Effect of Vitamin D Supplementation on the Incidence of Diabetes Mellitus

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Context: The effect of vitamin D supplementation on the risk of type 2 diabetes mellitus (T2DM) remains controversial because most randomized controlled trials (RCTs) have been small or have reported low doses of vitamin D.

Objective: To conduct a meta-analysis of RCTs testing vitamin D supplementation in the prevention of T2DM.

Data Sources: Database search of PubMed/MEDLINE, EMBASE, and the Cochrane Library was performed by 2 reviewers from inception through September 15, 2019.

Study Selection: We included RCTs that reported the effect of vitamin D supplementation for at least 1 year on T2DM prevention.

Data Extraction: Two independent reviewers extracted the data. The risk ratios (RRs) and 95% confidence intervals (CIs) were reported. Primary outcome of the meta-analysis was the incidence of T2DM.

Data Synthesis: Nine RCTs were included (43 559 participants). The mean age (standard deviation) was 63.5 (6.7) years. The RR for vitamin D compared with placebo was 0.96 (95% CI, 0.90-1.03); $P = 0.30$. In trials testing moderate to high doses of supplementation (≥1000 IU/day), all conducted among participants with prediabetes, the RR for vitamin D compared with placebo was 0.88 (95% CI, 0.79-0.99). In contrast, the trials testing lower doses, which were conducted in general population samples, showed no risk reduction (RR, 1.02; 95% CI, 0.94-1.10; *P, interaction by dose* = 0.04).

Conclusion: In patients with prediabetes, vitamin D supplementation at moderate to high doses (≥1000 IU/day), significantly reduced the incidence risk of T2DM, compared with placebo. **(*J Clin Endocrinol Metab* 105: 2857–2868, 2020)**

Key Words: vitamin D; diabetes mellitus; body mass index; prediabetes, meta-analysis.

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Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; D2d, Vitamin D and Type 2 Diabetes; DM, diabetes mellitus; DPVD, Diabetes Prevention with active Vitamin D; HbA1c, hemoglobin A1c; RCT, randomized controlled trial; RR, risk ratio; T2DM, type 2 diabetes mellitus; RECORD, Randomized Evaluation of Calcium Or vitamin D.

Diabetes mellitus (DM) is an important public health problem, affecting more than 500 million persons worldwide (1). Patients who have abnormally elevated glucose levels but do not meet the criteria of DM can be classified as having impaired glucose tolerance, impaired fasting glucose, or abnormally high average blood glucose level as manifested by high hemoglobin A1c (HbA_{1c}). In the United States, almost one-third of the population has impaired fasting glucose, impaired glucose tolerance, or elevated HbA_{1c} and are at elevated risk of developing DM within 5 years (2, 3).

Several risk factors for type 2 DM (T2DM) and abnormal glucose metabolism have been identified, including obesity and low physical activity (2, 4). In the past 10 to 15 years, increasing data from large-scale observational studies have shown an association between low 25-hydroxyvitamin D levels and development of T2DM (5, 6), with vitamin D supplementation being proposed as a potential intervention to lower the incidence of T2DM (7). An association between low vitamin D blood levels and impaired insulin secretion and increased insulin resistance has led to the hypothesis that vitamin D supplementation may reduce the risk of developing T2DM (8, 9). A short-term experimental study suggested that vitamin D supplementation leads to an improvement in pancreatic beta cell functioning and marginally lowers patients' HbA_{1c} (10). Furthermore, vitamin D supplementation decreased fasting blood glucose level and HbA_{1c} in patients with DM in some studies (11) but not others (12). Clinical data remain unclear regarding the benefit of vitamin D supplementation in prevention of T2DM in patients already classified as prediabetic (13, 14) or in those without glucose intolerance (15). Recently, several randomized controlled trials (RCTs) have evaluated whether vitamin D supplementation can reduce the incidence of T2DM, but most of these trials have been small or tested low doses of vitamin D. We therefore conducted a meta-analysis of RCTs of vitamin D supplementation in reducing the risk of T2DM.

Methods

Data sources and searches

In this meta-analysis, 2 reviewers (I.G. and O.B.) independently and similarly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (16) to retrieve RCTs from MEDLINE/PubMed, Embase, Cochrane Library, and ClinicalTrials.com from inception to September 15, 2019. Discrepancies between the reviewers were resolved by an independent third author (Y.Z.). The study protocol was developed and finalized before conducting the analyses, and it was registered with the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42019138943). The search terms ([vitamin D OR cholecalciferol OR ergocalciferol OR vitamin D analogue] AND [diabetes]) were used with no language restrictions. The references of the included trials were reviewed for any other potential trials. Abstracts from national conferences were also reviewed.

Study selection

Studies included in this meta-analysis met the following criteria: vitamin D supplementation trials of at least 1 year's duration, incidence of T2DM outcome reported in the trial, and patients with normal glucose tolerance or prediabetes at recruitment as defined by the American Diabetic Association: fasting glucose level, 100 to 125 mg/dL (5.6 to 6.9 mmol/L); glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg/dL (7.8 to 11.0 mmol/L); and HbA_{1c}, 5.7% to 6.4% (39 to 47 mmol/mol). Any vitamin D formulation, or analogue, with or without calcium was eligible. Studies that did not include the incidence of T2DM or measured the effect of vitamin D supplementation on patients already diagnosed with T2DM were excluded.

Data extraction and quality assessment

Two reviewers (A.B. and A.A.) extracted pertinent data from the included trials independently into prespecified data collection tables. Discrepancies between the reviewers were reconciled by an independent third author (M.B.). The methodologic quality of each RCT and the risk bias were assessed by the Cochrane Collaboration tool. The evaluation criteria in the bias risk assessment included random sequence generation, blinding of participants and health care personnel, blinded outcome assessment, allocation concealment, completeness of outcome data, evidence of selective reporting, or other biases.

The primary outcome of interest was the incidence of T2DM in patients who were assigned to vitamin D compared with placebo. The longest available follow-up time was used for each trial in the analysis. Sensitivity analyses compared results of trials testing moderate to high-dose supplementation (≥1000 IU/day) with those testing low-dose supplementation (<1000 IU/day). Eldecalcitol dosage ranged from 0.1 to 1.0 μg, and the dosage of 0.75 μg used in the Diabetes Prevention with active Vitamin D (DPVD) study is considered a high-dose equivalent to vitamin D3 (17).

Data synthesis and analysis

The Mantel-Haenszel random-effects model was used to calculate the risk ratio (RR) and 95% confidence interval (CI). The I^2 statistic was used to evaluate heterogeneity. A funnel plot was used for evaluation of publication bias regarding the primary outcome. Subgroup analysis according to the baseline mean age, gender composition, mean body mass index (BMI), formulation (daily vs bolus dosing), and mean pretreatment blood 25-hydroxyvitamin D (25OHD) level less than 30 ng/mL (to convert to nmol/L, multiply by 2.496) of each trial cohort. Sensitivity analyses through exclusion of the trials that used vitamin D analogue and calcium as a cotreatment were also conducted.

