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## The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies

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### Abstract

**Aims**—We aimed to assess whether vitamin D supplementation improves glucose metabolism in adults with type 2 diabetes.

**Methods**—PubMed and Cochrane database were searched up to July 1st 2016 for randomized controlled trials that assessed the relationship between vitamin D supplementation and glucose metabolism (change in hemoglobin A1C (HbA1C) and fasting blood glucose (FBG)) among adults with type 2 diabetes.

**Results**—Twenty nine trials (3324 participants) were included in the systematic review. Among 22 studies included in the meta-analysis, 19 reported HbA1C, 16 reported FBG outcomes and 15 were deemed poor quality. There was a modest reduction in HbA1C (−0.32% [−0.53 to −0.10],  $I^2 = 91.9\%$ ) compared to placebo after vitamin D supplementation but no effect on FBG (−2.33 mg/dl [−6.62 to 1.95],  $I^2 = 59.2\%$ ). In studies achieving repletion of vitamin D deficiency ( $n = 7$ ), there were greater mean reductions in HbA1C (−0.45%, [−1.09 to 0.20]) and FBG (−7.64 mg/dl [−16.25 to 0.97]) although not significant.

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**Conflicts of interest:** None.

#### Author contributions

CJL, GI, YL, NB, CBL and NM designed the study and CJL, GI, YL, NB, CBL, SV and NM undertook the literature search and reviewed the abstracts and full articles. CJL conceived the idea for the review and drafted the manuscript. GI and YL supervised data extraction and statistical analysis. All authors interpreted the results, contributed to the discussion and critically reviewed the final manuscript and take full responsibility for the work as a whole, including (if applicable) the study design, access to data, and the decision to submit and publish the manuscript.

**Conclusions**—We found a modest reduction of HbA1C after vitamin D treatment in adults with type 2 diabetes albeit with substantial heterogeneity between studies and no difference in FBG. Larger studies are needed to further evaluate the glycemic effects of vitamin D treatment especially in patients with vitamin D deficiency.

### Keywords

Vitamin D; Type 2 diabetes; Glucose metabolism; Randomized controlled trials; Systematic review

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## 1. Introduction

Observational association between vitamin D deficiency and diabetes has been well described.<sup>1–4</sup> However, whether vitamin D treatment improves glycemic control has not been convincingly demonstrated. Several mechanisms have been proposed to explain the potential role of vitamin D in glucose metabolism: (1) direct stimulation of insulin secretion through the vitamin D receptor on pancreatic beta cells, (2) lowering of systemic inflammation and subsequent improvement in insulin resistance and (3) improving peripheral insulin resistance via vitamin D receptors in muscles and liver.<sup>5–7</sup>

In past years, multiple randomized controlled trials (RCTs) have been conducted to evaluate whether supplementation with vitamin D can improve glycemic control in adults with type 2 diabetes mellitus. In contrast to observational studies supporting the beneficial role of vitamin D in glucose metabolism, three most recent systematic reviews examining the efficacy of vitamin D treatment for improving glycemic control in patients with type 2 diabetes showed no benefits.<sup>8–10</sup> These reviews, however, were limited by clinical and methodological heterogeneity in the included studies; two recent reviews included studies using various different forms of vitamin D such as intramuscular delivery of vitamin D or active vitamin (i.e., calcitriol); the meta-analysis by Nigil Haroon et al. included healthy as well as subjects with impaired fasting glucose of type 2 diabetes. They also included observational studies, which are limited in ability to give insight on causality. Further, neither review systematically examined the role of differing lengths and doses of vitamin D supplementation in the reported treatment effects and whether baseline vitamin D deficiency may impact glycemic outcomes after vitamin D repletion. Indeed, previous studies have reported glycemic benefits and improvements in beta cell function among vitamin D deficient adults upon vitamin D supplementation.<sup>11,12</sup> Since the previously published reviews on this topic,<sup>8,9</sup> we found 11 additional eligible studies; by updating the search and using a more comprehensive set of search terms compared to the prior reviews, we found six new RCTs completed since the previous review and five older studies not included in previous systematic reviews that met the inclusion criteria in our review.

