diabetes, we conducted an extensive literature search and meta-analysis.

Materials and Methods

Search Strategy and Selection Criteria

This meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1) [35]. Institutional Review Board approval (2016(8)) was obtained from Nanjing Maternity and Child Health Care Institute.

We retrieved relevant articles in the PubMed, Medline and Embase databases up to May 2017 using the following search parameters: any observational study investigating the association between vitamin D status and the risk of gestational diabetes, with "vitamin D" OR "25(OH)D" OR "25-hydroxyvitamin D" OR "cholecalciferol" AND "gestational diabetes" as the search terms. Furthermore, we reviewed the reference lists in the retrieved articles and review articles to identify additional studies that may be eligible for inclusion in this analysis.

Studies were included in our pooled analysis if: 1) the study population was pregnant women; 2) gestational diabetes was the outcome and the control group consisted of women with normal glucose tolerance; 3) the associations between vitamin D status and risk of gestational diabetes were evaluated; 4) an effect estimate [odds ratios (OR) or risk ratios (RR)] with 95% confidence intervals (CI) for comparisons of vitamin D insufficiency and sufficiency was provided or could be calculated; 5) the article was published in English (Fig. 1). We excluded studies that were case reports or not published as full reports, studies where the vitamin D level tested during or after delivery, and studies without control subjects or with an inappropriate comparison group.

Independent Assessment

Two investigators independently searched and reviewed all the retrieved articles using a standardized approach, and data were extracted via a standardized data extraction form and checked by other investigators. The two investigators were blinded to identify information from each study and judged the inclusion and exclusion criteria of the study.

The data collected included the first author's last name, publication year, study location, study design, number of participants and gestational diabetes cases, gestational diabetes criteria, assessment of vitamin D, mean (SD) or median (IQR) concentrations of 25(OH)D, vitamin D cut-off value, adjustment for confounders, the effect estimate with 95%CI, and other related information. As there were different vitamin D cut-off values among different studies, we defined the maternal vitamin D status in this meta-analysis based on any levels reported as vitamin D deficiency or insufficiency from these studies (range from 25 to 75 nmol/L). If any of these data were missing, the respective authors were contacted for relevant information. The

concordance rate between the two investigators was 98.7%. Any discrepancies were resolved by consensus with group discussion.

Statistical Analysis

The effect estimate (OR or RR) with 95%CI in each study was used to examine the association between vitamin D status and the risk of gestational diabetes. If the adjusted effect estimate was not given, a crude effect estimate was used. If the OR with 95%CI was not provided, the data were calculated by a 2 × 2 table. Forest plots were used to visually assess pooled estimates and corresponding 95% CIs. Statistical heterogeneity among studies was tested using the χ^2 test, I^2 statistics, and *P* values [36]. In the presence of non-significant heterogeneity ($P > 0.10$), a fixed-effects model was used to calculate the pooled effect size, otherwise, a random-effects model was applied. Sensitivity analyses were performed by removing individual studies to evaluate the influence of the included study in our meta-analysis. Subgroup analyses were also conducted for the subgroups based on population, study design, number of participants, gestational diabetes criteria, assessment of vitamin D, trimester, significant difference in 25(OH)D between groups, cut-off value, and adjustment for confounders. Potent publication bias was evaluated by using funnel plots, Begg's test and Egger's test [37]. A *P* value less than 0.10 was considered to indicate significant publication bias. All statistical analyses were two-sided and performed using Stata software (version 11.0; Stata Corp).

Results

The flow chart of the study selection is described in Fig. 1. The relevant 129 articles were identified in our initial search, of which 79 were excluded after screening titles and/or abstracts. A total of 50 potentially eligible studies were selected. After detailed evaluations, 29 observational studies were included for the final pooled analysis [4-13, 16-34].

A summary of the included studies is presented in Table 1. The earliest study was published in 2008 and the latest in 2017, but more than half of the studies were published within the past 5 years. The 29 included studies consisted of 13 cohort studies, 8 nested case-control studies, 5 case-control studies, and 3 cross-sectional studies. In total, these studies