Analyses were performed by using Review Manager (RevMan) version 5.3 (Cochrane Community) and Comprehensive Meta-Analysis version 3 (Biostat).

Results

A total of 6089 articles were retrieved from electronic databases. After reviewing the abstracts and full text details, 6080 articles were excluded. Nine RCTs were included in the final analysis, illustrated Figure. 1 in (17-25). Eight trials were available as a full text while 1 trial was available only as an abstract (17). Seven trials used moderate or high dose (≥1000 IU/day) of vitamin D. All of these 7 trials included only patients with prediabetes (17-20, 22-24). Of these 7 trials, 5 trials used a bolus dose of vitamin D for supplementation (18, 20, 22-24), 1 trial added calcium supplement to the vitamin D and placebo groups (23), 1 trial included only African American men (24), and 1 study included only elderly (≥60 years) patients (21). Two trials used low-dose vitamin D (<1000 IU/day) in average-risk populations for diabetes and were included in the sensitivity analysis (21, 25). In total, 43 559 patients were included in analyses, 21 792 of whom received vitamin D supplementation and 21 767 of whom received a placebo. Across all 9 trials, the range of mean age was 46.6 to 77 years. Follow-up durations were variable between the included trials (range, between 1 and 7 years). Seven trials used cholecalciferol (18-23, 25), 1 trial used ergocalciferol (24), and 1 trial used eldecalcitol (a vitamin D analogue) (17). The Randomized Evaluation of Calcium Or vitamin D (RECORD) and the Women's Health Initiative trials were designed to test fracture reduction (21, 25), but we included post hoc analyses of diabetes in our analyses. The features of the included trials with the patients' demographic features are illustrated in Tables 1 and 2, respectively. The risk of bias was low for most of the trials (Fig. 2); Kuchay et al and Dutta

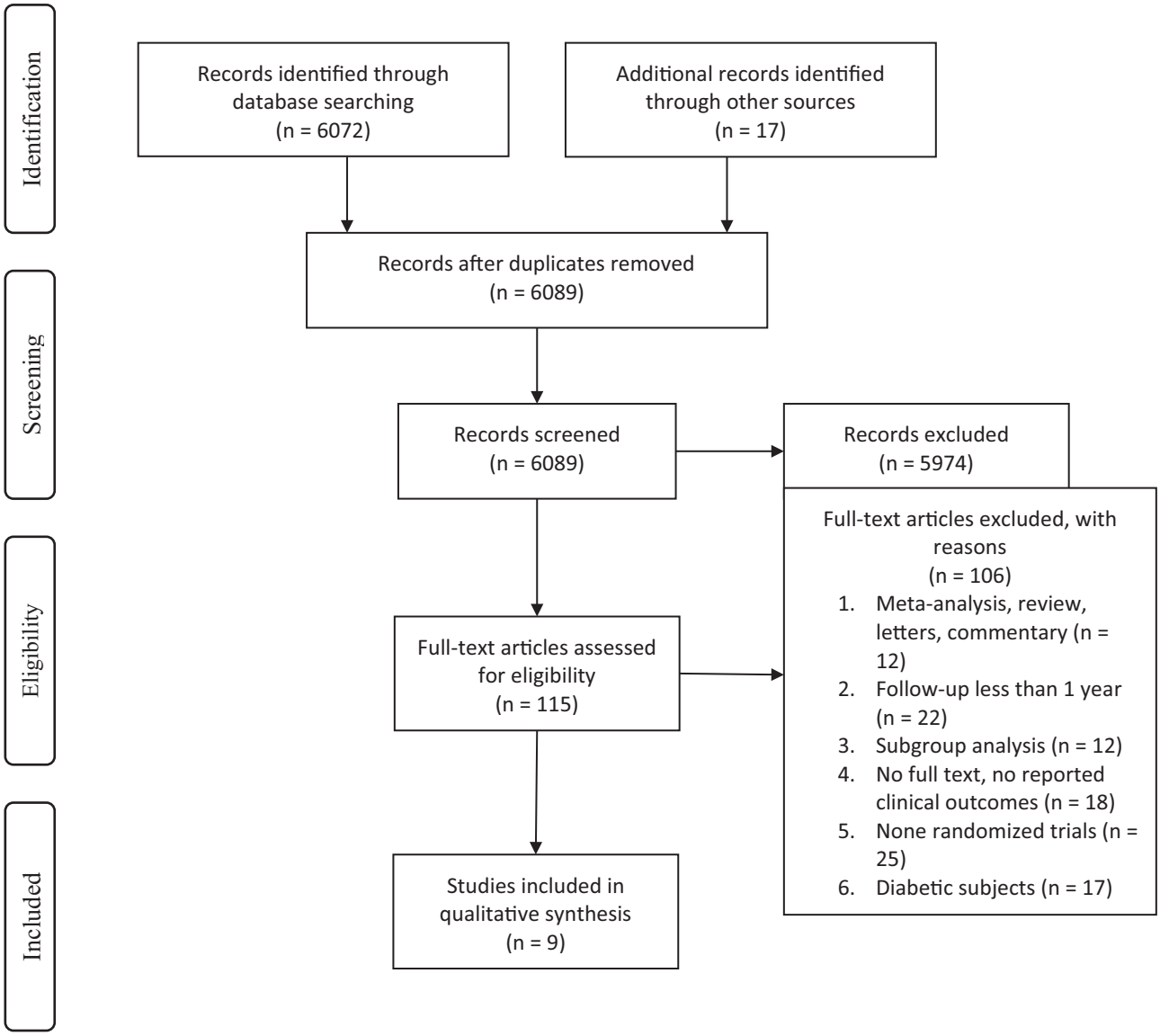

Figure 1. Trial selection (PRISMA chart). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Features of the included trials.

