Role of vitamin D in prevention of type 2 diabetes mellitus: A systematic review and meta-analysis

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Abstract. The escalating prevalence of diabetes mellitus, projected to affect over 700 million by 2045, underscores the urgent need for effective management and prevention strategies, with type 2 diabetes mellitus (T2DM) constituting over 90% of these cases globally. The present meta-analysis aims to rigorously evaluate the potential of vitamin D supplementation in mitigating the onset of T2DM, amidst the backdrop of its biological plausibility yet inconclusive evidence regarding its efficacy in reducing new incidences of the disease. A comprehensive literature search up to December 2023 in MEDLINE, EMBASE and the Cochrane Library, employing a strategy focused on diabetes and vitamin D, identified randomized controlled trials (RCTs) that explore the impact of vitamin D supplementation on T2DM onset in adults with impaired glucose regulation, incorporating quality assessment via the Cochrane ROB2 tool and utilizing meta-analysis with RevMan Web to evaluate effect magnitude and heterogeneity. In a meta-analysis of 11 RCTs with 5,221 prediabetic patients, vitamin D supplementation was associated with a 10% reduction in the progression to T2DM [RR, 0.90; 95% CI, (0.81-0.99)] and a significant increase in regression to normoglycemia [RR, 1.24; 95% CI, (1.08-1.43)], with no significant heterogeneity or publication bias observed. This meta-analysis of 11 RCTs shows that vitamin D supplementation in prediabetic patients lowers the risk of T2DM and promotes regression to normoglycemia, with no significant differences in subgroup analyses or interaction with baseline vitamin D levels, ethnicity, or body mass index (BMI). Despite indications from some trials that baseline vitamin D status may influence outcomes, the present comprehensive analysis found benefits of vitamin D across diverse populations, including non-obese individuals, without conclusive evidence linking supplementation to changes in BMI or age-specific advantages.

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Introduction

The prevalence of diabetes mellitus (DM) is on an upward trajectory, with projections indicating an increase to over 700 million individuals by the year 2045 (1). As of 2019, it is estimated that >463 million individuals globally are afflicted with DM, positioning the management and prevention of this condition as a primary global health objective (2). Type 2 DM (T2DM) is characterized by hyperglycemia, insulin resistance and compromised insulin secretion, representing the predominant form of diabetes and accounting for >90% of DM cases worldwide. This condition impacts hundreds of millions globally (3). Despite the significant lifetime risk associated with T2DM, accurately predicting and preventing the disease in the general populace remains a significant challenge.

Vitamin D, encompassing cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), serves as a precursor to hormones and plays a pivotal role in the regulation of calcium and phosphate metabolism (4). The biosynthesis of vitamin D initiates with the irradiation of 7-dehydrocholesterol in the skin by ultraviolet B radiation under the influence of strong sunlight, constituting the principal mechanism of vitamin D production (5). The intake of vitamin D and its protective effects against T2DM have been the focus of extensive research.

Several strands of evidence suggest a potential role for vitamin D in the prevention of T2DM. First, vitamin D may regulate numerous processes implicated in the initiation of T2DM, including the modulation of calcium ion concentration and the generation of reactive oxygen species (ROS) (6,7). Second, vitamin D is recognized for its role in maintaining normal mitochondrial function, crucial for cellular bioenergetics (8). Lastly, vitamin D has been shown to mitigate

inflammation, thereby aiding in the control of insulin resistance (9). Consequently, the proposition that vitamin D mitigates the onset of T2DM can be elucidated by its multifaceted mechanisms of action, a subject that has been rigorously examined within both clinical and basic research spheres.

Nevertheless, the hypothesis that vitamin D status could affect the risk of T2DM, despite its biological plausibility, is met with consistently inconclusive results. The real-world efficacy of vitamin D supplementation in diminishing the incidence of new T2DM cases remains ambiguous, notwithstanding theoretical rationale. This ambiguity underscores the critical necessity to integrate the findings from extant clinical trials, highlighting the imperative to rigorously evaluate the influence of vitamin D consumption on the development of T2DM. Accordingly, the present meta-analysis was designed to amalgamate the outcomes of clinical investigations concerning the impact of vitamin D supplementation on the progression of T2DM.

Materials and methods

Search strategy. A comprehensive search of English-language literature was conducted through MEDLINE (https://pubmed.ncbi.nlm.nih.gov), EMBASE (https://www.embase.com) and the Cochrane Library (https://www.cochranelibrary.com) for studies published from January 2010 to December 2023. The search strategy employed was '(diabetes* or hyperglycemia*) and (vitamin D or cholecalciferol* or ergocalciferol*)', with a restriction to randomized controlled trials.

Study selection criteria. Eligible studies were required to meet the following inclusion criteria: i) Inclusion of an adult population; ii) diagnosis of impaired glucose tolerance, prediabetes, or impaired fasting glucose; iii) investigation of the effect of vitamin D supplementation on the onset of T2DM, conversion to normoglycemia, oral glucose tolerance test, fasting serum glucose (FSG) and hemoglobin A1c (HbA_{1c}) levels; iv) restriction to randomized controlled trials (RCTs). Additionally, studies involving participants diagnosed with T2DM, which also considered combination therapy with other medications, such as calcium supplements, omega-3 fatty acids, or statins, were included. Such studies were specifically selected when they were designed to serve as appropriate control groups, thereby facilitating the examination of the effects of vitamin D. The screening and selection process of the studies for inclusion in the analysis were conducted by two independent reviewers.