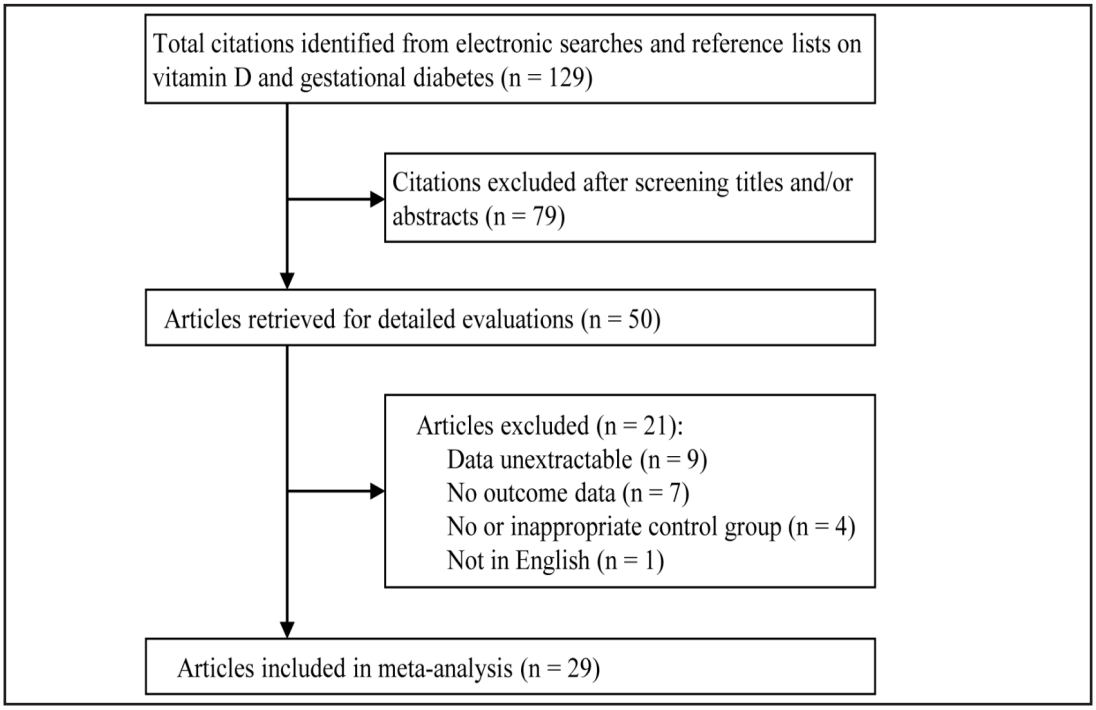

Fig. 1. Flow chart of study selection in review of the association of maternal serum 25-hydroxyvitamin D status with gestational diabetes.