Study/ Author Name	Year	Patients (n)		Study Period	Vitamin D Dose and Type	Study Follow-Up_ Year	Country	Major Inclusion Criteria	Primary Outcome
		Vitamin D	Placebo						
WHI/de Boer	2008	16 999	16 952	1995-2000	Vitamin D3, 400 IU/ day and calcium 1000 mg/day	Median, 7	USA	Women aged 50-79 years with no evidence of a medical condition associated with anticipated survival <3 years and no safety, adherence, or retention risks	Total number of fractures; post hoc analysis outcome was the incidence of diabetes
RECORD/ Avenell	2009	2416	2413	1999-2002	Vitamin D3, 800 IU/ daily	2-5.2	UK	Participants aged ≥70 years who had had a low trauma, osteoporotic fracture in the previous 10 years	The incidence of new low-energy fractures; post hoc analysis outcome was the incidence of diabetes
Davidson	2013	56	53	-	Vitamin D3, mean ± SD, 88 865 ± 16 154 IU/ weekly	1	USA	Aged ≥40 years who may have prediabetes (waist circumference ≥40 inches in men and ≥35 inches in women, family history of diabetes in first-degree relatives, hypertension, and history of gestational diabetes	The change in FBG, 2-hour glucose or insulin secretion level, and the incidence of diabetes
Dutta	2014	68	102	2009-2013	Vitamin D3, 60 000 IU/weekly	28.3 ± 8	India	Aged 30-80 years; persistent IFG and/or IGT over 2 OGTTs done within a week	Change in FBG and 2-hour post glucose blood glucose, HbA_{1c}, 25-hydroxyvitamin D3, insulin, TNF-α, IL-6, hsCRP, and lipid profile
DIVA / Barengolts	2015	87	86	-	Vitamin D2 50 000 IU/weekly	1	USA	African American veteran men, aged 35-85 years, BMI 28-39 kg/m^2, fasting glucose 95-125 mg/dL and/or HbA_{1c} 5.7-6.4% (38.8–46.5 mmol/mol)	Change in oral glucose tolerance test results
Kuchay	2015	64	65	-	Vitamin D3 60 000 IU/week for 4 weeks then maintenance dose of 60 000 IU/ month	1 year	India	Patients diagnosed with prediabetes on the basis of elevated HbA_{1C} levels, FPG, and 2-hour plasma glucose during an OGTT	Change in FBG, 2-hour plasma glucose and HbA_{1c} levels
Tromsø/ Jorde	2016	256	255	2007-2008	Vitamin D3 20 000 IU/week	5	Norway	Patients aged 25-80 years with IFG and/or IGT at the OGTT with 75 g glucose	Incidence of new-onset diabetes
DPVD/ Kawahara	2018	630	626	-	eldecalcitol	2.6	Japan	Patients with impaired glucose tolerance	Incidence of new-onset diabetes

Table 1. Continued

Study/ Author Name	Year	Patients (n)		Study Period	Vitamin D Dose and Type	Study Follow-Up_ Year	Country	Major Inclusion Criteria	Primary Outcome
		Vitamin D	Placebo						
D2d/Pittas	2019	1211	1212	2013-2017	Vitamin D3 4000 IU/ day	Median (IQR), 2.5 (1.9-3.5)	USA	Patients met at least 2 of 3 glycemic criteria for prediabetes as defined by the 2010 American Diabetes Association guidelines: IFG level; impaired plasma glucose level 2 hours after a 75-g OGTT; and elevated HbA_{1c}	Incidence of new-onset diabetes

Abbreviations: BMI, body mass index; D2d, Vitamin D and Type 2 Diabetes; DIVA, D Vitamin Intervention in Veteran Administration; DPVD, Diabetes Prevention with active Vitamin D; FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin; hsCRP, highly sensitive C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-6, interleukin-6; IQR, interquartile range; OGTT, oral glucose tolerance test; RECORD, Randomized Evaluation of Calcium or Vitamin D; SD, standard deviation; TNF, tumor necrosis factor; WH,: Women's Health Initiative.

et al (22, 23) were specified as having a considerable risk of bias due to open study design. Also, the study by Jorde et al showed a significant dropout at the end of the study. The risk of bias could not be fully assessed in the DPVD study since only the abstract was available.

Primary endpoint

Vitamin D supplementation (all populations, all vitamin D doses compared with placebo) did not lower the incidence of T2DM (3424 cases; 0.96; 95% CI, 0.90-1.03; P = 0.30; I^2 = 3%, Fig. 3). Post hoc sensitivity analyses according to the vitamin D dosage, however, showed different results. Vitamin D supplementation at moderate or high dose (≥1000 IU/day) was associated with significant reduction in incidence of T2DM (1019 cases; RR, 0.88; 95% CI, 0.79-0.99; P = 0.03; I^2 = 0%, Fig. 4). These higher-dose trials all tested participants with prediabetes, and incident diabetes was the primary outcome. In contrast, analysis of the 2 trials testing low doses (<1000 IU/day) of vitamin D showed no risk reduction (RR, 1.02; 95% CI, 0.94-1.10; P = 0.68; I^2 = 0%; P for interaction by dose = 0.04; Fig. 4). These 2 trials tested participants at average risk, and incident diabetes was a post hoc hypothesis. Excluding trials that used vitamin D analogue or used calcium as a cotreatment did not change the results (Fig. 5). Publication bias was assessed by analyzing the funnel plot provided in Fig. 6, which showed no significant publication bias. When combining data from trials with cohorts that had a mean baseline BMI <30 kg/m^2, the RR of T2DM with moderate or high dose (≥1000 IU/day) of vitamin D supplementation was 0.68 (95% CI, 0.53-0.89; P = 0.005; I^2 = 0%), while no benefit was found in those with a mean BMI ≥30 kg/m^2 (RR, 0.98; 95% CI, 0.83-1.16; P = 0.79; I^2 = 0%), with a significant subgroup difference (P = 0.03; Fig. 7). Subgroup analysis according to baseline mean age, sex composition, formulation (daily vs bolus dosing), and mean pretreatment blood 25OHD level less than 30 ng/mL (to convert to nmol/L, multiply by 2.496) of each trial cohort did not reveal any significant modifying effects of these variables (Figs. 8-11).

Discussion

In this updated meta-analysis of 9 randomized controlled trials (N = 43 559) evaluating the benefit of vitamin D supplementation in reducing the incidence of T2DM, we found that vitamin D supplementation at moderate or high doses (≥1000 IU/day), tested in patients with prediabetes, resulted in a significantly lower risk of T2DM, whereas lower doses tested in average

Table 2. Demographic features of the involved studies.