To enhance the reliability, and validity of meta-analysis research, the study protocol is registered on the Open Science Framework. The study protocol is available in the Open Science Framework (https://doi.org/10.17605/OSF.IO/XJ3EN).

Quality assessment methodology. To assess the quality of the RCTs, the Cochrane Risk of Bias tool for randomized trials (ROB2) was utilized (10). This tool evaluates five domains of potential bias: The randomization process, the blinding of participants and personnel, the handling of missing outcome data, the completeness of outcome data measurement, and the reporting of selected outcomes. Each study was independently assessed by two reviewers for its risk of bias, categorizing the risk level as 'high', 'some concern' or 'low'.

Statistical analysis. Meta-analyses were performed utilizing Review Manager software (RevMan, version 5.4.1; The Cochrane Collaboration, 2020) for statistical analysis. The magnitude of the effect was determined based on the mean difference (MD) along with its 95% confidence interval (CI) for continuous outcomes. For dichotomous outcomes, the risk ratio (RR) with its 95% CI was calculated. An inverse-variance method and Mantel-Haenszel method were applied to combine data for continuous outcomes and dichotomous outcomes, respectively. Heterogeneity among studies was quantified using the I^2 statistic, with ≤25% indicating low heterogeneity, 26-50% indicating moderate heterogeneity, and >50% indicating high heterogeneity. Random effects meta-analysis was used due to differences in patient baseline characteristics in each study affecting treatment effectiveness.

Subgroup analyses were undertaken to explore the influence of specific covariates on the outcomes, including body mass index (BMI), ethnicity, baseline vitamin D deficiency, concurrent calcium intake, dosage of vitamin D supplementation, baseline vitamin D levels, and duration of vitamin D intake. Publication bias was evaluated using a funnel plot and Egger's test. Sensitivity analyses by sample size were also conducted to verify the stability of the findings.

Results

Study selection and quality assessment. In the initial phase of the literature search, a total of 2,338 potential studies were identified. The process of study selection, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, is delineated in Fig. 1 (11). Subsequent to the preliminary screening, a total of 556 studies were removed due to duplication. An additional 1,765 studies were deemed ineligible and thus excluded based on an assessment of their titles and abstracts, which indicated a lack of direct relevance to the research query. Upon a more detailed examination, involving the full-text review of the 17 studies preliminarily selected, 6 were further excluded for failing to satisfy the established inclusion criteria (12-17). Consequently, the present systematic review ultimately incorporated 11 studies that conformed to the rigorous selection criteria.

In total, 11 RCTs were included in the final analyses (18-28). Upon evaluating the methodological quality of the included studies, each demonstrated a low risk of bias when appraised utilizing the ROB2 tool for randomized trials. The follow-up duration of all trials ranged from 6 months to 5 years. The risk of bias is shown in Fig. 2. All these trials were conducted on prediabetic patients. The characteristics of the included trials are shown in Tables I and II. A total of 5,221 patients were included in the analyses, 2,619 patients were supplemented with vitamin D and 2,602 patients were assigned to the control group. In total, 9 trials used vitamin D_3 (cholecalciferol) (19-22,24-28), 1 trial used vitamin D_2 (ergocalciferol), and 1 trial used eldecalcitol, a vitamin analog (23). A total of 10 trials reported the progression of