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

Study	Population	Study design	Participants (n)	Gestational diabetes (n)	Gestational diabetes criteria *	Assessment of vitamin D †	Current status	25(OH)D nmol/L Mean (SD) or Median (IQR)		Significant ‡	Cut-off value (nmol/L)	Adjustments §
								Gestational diabetes	Controls			
Maghbooli 2008 [16]	Iran	Cross-sectional	579	52	C&C	RIA	24-28 weeks	16.5 (10.4)	23.0 (18.3)	Yes	35	(1), (2)
Clifton-Bligh 2008 [18]	Australia	Cohort	307	81	ADPS	LC-MS	Second/third trimester	48.6 (24.9)	55.3 (23.3)	Yes	50	(1) - (3)
Zhang 2008 [4]	US	Nested case-control	171	57	ADA	ELISA	24-28 weeks	60.5 (21.2)	75.3 (24.3)	Yes	50	(1) - (4)
Farrant 2009 [19]	India	Cohort	599	39	C&C	RIA	< 32 weeks	38.8 (NR)	37.8 (NR)	No	50	(1), (2), (5)
Soheilykhah 2010 [20]	Iran	Case-control	165	54	C&C	ELISA	24-28 weeks	24.1 (20.7)	32.3 (35.8)	Yes	50	NR
Makgoba 2011 [21]	UK	Case-control	248	90	WHO	LC-MS	First trimester	47.2 (26.7)	47.6 (26.7)	No	50	(1) - (6)
Savvidou 2011 [22]	UK	Case-control	1100	100	WHO	LC-MS	11-13 weeks	NR	NR	NR	75	(1) - (3), (6) - (8)
Baker 2012 [23]	US	Nested case-control	180	60	NDDG	LC-MS	First trimester	97.0 (29.0)	86.0 (22.0)	Yes	50	(1), (2), (6), (9)
Parlea 2012 [5]	Canada	Nested case-control	335	116	NDDG	CLIA	15-18 weeks	56.3 (19.4)	62.0 (21.6)	Yes	73.5	(9), (10)
Fernández 2012 [25]	Spain	Cross-sectional	466	36	ADA	ECLIA	11-14 weeks	NR	NR	NR	50	NR
Wang 2012 [7]	China	Nested case-control	400	200	ADA	ELISA	26-28 weeks	22.4 (11.7)	25.9 (15.8)	Yes	25	(1), (4), (11)
Burris 2012 [24]	US	Cohort	1155	68	ADA	CLIA	26-28 weeks	NR	NR	NR	25	(1) - (3), (6), (7), (9), (12) - (17)
Perez-Ferre 2012 [6]	Spain	Cohort	266	49	ADA	CLIA	24-28 weeks	NR	NR	NR	50	(1), (3) - (5)
Parildar 2013 [9]	Turkey	Case-control	122	44	IADPSG	CLIA	24-32 weeks	48.8 (23.3)	57.3 (25.0)	No	50	NR
Zuhur 2013 [10]	Turkey	Cross-sectional	402	234	IADPSG	ECLIA	24-28 weeks	30.8 (16.3)	36.0 (16.2)	Yes	50	(1), (2), (4), (5)
Bener 2013 [8]	Qatar	Cohort	1873	260	WHO	RIA	> 24 weeks	NR	NR	NR	75	NR
Schneuer 2014 [26]	Australia	Nested case-control	4090	376	ADPS	AIA	First trimester	52.1 (22.1)	56.9 (26.9)	Yes	37.5	(1), (3), (5) - (7), (10), (17) - (19)
Kramer 2014 [17]	Canada	Cohort	524	142	NDDG	ECLIA	Second/third trimester	NR	NR	NR	50	(1) - (4), (6), (14), (15), (20)
Lacroix 2014 [27]	Canada	Cohort	655	54	IADPSG	LC-MS	6-13 weeks	57.5 (17.2)	63.5 (18.9)	Yes	50	(1), (3) - (6), (17), (21) - (23)
Park 2014 [28]	Korea	Cohort	523	23	C&C	ECLIA	24-28 weeks	49.4 (19.4)	48.0 (24.8)	No	50	(1), (2), (5), (6), (9), (20)
Zhou 2014 [29]	China	Cohort	1953	331	IADPSG	ECLIA	16-20 weeks	NR	NR	NR	50	(1), (2), (24), (25)
Rodriguez 2015 [33]	Spain	Cohort	2382	93	NDDG	HPLC	13.5 weeks	71.1 (NR)	71.0 (NR)	No	50	(1) - (3), (7), (9), (12), (17), (19), (26), (27)
Arnold 2015 [11]	US	Nested case-control	652	135	ADA	LC-MS	< 20 weeks	68.3 (21.8)	73.3 (20.8)	Yes	50	(1) - (4), (6)
Pleskacová 2015 [32]	Czech	Case-control	76	47	WHO	ELISA	24-30 weeks	28.5 (13.0)	31.7 (16.0)	No	50	(2),
Nobles 2015 [31]	US	Cohort	237	31	ADA	CLIA	15.2 weeks	NR	NR	NR	75	(1) - (3), (6), (9), (14)
Loy 2015 [30]	Asian	Cohort	940	155	WHO	LC-MS	26-28 weeks	NR	NR	NR	75	(1) - (3), (5), (7), (12), (15), (17), (26)
Boyle 2016 [34]	New Zealand	Cohort	1544	32	ADHB	LC-MS	15 weeks	61.6 (23.9)	72.9 (27.0)	Yes	50	(2), (3)
Dodds 2016 [12]	Canada	Nested case-control	2320	395	CDA	AIA	before 20 weeks	45.5 (20.8)	51.9 (21.8)	NR	50	(1), (2), (6), (9), (28), (29)
Wen 2017 [13]	China	Nested case-control	4718	1280	ADPS	ELISA	Second/third trimester	42.4 (19.5)	44.3 (22.8)	Yes	50	(1) - (6), (17), (30) - (34)

involved 28, 982 participants and 4, 634 gestational diabetes cases with various ethnicities. The sample size of the participants in each study ranged from 76 to 4718. Only 9 of the 29 studies had more than 1, 000 participants, and the majority of studies (72%) were conducted in developed countries. Furthermore, the gestational diabetes criteria, assessment of vitamin D and the current status of pregnant women in these studies were different. The 25(OH)D levels in gestational diabetes cases in each study showed a wide variety, ranging from 16.5 to 97.0 nmol/L with a median of 48.7 nmol/L. Thirteen studies found a significant difference in maternal 25(OH)D between gestational diabetes cases and controls. For the cut-off value, the included studies primarily used 50 nmol/L. Twenty studies used 50 nmol/L, 5 studies used 73.5-75 nmol/L, and the remaining 4 studies used 25-37.5 nmol/L as the cut-off value. A few of the studies matched the cases and controls, but most of the studies (86%) adjusted for confounding factors, such as age, body mass index (BMI), ethnicity, season, gestational age, pregnancy weight gain, physical activity, parity, socio-economic status, vitamin D intake, alcohol consumption, etc. in different combinations.