Study/ Author Name	Patient (n)	Subgroup	Age_Mean (SD)_Year	Female n (%)	Race_n (%)				Body Mass Index_Mean (SD)	FBG_Mean (SD) - mg/dL	2-Hr Postload Plasma Glucose _Mean (SD) - mg/dL	Glycated Hemoglobin_Mean (SD) - %	Serum 25-hydroxyvitamin D Level_ Mean-(SD) ng/mL
					White	Black	Asian	Other					
WHI/ deBoer	16 999	Vitamin D3 and calcium	No. of patients 50-59: 6384 60-69: 7696 70-79: 2919	16 999 (100)	14 260 (83.9)	1430 (8.4)	338 (2)	971 (5.7)	No. of patients <25: 4628 25-30: 6166 >30: 6120	No. of patients <100: 767 ≥100: 261	-	-	No. of patients <12.9: 381 12.9-17.4: 371 17.5-24.0: 366 ≥ 24 1: 395
	16 952	Placebo	No. of patients 50-59: 6358 60-69: 7674 70-79: 2920	16 952 (100)	14 297 (84.3)	1409 (8.3)	313 (1.8)	933 (5.5)	No. of patients <25: 4720 25-30: 6183 >30: 5958	No. of patients <100: 777 ≥100: 275	-	-	No. of patients <12.9: 391 12.9-17.4: 394 17.5-24.0: 402 ≥ 24 1:397
RECORD/ Avenell 2009	2416	Vitamin D3 and calcium	77 ± 6	2240 (84·6)	2629 (99)	-	-	-	Weight in kg =65 ± 13	-	-	-	-
	2413	Placebo	77 ± 6	2241 (84·8)	2623 (99)	-	-	-	Weight in kg =65 ± 12	-	-	-	-
Davidson, 2013	56	Vitamin D3	52.3 ± 8.0	36 (64)	0	5 (9)	0	Latino 51 (91)	32.1 ± 4.7	98.7 ± 8.7	158 ± 22	6.1 ± 0.3	22.0 ± 4.5
	53	Placebo	52.5 ± 7.0	38 (71)	0	9 (17)	0	Latino 44 (83)	32.9 ± 4.3	97.5 ± 9.4	162 ± 18	6.1 ± 0.4	22.0 ± 4.8
Dutta, 2014	68	Vitamin D3 and calcium	48.37 ± 10.47	43 (63.2)	-	-	-	-	26.32 ± 4.52	109.91 ± 9.06	152.84 ± 27.6	6.15 ± 0.6	17.04 ± 7.66
	57	Placebo and calcium	47.4 ± 11.51	31 (54.4)					26.83 ± 4.63	110 ± 9.25	155.16 ± 25.1	6.05 ± 0.57	18 ± 7.16
	45	Placebo and calcium	46.6 ± 11.01	27 (60)					25.51 ± 4.44	109.56 ± 10.2	155.69 ± 23.8	6.19 ± 0.54	37.89 ± 8.26
DIVA/ Barengolts, 2015	87	Vitamin D2	58.2 ± 6.0	0	-	87 (100)	-	-	32.4 ± 2.9	98.3 ± 9.3	131.9 ± 31.8	6.14 ± 0.26	<10: 20 (22.7) 10-19: 52 (59.1) 20-29: 15 (18.2)
	86	Placebo	59.8 ± 6.0	0	-	86 (100)	-	-	31.5 ± 2.4	97.7 ± 10.3	129.7 ± 34.6	6.08 ± 0.20	<10: 24 (27.9) 10-19: 51 (59.3) 20-29: 11 (12.8)
Kuchay, 2015	64	Vitamin D3	47.6 ± 9.5	-	-	-	-	-	25.9 ± 2.6	109 ± 6	144 ± 24	5.9 ± 0.3	19.8 ± 15.5
	65	Placebo	48.5 ± 11.8	-	-	-	-	-	25.2 ± 3.1	110 ± 6	149 ± 23	5.9 ± 0.2	18.9 ± 13.4
Tromsø/ Jorde, 2016	256	Vitamin D3	62.3 ± 8.1	95 (37.1)	-	-	-	-	30.1 ± 4.1	110 ± 8	131 ± 38	5.98 ± 0.28	24.0 ± 8.8
	255	Placebo	61.9 ± 9.2	102 (40.0)	-	-	-	-	29.8 ± 4.4	109 ± 9	133 ± 33	5.97 ± 0.34	24.4 ± 8.5
Kawahara, 2018	630	Eldecalcitol	-	-	-	-	-	-	-	-	-	-	-
	626	Placebo	-	-	-	-	-	-	-	-	-	-	-
D2d/Pittas, 2019	1211	Vitamin D3	59.6 ± 9.9	541 (44.7%)	810 (66.9)	301 (24.9)	66 (5.5)	34 (2.8)	32.0 ± 4.5	108.0 ± 7.4	136.9 ± 34.3	5.9 ± 0.2	27.7 ± 10.2
	1212	Placebo	60.4 ± 10.0	545 (45.0)	806 (66.5)	315 (26.0)	64 (5.3)	27 (2.2)	32.1 ± 4.4	107.8 ± 7.4	137.6 ± 34.3	5.9 ± 0.2	28.2 ± 10.1

Abbreviations: D2d, Vitamin D and Type 2 Diabetes; DIVA, D Vitamin Intervention in Veteran Administration; FBG, fasting blood glucose; RECORD, Randomized Evaluation of Calcium or Vitamin D; SD, standard deviation; WHI,Women's Health Initiative.

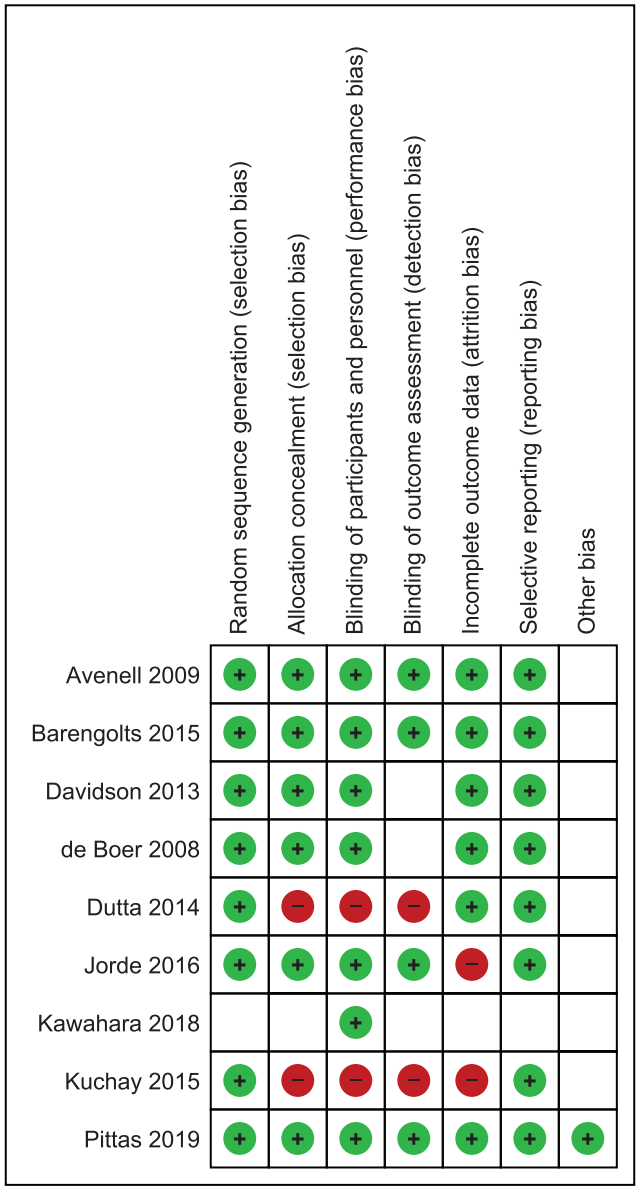

Figure 2. Risk of bias summary. Review authors' judgments about each risk of bias item for each included study. The green circles indicate low risk of bias, red circles indicate a high risk of bias, and the empty squares mean the risk cannot be ascertained.

risk populations for diabetes did not confer risk reduction (*P*, interaction = 0.04).