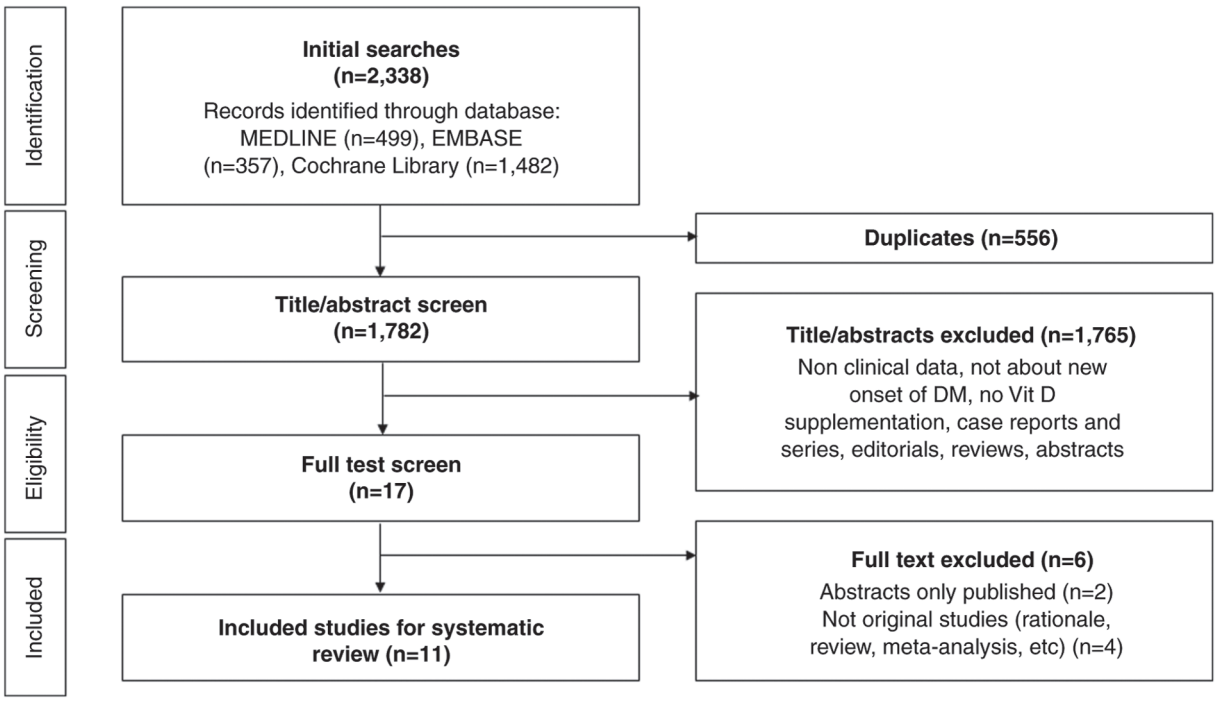

Figure 1. Flow chart illustrating the literature search and study selection.

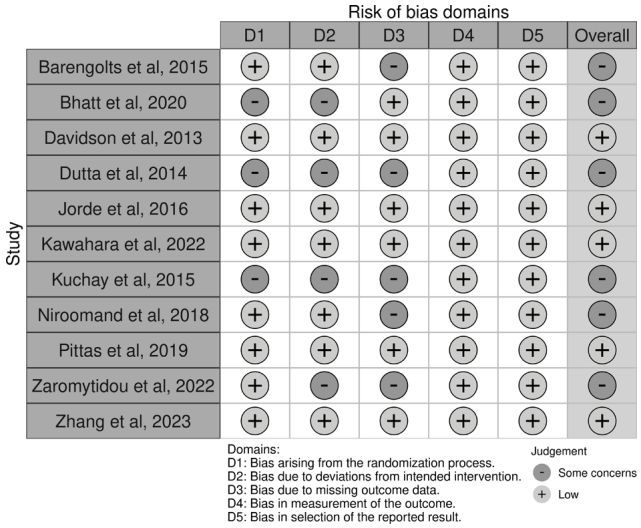

Figure 2. Risk of bias assessment of selected studies.

prediabetes to T2DM (18-27) and 8 trials measured regression to normoglycemia (18-23,25,27). Of those 10 trials, 5 trials progressed over 12 months (19,21-23,26), 3 trials included only Indians (19,21,24), 7 trials had mean BMI >30 (18-20,22,25-27), and 3 trials used calcium carbonate or supplements along with vitamin D (19,21,26). The median age of 10 trials was 59.5 years.

New onset of T2DM. A total of 10 out of 11 trials reported the progression of prediabetes to T2DM (18-27). Pooled data from all 10 trials reporting in RR revealed that vitamin D supplementation in prediabetes patients decreased the new-onset T2DM by 10% [RR, 0.90; 95% CI, (0.81, 0.99); P=0.04 and I^2=0%)] (Fig. 3).

Subgroup analyses were conducted to identify any covariates for between-study heterogeneity. The pooled effect sizes found in each subgroup (based on treatment duration, ethnicity, mean BMI, baseline vitamin D level, inclusion of vitamin D deficiency, median age and vitamin dose) were not significantly different. Among the subgroups, the group that received only vitamin D showed a statistically insignificant difference in the incidence of T2DM compared with the control group [RR, 0.89; 95% CI, (0.71, 1.11); P=0.30]. However, when the analysis included all clinical trials that used a combination of calcium carbonate and vitamin D supplements, a statistically significant difference was observed [RR, 0.89; 95% CI, (0.79, 1.00); P=0.04] (data not shown).

Regression to normoglycemia. A total of 8 out of 11 trials reported the regression of prediabetes to normoglycemia (18-23,25,27). It appeared that supplementing vitamin D to prediabetes patients leads to normoglycemia significantly [RR, 1.24; 95% CI, (1.08, 1.43); P=0.003; I^2=0%] (Fig. 4). Subgroup analyses were conducted to identify any covariates for between-study heterogeneity. Pooled effect sizes found in these subgroups did not differ significantly from each other.

Sensitivity analysis. Sensitivity analysis was performed, and the results are illustrated in Fig. 5. The trials were added following the publication year, and since the addition of Pittas *et al* (26), published in 2019, T2DM RR has changed to significantly lower in Vitamin D group than in the control group [RR, 0.90; 95% CI, (0.81, 1.00); P=0.06] (Fig. 5A). Exclusion of the largest trial (26) didn't affect the significance; it was still marginally significant [RR, 0.88; 95% CI, (0.75, 1.03); P=0.11] (Fig. 5B). In regression to normoglycemia outcomes, RR changed significantly when Jorde *et al* (22) was added [RR, 1.35; 95% CI, (1.04, 1.73); P=0.02] (Fig. 5C).

Table I. Demographic features of randomized controlled trials that evaluated the association between vitamin D supplements and type 2 diabetes included in the meta-analysis.