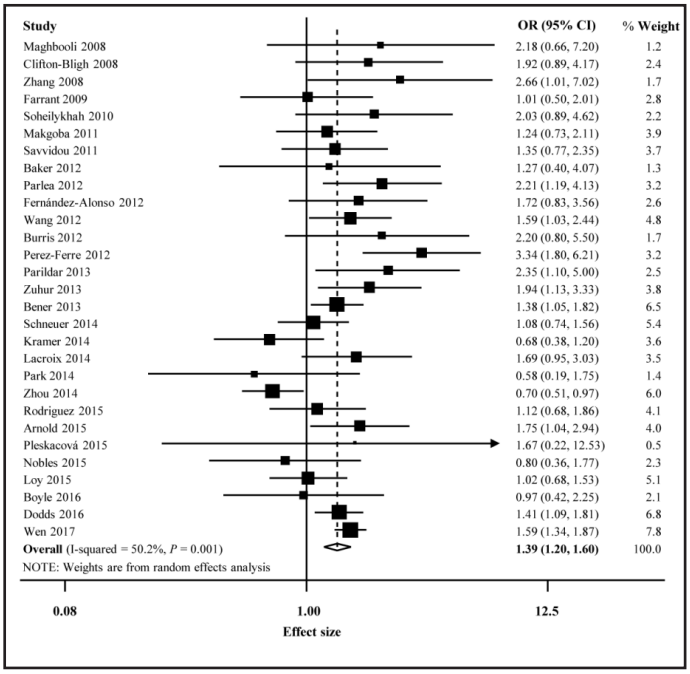

Fig. 2. Meta-analysis of the association between vitamin D insufficiency and risk of gestational diabetes.

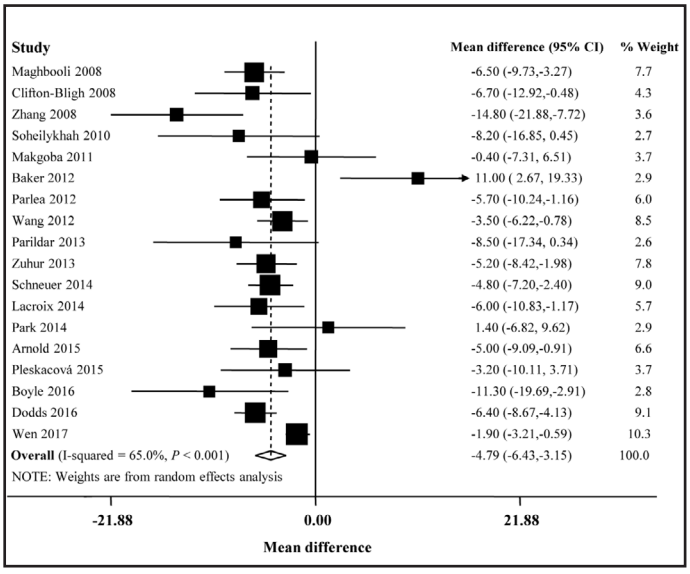

Fig. 3. Meta-analysis of the association between 25(OH)D level and gestational diabetes.

Overall, 29 studies were used for the meta-analysis to determine the association between vitamin D status and the risk of gestational diabetes (Fig. 2). Ten studies showed an increased risk of gestational diabetes for vitamin D insufficiency, eighteen studies showed no significant association between the two, and only one study showed a reduced risk of gestational diabetes for vitamin D insufficiency. The summary OR showed that maternal vitamin D insufficiency was associated with a significantly increased risk of gestational diabetes by 39% (pooled OR = 1.39, 95%CI = 1.20-1.60), and moderate heterogeneity was detected across the included studies (I^2 = 50.2%; P = 0.001). The individual risk estimate for these studies ranged from 0.58 to 3.34. We also conducted a sensitivity analysis to