In a large-scale prospective observational study including more than 83 000 participants who reported their personal use of vitamin D and calcium supplements, those who took high-dose supplements had a lower risk of T2DM than those who took lower doses (26). This was followed by several observational studies that suggested an association between low serum vitamin D levels and an increased risk of T2DM. However, these observational studies have a high risk of bias due to uncontrolled confounding (7, 27). A previous meta-analysis of patients with prediabetes indicated that vitamin D supplementation led to significant improvement in glycemic control, including reductions in fasting blood glucose and HbA_{1c} levels, suggesting that vitamin D supplementation may play a role in preventing T2DM (14). However, an updated meta-analysis was published in 2018 reporting no significant reduction in T2DM incidence. Although a prior meta-analysis assessed the role of vitamin D dosing, the result remained nonsignificant (13). In our meta-analysis, we included the most recent RCTs designed for diabetes prevention and found a significant benefit of vitamin D supplementation at moderate or high dose (≥1000 IU/day) with regard to the incidence of T2DM.

The Vitamin D and Type 2 Diabetes (D2d) trial was the largest trial designed to study the incidence of diabetes with vitamin D supplementation (19). In this trial, 2423 patients with prediabetes were randomized to receive a large daily dose of vitamin D3 (4000 IU) or a placebo. Despite this large dose of vitamin D, the study yielded a nonsignificant reduction in the incidence of T2DM. The D2d trial investigators speculated that the null result was due to inclusion of many participants with normal serum levels of 25OHD (28). To address this concern, many RCTs have been conducted on patients with prediabetes and low serum vitamin D levels

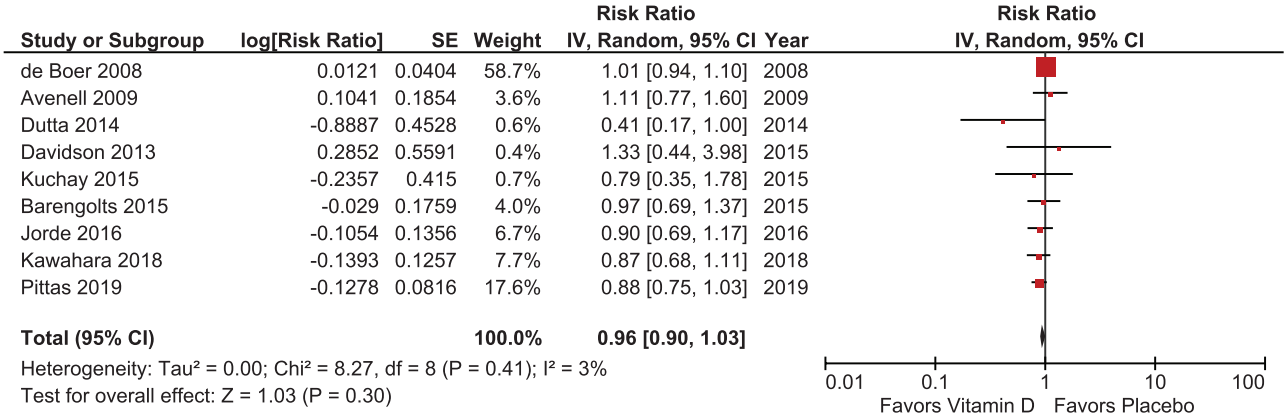

Figure 3. Forest plot illustrating the results of the incidence of DM in patients who received vitamin D compared with placebo. CI, confidence interval; df, degree of freedom; DM, diabetes mellitus, IV, intravenous; SE, standard error.

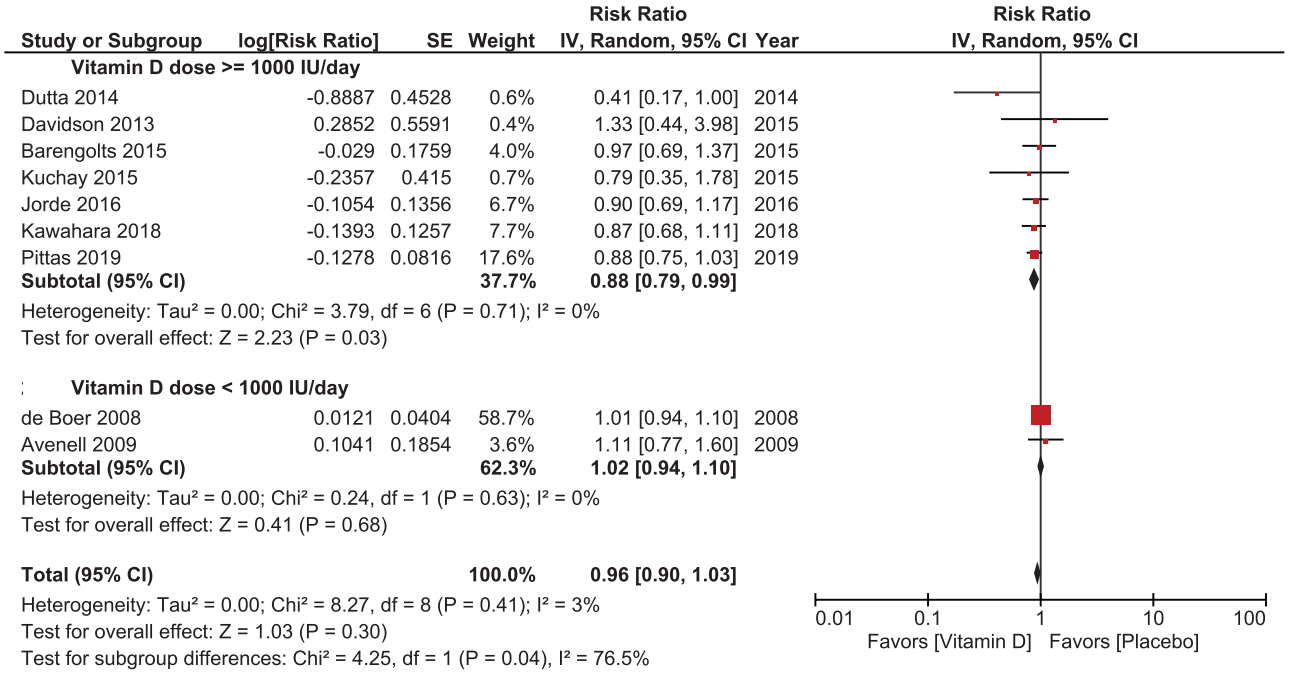

Figure 4. Forest plot of the subgroup analysis according to the total daily dosage of vitamin D: ≥1000 IU/day or <1000 IU/day. CI, confidence interval; df, degree of freedom; IV, intravenous; SE, standard error.