		Patients		Age (years)		BMI (kg/m^2)		Female (%)		Baseline vitamin D level (ng/ml)		
First author, year	Ethnicity (nation)	Vitamin D	Control	Vitamin D	Control	Vitamin D	Control	Vitamin D	Control	Vitamin D	Control	(Refs.)
Barengolts *et al*, 2015	African American (United States)	87	86	58.2±6	59.8±6.0	32.4±2.9	31.5±2.4	0	0	14.7±4.7	14.0±4.8	(18)
Bhatt *et al*, 2020	Indian (India)	61	60	20-60 years		31.1±6.2	28.8±3.9	100%	100%	12±5.4	12.9±2.1	(19)
Davidson *et al*, 2013	Latino and African American (United States)	56	53	52.3±8	52.5±7	32.1±4.7	32.9±4.3	64%	71%	22.0±4.5	22.0±4.8	(20)
Dutta *et al*, 2014	Indian (India)	68	57	48.37±10.47	47.4±11.51	26.32±4.52	26.83±4.63	63.2%	54.4%	17.04±7.66	18±7.16	(21)
Jorde *et al*, 2016	Norwegian (Norway)	256	255	62.3±8.1	61.9±9.2	30.1±4.1	29.8±4.4	37.1%	40%	24.0±8.8	24.4±8.5	(22)
Kawahara *et al*, 2022	Japanese (Japan)	630	626	61.1±8.8	61.4±9.1	24.1±2.7	24.5±1.8	45.7%	45.2 %	21±6.2	20.7±6.1	(23)
Kuchay *et al*, 2015	Indian (India)	64	65	47.6±9.5	48.5±11.8	25.9±2.6	25.2±3.1	NA	NA	19.8±15.5	18.9±13.4	(24)
Niroomand *et al*, 2019	Iranian (Iran)	81	81	45±14	48±11	31±6	32±6	77.8%	75.3%	12.3±6.6	12.7±6.3	(25)
Pittas *et al*, 2019	Hispanic or Latino (United States)	1,211	1,212	59.6±9.9	60.4±10.0	32.0±4.5	32.1±4.4	44.7%	45 %	27.7±10.2	28.2±10.1	(26)
Zaromytidou *et al*, 2022	Greek (Greece)	45	45	73.1±7.16	74.03±7.63	29.90±4.16	30.29±4.14	NA	NA	19.98±6.73	19.85± 5.72	(27)
Zhang *et al*, 2023	Chinese (China)	60	62	56.5 (median, IQR: 48-62)	56 (median, IQR: 50-65)	26.07±3.26	25.55±3.32	66.67%	70.97%	26.23±8.30		(28)

Data are summarized as the arithmetic mean ± standard deviation, or the median (1st quartile-3rd quartile). BMI, body mass index; IQR, Interquartile Range; NA, not applicable.

Table II. Characteristics of therapeutic interventions of randomized controlled trials included in meta-analysis.

First author, year	Treatment duration	Treatment	Control	Follow-up duration	Hb1Ac outcome level		(Refs.)
					Vitamin D	Control	
Barengolts *et al*, 2015	12 months	Vitamin D_2 50,000 IU/week and Vitamin D_3 400 IU/day	Placebo/week and Vitamin D_3 400 IU/day	12 months	6.14±0.30	6.09±0.26	(18)
Bhatt *et al*, 2020	78 weeks	Cholecalciferol 60,000 IU/week for eight weeks. After every 24 weeks blood 25(OH)D levels were assessed. If subjects were still vitamin D deficient, cholecalciferol 60,000 IU/week for eight weeks was repeated. If 25(OH)D level was normal, cholecalciferol 200 IU/day was given as maintenance dose. Also, calcium carbonate 1 g/day was given.	Placebo and Calcium carbonate 1 g/day	78 weeks	5.8±1.05	6.21±1.45	(19)
Davidson *et al*, 2013	12 months	Vitamin D_3 88,865 IU/week and allowed to continue (and encouraged not to change) any current vitamin/mineral supplements that they were taking.	Placebo	12 months	6.0	6.2	(20)
Dutta *et al*, 2014	28.2±8.83 months	Vitamin D_3 60,000 IU/week for 8 weeks and then 60,000 IU/month along with calcium carbonate 1250 mg/day (equivalent to elemental calcium 500 mg)	Calcium carbonate	40 months	6.34±0.84	6.43±1	(21)
Jorde *et al*, 2016	5 years	Cholecalciferol 20,000 IU/week	Placebo	5 years	6.09±0.36	6.1±0.54	(22)
Kawahara *et al*, 2022	2.9 years	Eldecalcitol 0.75 μg/day	Placebo	Median 2.9 years, IQR: 2.8-3.0	5.9±0.2	6.0±0.2	(23)
Kuchay *et al*, 2015	12 months	Cholecalciferol 60,000 IU weekly for 4 weeks and then 60,000 IU monthly followed, 12 months long totally	Nothing	12 months	5.7±0.4	6.0±0.3	(24)
Niroomand *et al*, 2019	6 months	Vitamin D_3 50,000 IU/week for 3 months, followed by 50,000 IU/month pearl per month for an additional period of 3 months	Placebo	6 months	NA	NA	(25)

Table II. Continued.

First author, year	Treatment duration	Treatment	Control	Follow-up duration	Hb1Ac outcome level		(Refs.)
					Vitamin D	Control	
Pittas *et al*, 2019	4 years	Vitamin D_3 4,000 IU/day	Placebo	median 2.5 years IQR: 1.9-3.5 (treatment), 1.7-3.5 (control)	NA	NA	(26)
Zaromytidou *et al*, 2022	12 months	Vitamin D_3 25,000 IU/week	Nothing	12 months	5.80±0.2	5.83±0.24	(27)
Zhang *et al*, 2023	24 weeks	Vitamin D_3 1,600 IU/day	Placebo	24 weeks	5.68±0.57	5.64±0.38	(28)

Data are summarized as the arithmetic mean ± standard deviation, or the median (1st quartile-3rd quartile). Hb1Ac, Hemoglobin A1c; Vitamin D_2, ergocalciferol; Vitamin D_3, cholecalciferol; IQR, Interquartile Range; NA, not applicable.