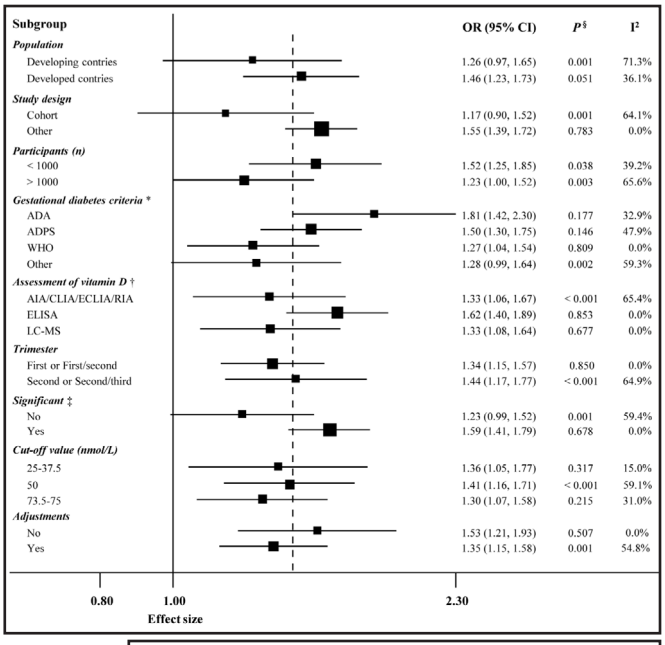

Fig. 4. Subgroup meta-analysis of the association between vitamin D insufficiency and risk of gestational diabetes. * Diagnostic criteria of gestational diabetes (1) ADA: American Diabetes Association; (2) ADPS: Australasian Diabetes in Pregnancy Society; (3) WHO: World Health Organization. † Assay method of 25(OH)D (1) AIA: automated immunoassay; (2) CLIA: chemiluminescence immunoassay; (3) ECLIA: electrochemiluminescence immunoassay; (4) RIA: radioimmunoassay; (5) ELISA: enzyme-linked immunosorbent assay; (6) LC-MS: liquid chromatography-tandem mass spectrometry. ‡ Significant difference in serum 25(OH)D between gestational diabetes and controls. § P for heterogeneity among studies.

sequentially exclude each study from the pooled analysis. The conclusion was not affected by excluding any specific study.

Fig. 3 shows the results comparing the mean difference of 18 studies including 17, 487 participants. Sixteen of the 18 studies reported that a reduced 25(OH)D level was associated with gestational diabetes. However, the mean difference for each study varied from -14.80 to 11.00. The pooled effect was -4.79 nmol/L (95% CI = -6.43, -3.15) and significant heterogeneity was also detected (I^2 = 65.0%, P < 0.001). The results showed that the 25(OH)D level was significantly lower in gestational diabetes cases than in controls and demonstrated that vitamin D insufficiency was significantly associated with an increased risk of gestational diabetes.

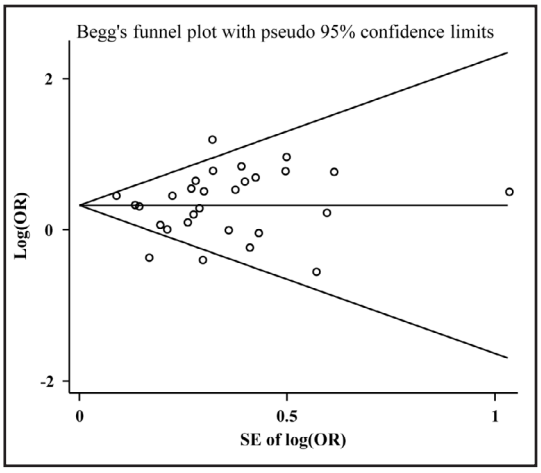

Fig. 5. Funnel plot of log (OR) against SE of log (OR) for all studies.

We also stratified our analysis based on population, study design, number of participants, gestational diabetes criteria, assessment of vitamin D, trimester, significant difference in 25(OH)D between groups, cut-off value, and adjustment for confounders to minimize heterogeneity among the included studies (Fig. 4). In our results, the ORs of the studies conducted in developed countries (vs. developing countries); with a sample size less than 1, 000 (vs. sample size greater than 1, 000); and adjusted for confounders (vs. non-adjustments) were larger, but statistical significance for heterogeneity was not reached (heterogeneity test: all P > 0.100). The OR of the cohort studies (1.17) was significantly smaller than that of studies with other study designs (1.55) (heterogeneity test: P = 0.051); and the OR of studies with a significant difference in serum 25(OH)D between gestational diabetes and controls (1.59) was significantly larger than that of studies with non-significant difference (1.23) (heterogeneity test: P = 0.039). In addition, subgroup analysis by assessment of vitamin D, trimester, cut-off value, and adjustment for confounders were all significant (Fig. 4).