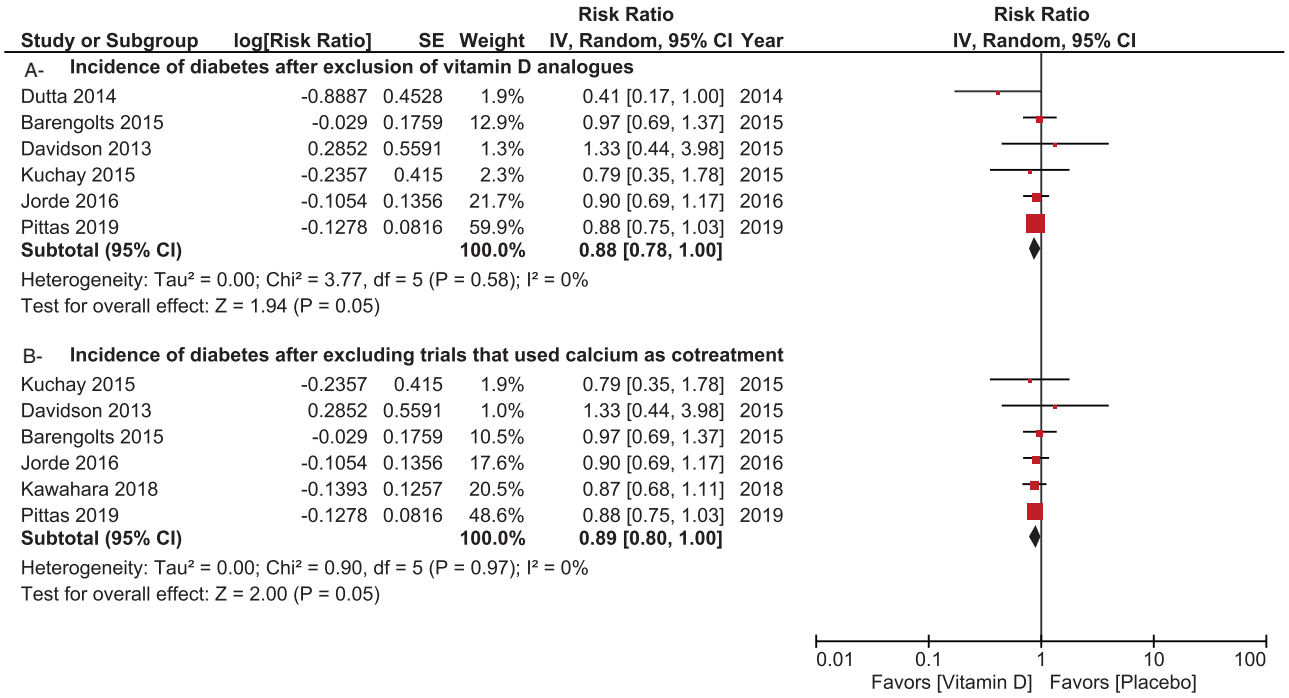

Figure 5. Forest plot of the sensitivity analysis by A) excluding studies that used vitamin D analogues, and B) excluding studies that used calcium as a cotreatment with the vitamin D. CI, confidence interval; df, degree of freedom; IV, intravenous; SE, standard error.

(18, 22-24); however, analyses of these groups showed no clear correlation between the pretreatment vitamin D level and the reduction of T2DM incidence with vitamin D supplementation. Similar to the D2d trial, most of the higher-dose trials were designed for glycemic outcomes in high-risk populations and, when examined individually, did not show a significant reduction in the incidence of T2DM but did show a trend toward lower incidence of T2DM in the vitamin D supplement group. In our meta-analysis, these results became statistically significant due to the improved statistical power from aggregating these trials.

The trials that tested low doses of vitamin D, the Women's Health Initiative and RECORD trials (21, 25),

were not designed to assess glycemic outcomes and were conducted in average-risk populations. We did a post hoc subgroup analysis according to the total daily dosing of vitamin D supplementation, to test the subgroup difference, and we found a significant reduction in the incidence of DM in the higher-dose trials compared with lower-dose trials, with significant interaction, which supports the role of moderate or high-dose supplementation in reducing the incidence of T2DM. Another factor that may have weakened the results for vitamin D supplementation in these 2 trials is inclusion of patients with normal glucose tolerance.

An important modifier of trial results was the BMI; trials with cohorts that had a mean baseline non-obese BMI (<30 kg/m^2) had a significant reduction in the incidence of T2DM with vitamin D supplementation, while those with a higher mean BMI (≥30 kg/m^2) did not. Although this could be related to the fact that vitamin D is a fat-soluble vitamin, leading to decreased bioavailability in patients who are obese (29), the serum 25OHD levels achieved with treatment did not differ substantially by BMI group in some studies (30). Thus, the interaction by BMI in these vitamin D trials warrants further study as we have used the mean cohort BMI in the analyses, which is not as reliable as an individual participant analysis.

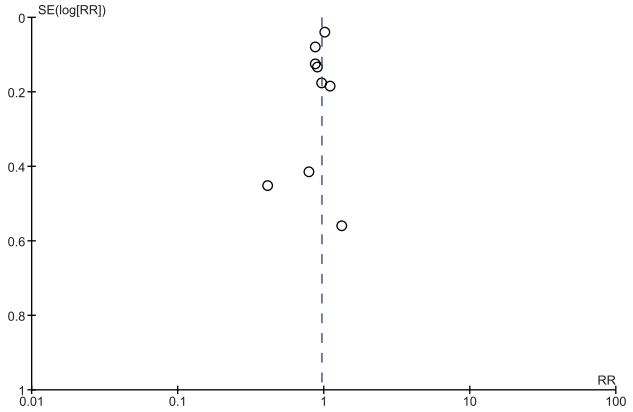

Figure 6. Funnel plot of primary endpoints (incidence of DM). DM, diabetes mellitus; RR, risk ratio; SE, standard error.

Lower vitamin D synthesis in darker skin has been proposed as the main factor behind the high prevalence of vitamin D deficiency among racial groups with darker skin types (24, 31). These patient populations have a higher reported prevalence of chronic conditions like cardiovascular disease and diabetes, which can be, in part, attributed to the vitamin D deficiency (31). However, Barengolts et al (24) and the subgroup analysis of Pittas et al did not indicate a greater protective effect of vitamin D supplementation in decreasing the incidence of T2DM in these groups. Furthermore, our stratified analysis did not show any significant difference based on sex, age, vitamin D formulation (bolus vs daily), and low pretreatment 25OHD levels (less than 30 ng/mL). These results should be interpreted cautiously because of low data counts, and additional large trials are needed for definitive conclusions.