Exclusion of the largest trial (23) didn't affect the significance; it was still significant [RR, 1.32; 95% CI, (1.09, 1.61); P=0.004] (Fig. 5D).

Secondary outcome. The definition of prediabetes is variant according to the glycemic indices; raised glycosylated HbA_{1c}, 2-h plasma glucose (2OGT) and FSG. All three indices decreased after supplementing vitamin D. All HbA1c, 2OGT, and FSG levels showed no statistically significant reduction in the vitamin D supplement group compared with the control group (Fig. 6).

Publication bias. Visual inspection of the funnel plot revealed relatively symmetrical distribution, indicating the absence of publication bias. The funnel plots for onset of T2DM and regression to normoglycemia are illustrated in Fig. 7A and B, respectively.

Discussion

Vitamin D treatment in prediabetes patients lowers the risk of T2DM and regresses to normal glucose blood levels, as revealed in the present meta-analysis of 11 randomized controlled studies. Treating prediabetes patients with vitamin D had significant effects compared with the control group in the subgroup analyses without significant subgroup differences. It was expected that long-term use of vitamin D would be effective, but the subgroup analysis found that it had no interaction.

The trial, which lasted for 5 years, performed subgroup analysis to examine the effect of vitamin D in subjects with low baseline vitamin D levels of <20 ng/ml (22). However, there was no statistically significant difference according to baseline vitamin D levels. Pittas *et al* (26), the largest trial, conducted a post-hoc subgroup analysis based on baseline vitamin D level of 12 ng/ml, and only in participants with a baseline vitamin D level <12 ng/ml, the effect of vitamin D lowering T2DM HR was significantly greater compared with the control group. These two trials suggested the possibility of an interaction between baseline vitamin D levels and the effect of vitamin D supplementation on the incidence of T2DM. However, the present subgroup analysis showed no association with this and baseline vitamin D levels.

Patterns of vitamin D deficiency among Indians have been proposed (29). Also, Asian Indians have one of the highest numbers of individuals with pre-diabetes and diabetes among all major ethnic groups (30). The 3 trials were designed to find the effect of vitamin D on prediabetes patients with a population of Indians (19,21,24). The result of the subgroup analysis in this meta-analysis was that there was no interaction with ethnicity. There are not many trials tested on Indians, and Bhatt *et al* (19) only included females. To find a relation with ethnicity, it needs to be interpreted with caution, and more extensive researches are needed.

Calcium is a common supplement that people take with vitamin D. Depending on the symptoms of the patient, there are several alternative suggestions to take calcium with vitamin D. A recent study showed that whether used alone or in combination, vitamin D and calcium supplementation do not exert meaningful effects on all-cause mortality, cardiovascular

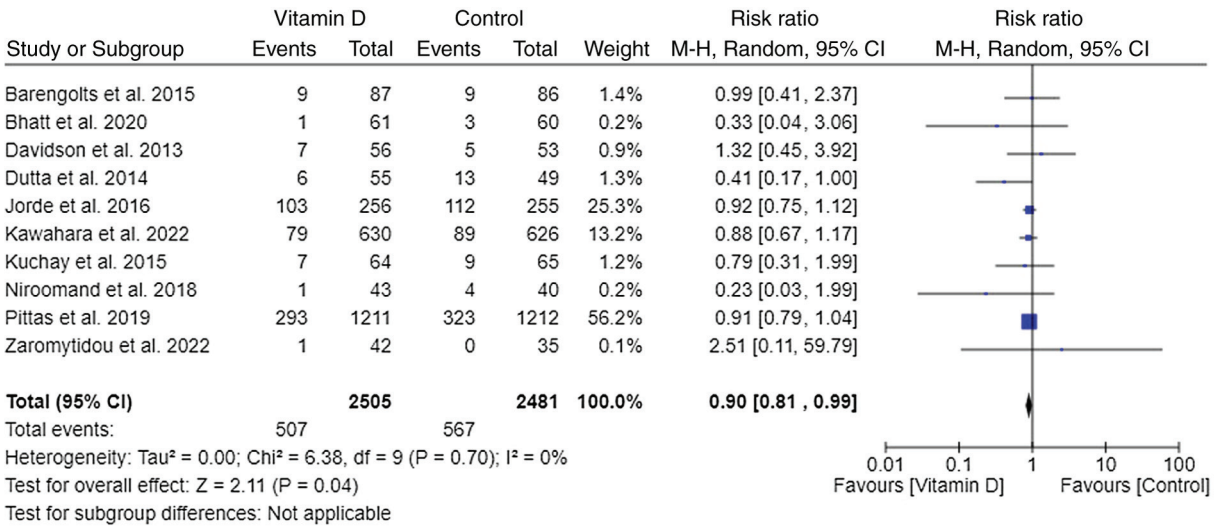

Figure 3. Forest plot of onset of T2DM risk ratio in vitamin D supplementation compared with that in control. M-H, Mantel-Haenszel method; CI, confidence interval.