We then evaluated publication bias by using funnel plots, Begg's test and Egger's test (Fig. 5). The *P* values of the Begg's and Egger's tests were 0.499 and 0.769, respectively, revealing no obvious publication bias in our analysis.

Discussion

This report reviewed and pooled epidemiological data assessing the association between vitamin D status and the risk of gestational diabetes. This comprehensive quantitative meta-analysis included 28, 982 participants and 4, 634 gestational diabetes cases with various ethnicities. Our results suggested that maternal vitamin D insufficiency might play an important role in the risk of gestational diabetes, and that the 25(OH)D level of gestational diabetes cases was decreased by 4.79 nmol/L compared to the control group.

Several previous meta-analyses have suggested that vitamin D insufficiency was associated with an increased risk of gestational diabetes [38-41]. However, these previous studies did not include several important observational studies. Furthermore, the studies did not evaluate the association between the serum 25(OH)D level and gestational diabetes, nor did they evaluate the association in specific subpopulations. Therefore, we conducted an updated meta-analysis including all of the important observational studies to evaluate the association between vitamin D deficiency and the risk of gestational diabetes, the association between the serum 25(OH)D level and gestational diabetes, as well as subgroup analysis in various subgroups. The subgroup analysis that was performed to reduce selection bias and increase the generalizability of the present results to other populations is the main strength of this study.

There was considerable heterogeneity among the 29 included studies, which was not surprising given the different ethnicities, study designs, number of participants, gestational diabetes criteria, assessment of vitamin D, trimester, cut-off values, and adjustments for confounders. Subgroup analysis suggested that maternal vitamin D insufficiency was associated with increased risk of gestational diabetes only if the following parameters were met: the study was conducted in developed countries, cohort design was not used in the study, criteria from the American Diabetes Association (ADA), Australasian Diabetes in Pregnancy Society (ADPS) or World Health Organization (WHO) was used for the gestational diabetes diagnosis, and a significant difference in serum 25(OH)D was observed between gestational diabetes cases and controls. According to the number of participants, we divided the publications into studies with sample sizes less than 1, 000 and greater than 1, 000. The OR of the group with a sample size less than 1, 000 was significantly larger than that of the group with a sample size of greater than 1, 000. Because larger studies are more representative and have less bias, the results of the studies with a larger sample size tended to be more reliable. In addition to vitamin D, there are also many competing risks that could increase the rate of gestational diabetes, including age, BMI, ethnicity, pregnancy weight gain, physical activity, socio-economic status, alcohol consumption, family history of diabetes, previous history of diabetes, etc. Thus, the overall effect decreased after adjustment for some variables.

The observed association between maternal vitamin D insufficiency and increased risk of gestational diabetes is biologically plausible. Alvarez et al. summarized the potential influence of vitamin D on glucose homeostasis [42], including the presence of specific vitamin D receptors (VDRs) on pancreatic β-cells and skeletal muscle, the presence of a vitamin D response element in the human insulin gene promoter, and the expression of the 1-α-hydroxylase enzyme in pancreatic β-cells which catalyzes the conversion of 25(OH)D to 1, 25-dihydroxyvitamin D (1, 25(OH)2D). In addition, animal and *in vitro* studies also provided compelling evidence that vitamin D may play a functional role in the preservation of glucose tolerance through its effects on insulin secretion and insulin sensitivity. However, it remains unclear whether the measurement of vitamin D levels and vitamin D supplementation during pregnancy should be recommended. Furthermore, the definition of vitamin D insufficiency

is still not globally uniform. Additional well-designed large-scale clinical trials are needed to verify the association between vitamin D status and the risk of gestational diabetes.

This meta-analysis has several limitations. First, the diagnostic criteria for gestational diabetes, the assay method for 25(OH)D, and the vitamin D cut-off values differed between studies. Further, potential confounding factors in several studies could not be adjusted for, and the adjusted models across the studies differed. Moreover, the long-term risk of adverse outcomes for mother and their offspring as well as data on sunlight exposure were not available and had not been reported by the included studies. Furthermore, the cause of the association between vitamin D insufficiency and the risk of gestational diabetes remains unclear due to the varied study designs across the included studies. Further well-designed randomized controlled trials are needed to evaluate this association and to determine the explicit effect of vitamin D supplementation on the prevention of gestational diabetes.

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Disclosure Statement

There are no relevant conflicts of interest to disclose.

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