Limitations

There are several limitations that should be considered. The performed analyses have many potential variables that could affect the results, including the pretreatment blood 25OHD levels, vitamin D dosing, and different vitamin D formulations. To overcome this, we performed subgroup and sensitivity analyses to test each

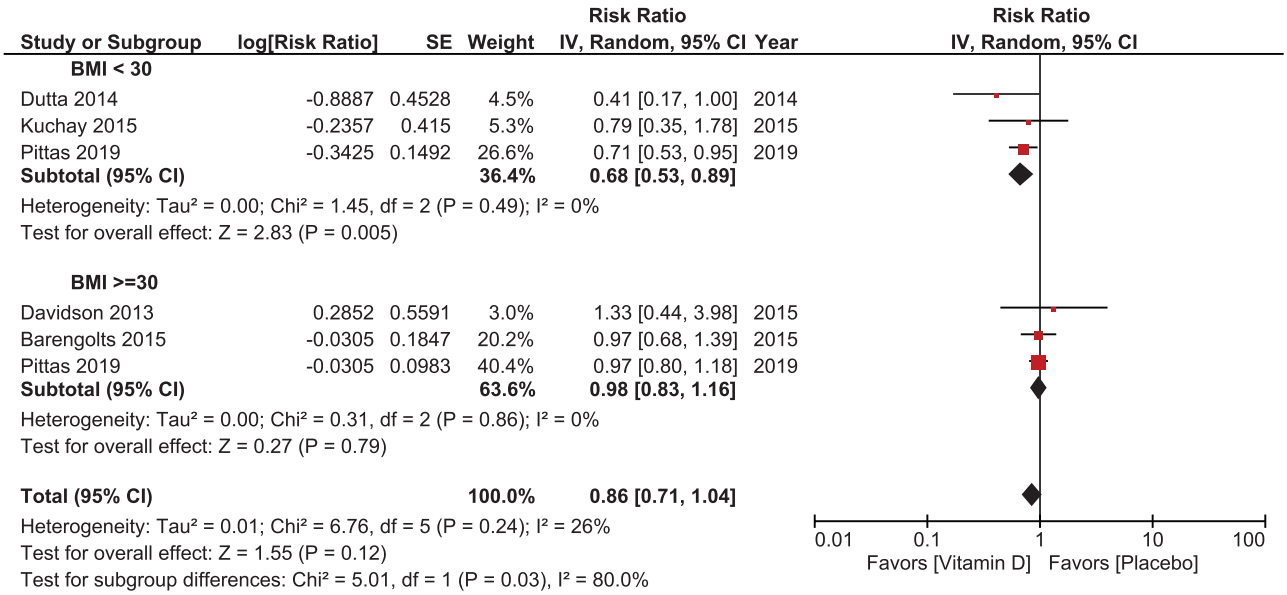

Figure 7. Forest plot of the subgroup analysis according to body mass index (BMI). CI, confidence interval; df, degree of freedom; IV, intravenous; SE standard error.

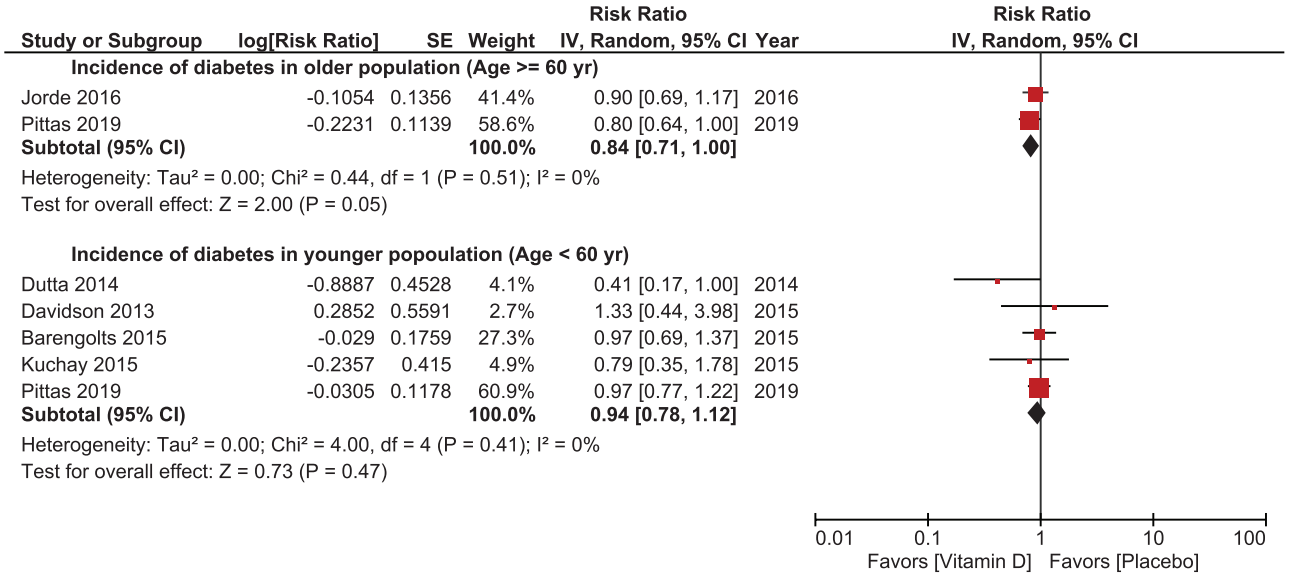

Figure 8. Forest plot of the subgroup analysis according to the patient age. CI, confidence interval; df, degree of freedom; IV, intravenous; SE, standard error.

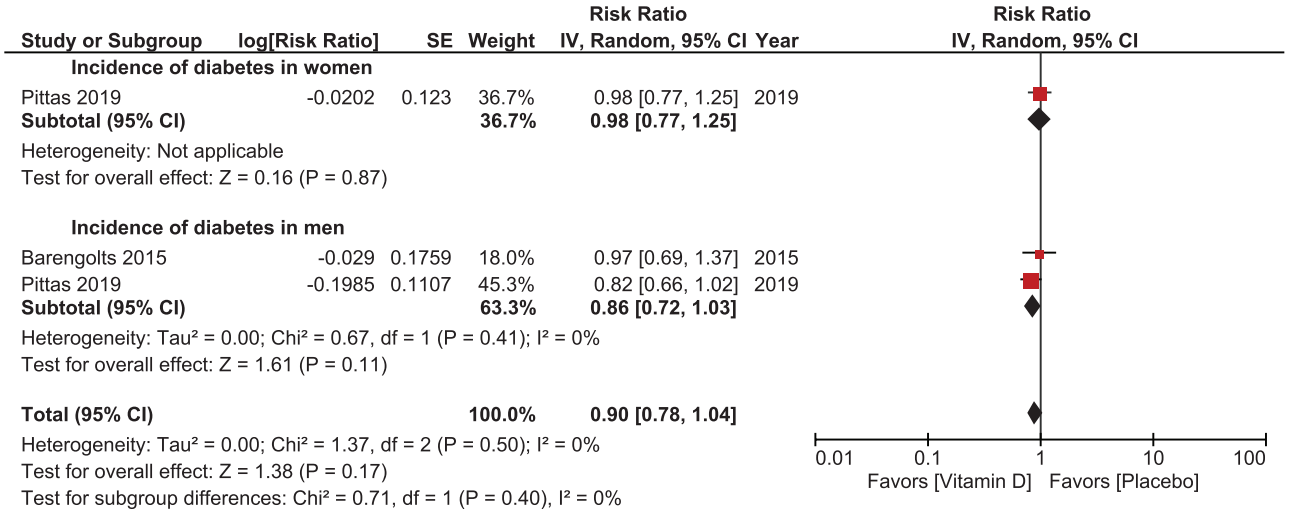

Figure 9: Forest plot of the subgroup analysis according to the patient sex. CI, confidence interval; df, degree of freedom, IV, intravenous; SE, standard error.