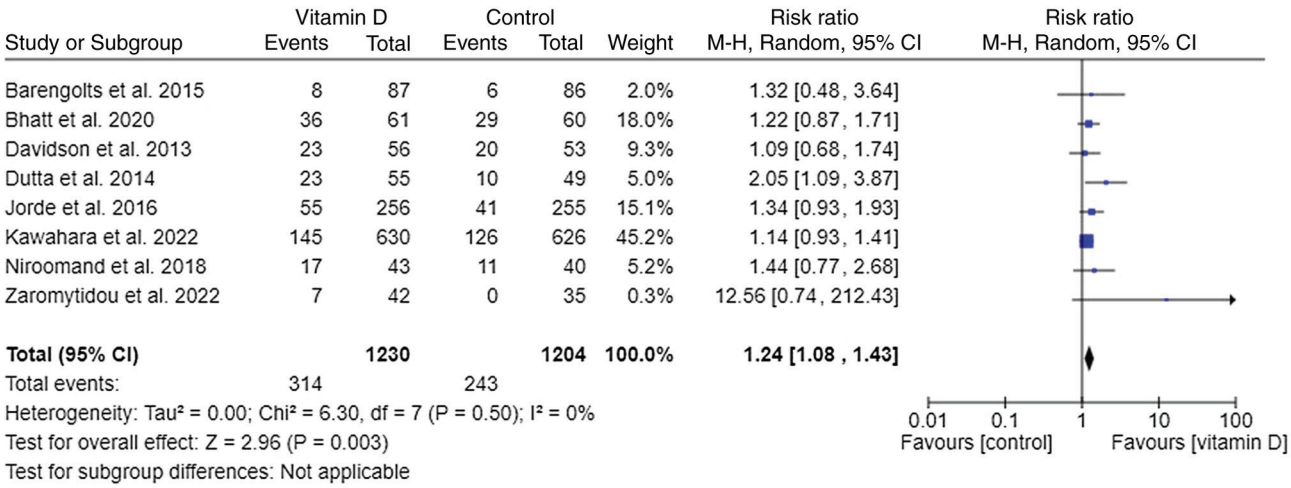

Figure 4. Forest plot of regression to normoglycemia risk ratio in vitamin D supplementation compared with that in control. M-H, Mantel-Haenszel method; CI, confidence interval.

mortality, major adverse cardiovascular events or myocardial infarction (31). Moreover, vitamin D administration may worsen the risk of stone formation in patients with hypercalciuria (32). In accordance with the present meta-analysis, vitamin D supplements with calcium may help people with prediabetes avoid developing type 2 diabetes.

An interesting result has been drawn about the BMI. Non-obese patients (BMI <30 kg/m^2) had a significant reduction in T2DM while obese patients did not. However, it is controversial whether vitamin D has a relationship with obesity. A different meta-analysis concluded that 25(OH)D level is inversely associated with percentage body fat mass (PFM) but cholecalciferol supplementation had no effect on PFM (33). Another meta-analysis proved that cholecalciferol supplementation decreases the BMI and the waist circumference, but does not statistically affect weight loss (34).

Previous meta-analyses constantly revealed an association between vitamin D supplementation and BMI. A meta-analysis that was published in 2020, included 8 trials and found the benefit of vitamin D supplementation on the prevention of diabetes in non-obese patients (35) [mean BMI <30 kg/m^2; RR, 0.73; 95% CI, (0.57-0.92); I^2=4%; $P_{interaction}$=0.048]. In a different meta-analysis that was also released in 2020, subgroup analysis was carried out, including the trials that provided vitamin D supplements 1,000 IU/day or less. As a result, patients with a mean baseline BMI <30 kg/m^2 reduced the risk of T2DM significantly (36) [RR, 0.68; 95% CI, (0.53-0.89); P=0.005; I^2=0%, $P_{interaction}$=0.03]. Only non-obese patients gained benefits from either of the two meta-analyses and proved a significant subgroup difference. However, the present meta-analysis found no interaction between BMI and vitamin D supplementation. The difference of the present meta-analysis from the two previous ones was that in the present meta-analysis, the large trial was considered (23). The Kawahara *et al* (23) study recruited 1,256 participants and was published in 2022. There should be additional studies needed to identify the possibility that vitamin D supplementation and BMI interact. However, the quality of