of these potential modifiers. However, the result of each of these subanalyses should be interpreted cautiously due to low data counts and multiple comparisons. Also, a trial data-based meta-analysis cannot assess the results of the effect of these modifiers as reliably as an individual participant data meta-analysis. For example, although our post hoc analyses showed that BMI is a significant effect modifier, we have used the mean cohort BMI in the analyses, which may not be as reliable as using individual participant BMI. The same limitations apply to the subgroup analyses according to age and pretreatment blood 25OHD levels. Another limitation that should be considered is that the DPVD trial has been published only in abstract form, which limited our quality assessment. Finally, some of the included studies did not prespecify incidence of T2DM as a designated primary outcome (21, 25), and the incidence of DM was defined by the patient self-reporting taking pills or insulin for newly diagnosed T2DM.

Conclusion

In this meta-analysis, vitamin D supplementation at moderate to high doses (≥1000 IU/day) significantly lowered risk of T2DM when compared with placebo in patients with prediabetes. The results of these subgroup analyses according to mean age, baseline sex composition, BMI, formulation (daily vs bolus dosing), and mean pretreatment 25OHD level should be interpreted

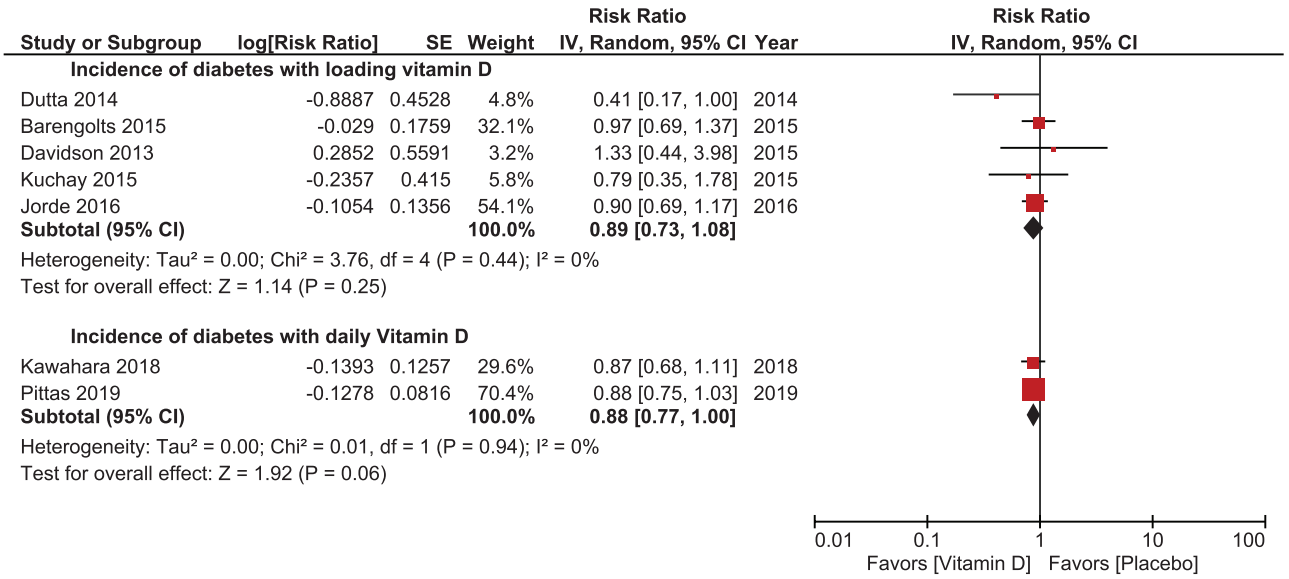

Figure 10. Forest plot of the subgroup analysis according to the vitamin D regimen (daily vs bolus dosing). CI, confidence interval, df, degree of freedom; IV, intravenous; SE, standard error.

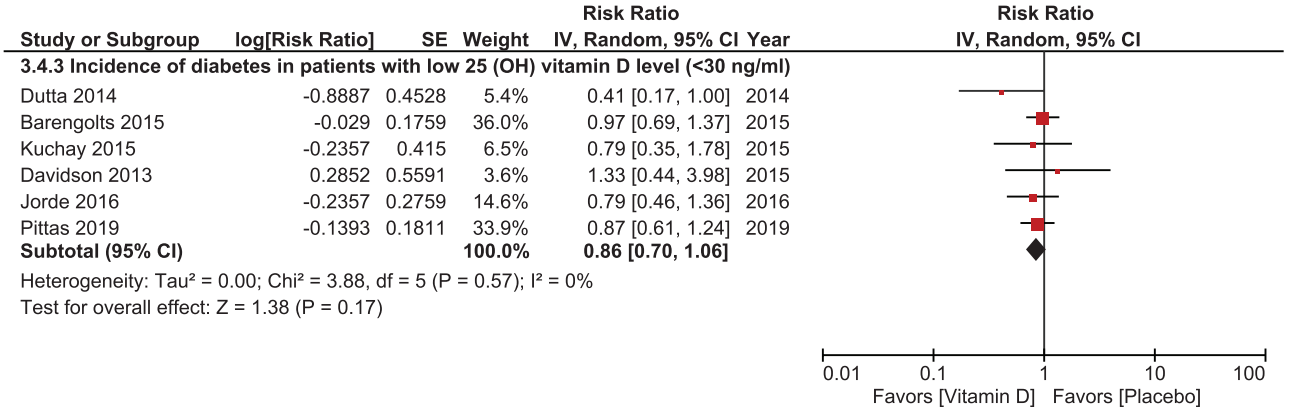

Figure 11. Forest plot of the subgroup analysis according to the pretreatment 25-hydroxyvitamin D level: < or ≥30 ng/mL. CI, confidence interval; df, degree of freedom; IV, intravenous; SE, standard error.

cautiously, and a participant-level meta-analysis would enhance our understanding of these relationships.

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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