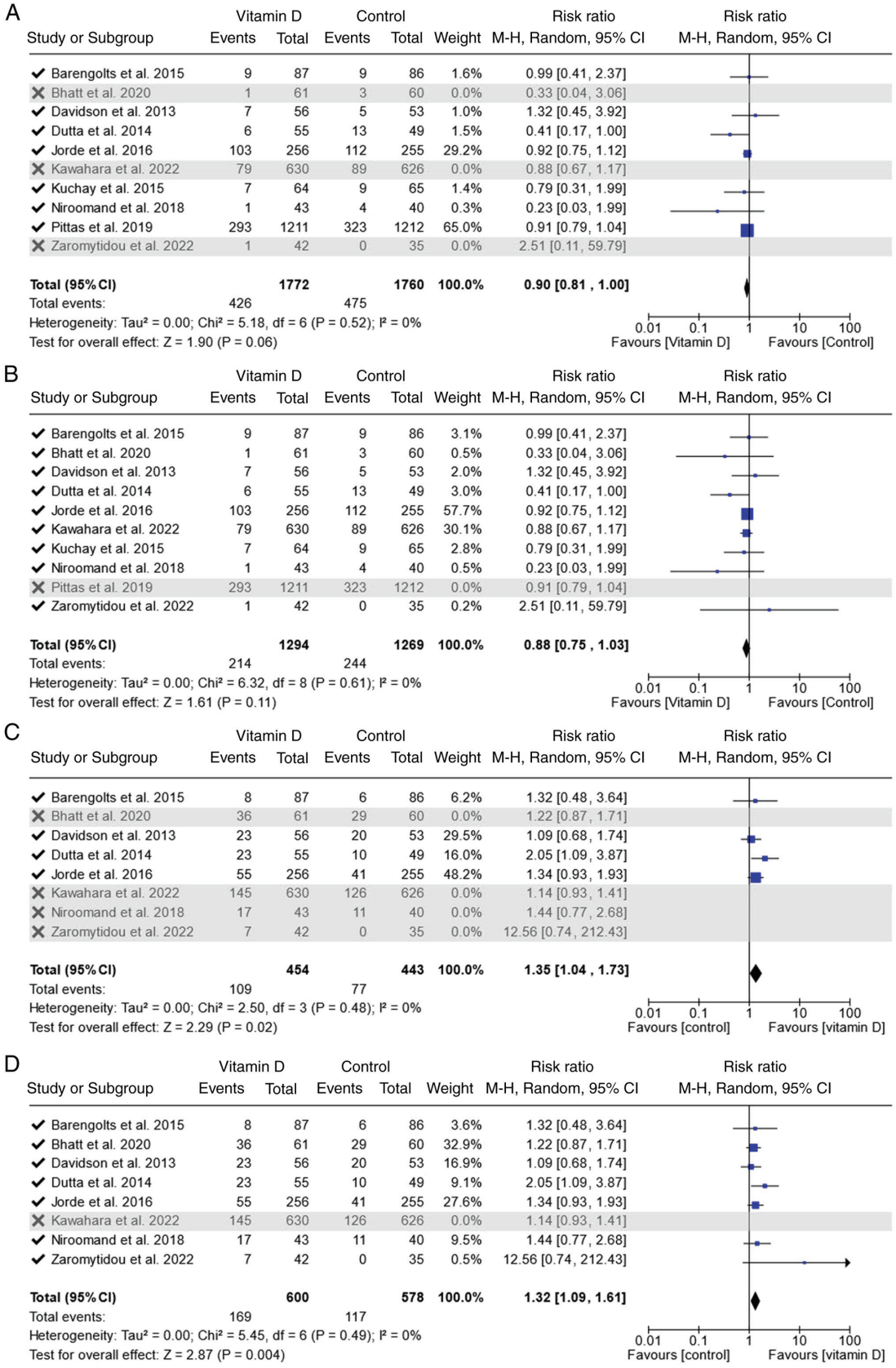

Figure 5. Sensitivity analysis of T2DM onset outcome by (A) cumulative publication year and (B) exclusion of largest sample size. Sensitivity analysis of regression to normoglycemia outcome by (C) cumulative publication year and (D) exclusion of largest sample size. M-H, Mantel-Haenszel method; CI, confidence interval.

Kawahara *et al* (23) study was shown to be favorable through the Cochrane Risk of Bias tool for randomized trials (ROB2) test, thus the results of the present meta-analysis are considered to be reliable.

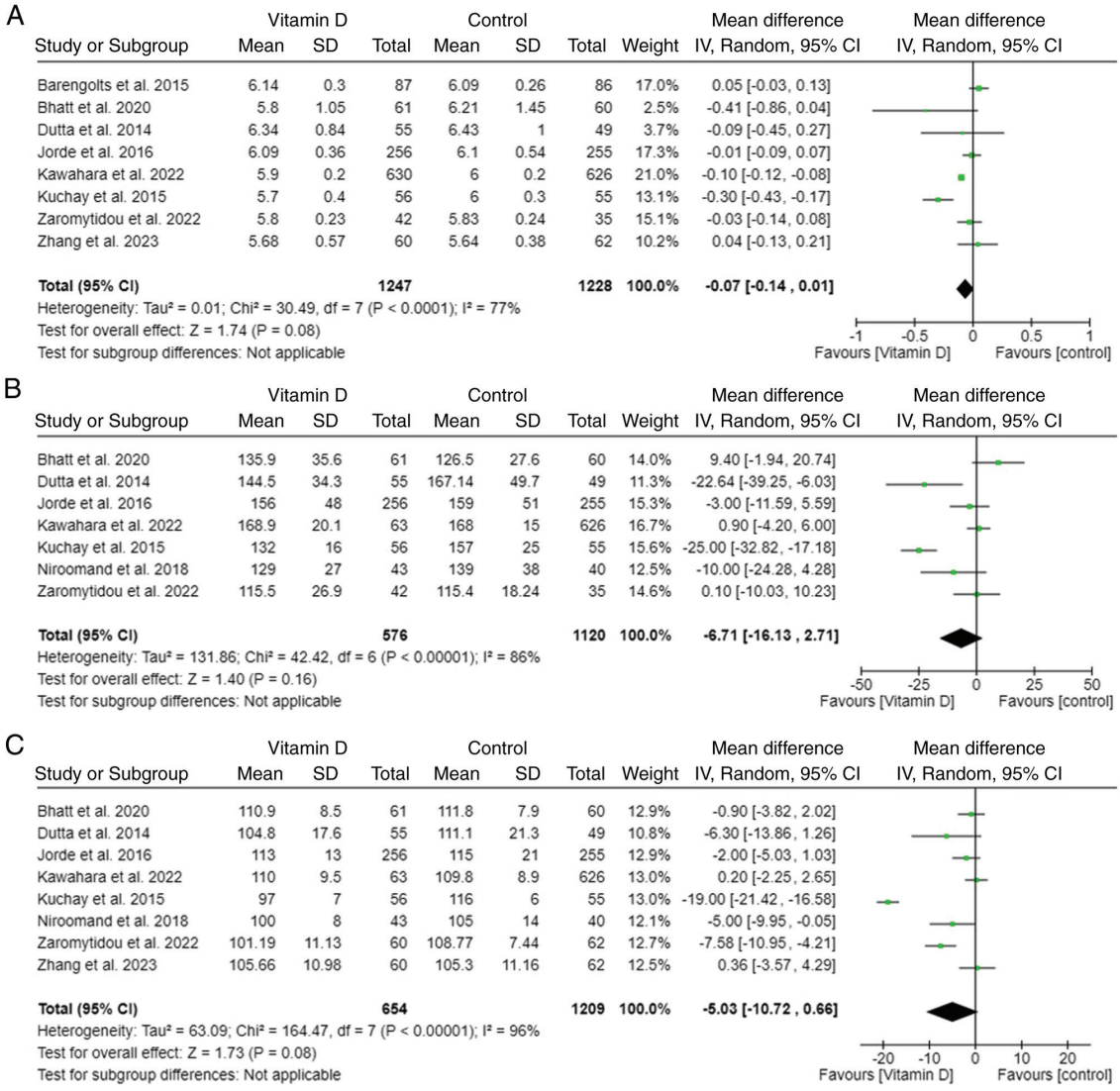

Figure 6. Forest plot of mean difference in vitamin D supplementation compared with that in control in outcome of (A) HbA1c (B) 2OGT and (C) FSG. 2OGT, 2-h plasma glucose; FSG, fasting serum glucose; IV, inverse-variance method; CI, confidence interval; SD, standard deviation.

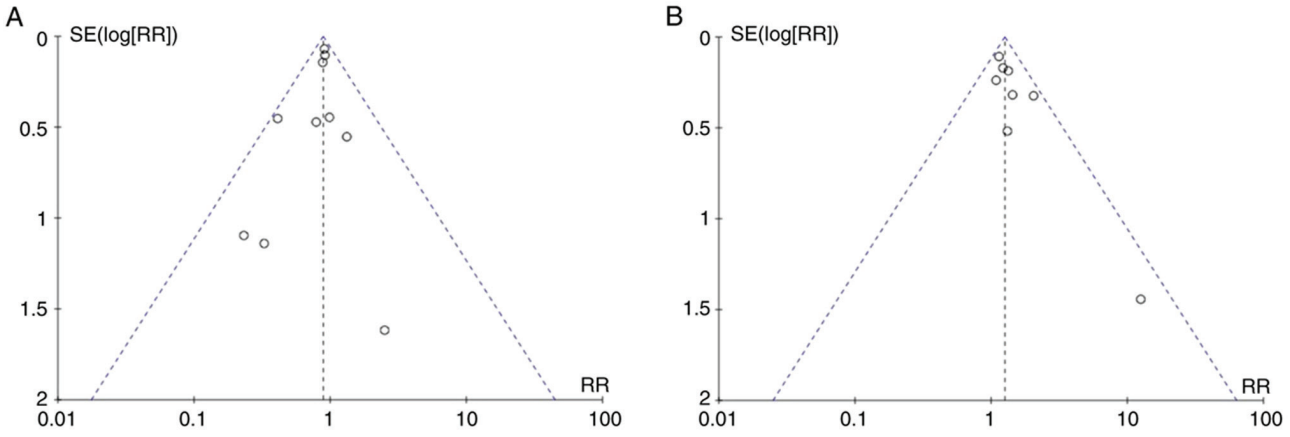

Figure 7. Funnel plot of outcome of onset of (A) T2DM and (B) regression to normoglycemia. SE, standard error; RR, risk ratio.

There are several limitations to be considered. First, the subgroup analyses used the mean data of the trials. For example, the present study followed the median age of the trials, 59.5 years. It was expected that senior patients would benefit from supplementing vitamin D, but there was no advantage for them. The broad age range of the trials could be

the reason for it. To determine the relationship depending on the specific age range, more research needs to be conducted. Second, some results of the subgroup analyses should be interpreted cautiously because of the lack of data. There were only three studies using calcium and vitamin D, as well as those that targeted Indians. Third, the study that resulted in no patients who regressed to normoglycemia was included in the present meta-analysis (27). The RR and 95% CI of Zaromytidou *et al* (27) were extremely high, and the study was conducted with small numbers. Furthermore, it would be the reason for the only asymmetry in the funnel plot.

In conclusion, vitamin D supplement is associated with a decreased risk of T2DM onset and an increase of reversion to normoglycemia in prediabetic patients. Further studies are needed to ensure the detailed effects of vitamin D long-term use, baseline vitamin D levels, BMI and obesity on vitamin D benefits for T2DM.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SML, JH and JK designed the study. GS and YJK have done systematic search and selected studies independently. JK and SML confirmed the authenticity of all the raw data. JH and YJK analyzed the data. GS, YJK and SML drafted the manuscript. JK and JH supervised the study process and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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