Given the theorized mechanisms by which vitamin D could affect glycemic control and continued investigation of this topic throughout the world, we sought to expand upon the previous systematic reviews and meta-analysis to include more recently published studies in order to examine the effect of vitamin D supplementation on fasting blood glucose (FBG) and hemoglobin A1C (HbA1C) in adults with type 2 diabetes and whether the glycemic

control response is related to factors such as baseline vitamin D status, treatment dose and duration.

## 2. Materials and methods

This study was performed according to the *Cochrane Handbook* recommendations and PRISMA (Preferred Reporting Items for Systematic Reviews) Statement guidelines for the reporting of systematic reviews and meta-analysis of intervention studies.<sup>13,14</sup> The protocol for this study is provided in the Supplemental Data (S1).

### 2.1. Data sources and searches

We searched two electronic databases, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) published up to July 1st 2016, without imposing language or date restrictions. The primary outcomes evaluated in this review were the changes in FBG (mg/dl) and HbA1C (%). We developed a pre-specified search strategy for key terms including *randomized controlled trial*, *diabetes*, and *Vitamin D* using controlled vocabulary and free text (see protocol in Supplementary Data). We searched NIH's clinical trials registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) using similar search terms for unpublished but completed studies. We also reviewed the reference lists of the index reviews and a subset of the articles identified by our search, to further identify additional relevant studies and searched the Web of Science for articles that cited a subsample of the included articles.<sup>8-10</sup>

### 2.2. Study selection

A subset of authors (CJL, GI, YL, NB, CBL, SV, NM) selected relevant studies using the following inclusion criteria: randomized, controlled trials, both open-label and blinded, that evaluated the glyceic effect of vitamin D supplementation on patients with type 2 diabetes. The diagnosis of type 2 diabetes in the included studies was confirmed by baseline HbA1c or FBG levels consistent with the American Diabetes Association diagnostic criteria as per year of publication or as defined by the investigators if evidence was presented that baseline glyceic control had been quantitatively assessed. We included studies of oral vitamin D formulation containing cholecalciferol or ergocalciferol.

We excluded studies using active vitamin D (1,25-dihydroxyvitamin D) because they carry an increased risk of hypercalcemia and would be unlikely to be used in clinical practice for the indication of vitamin D deficiency. In addition, we excluded studies with intramuscular delivery of vitamin D given different absorptions between oral and intramuscular routes. We excluded studies involving participants with type 1 diabetes, participants less than 18 years of age, or involving participants with the following conditions that could potentially alter vitamin D metabolism: gestational diabetes, chronic kidney disease Stage 4 or higher, hyperparathyroidism, lymphoma, and granulomatous diseases (e.g., tuberculosis, or sarcoidosis). Interventions could be crossover trials, but only initial arm versus control results before crossover were considered for meta-analysis. Non-placebo controls, such as calcium, were allowed when given to both groups, as were dual-intervention studies such as vitamin D with and without exercise. We included any duration of study, and in post-hoc analysis divided studies into long-term and short-term studies based on whether the duration

of follow-up exceeded 12 weeks, since HbA1C reflects average blood glucose over a period of 12 weeks.

### 2.3. Data extraction and quality assessment

Pairs of independent reviewers screened the title and the abstract of each study prior to full text screening of candidate studies. Any discrepancies in the decision to include a given study were adjudicated through review by all authors. For all included studies, two reviewers independently extracted, using a pre-specified form, information on: study sample size, country, age, baseline vitamin D status, type, dose, frequency and duration of vitamin D treatment, HbA1C and FBG.

Study quality and risk of bias were assessed using the Cochrane Collaboration tool for assessing risk of bias.<sup>13</sup> Studies were classified as low, high, or unclear risk of bias in each of the following five bias domains: selection bias, detection, bias, performance bias, attrition and reporting bias.

### 2.4. Data synthesis and analysis

For our continuous outcomes (e.g., change in HbA1c, change in FBG), we extracted information about the mean difference between intervention (vitamin D) and placebo groups with 95% confidence interval. Studies with multiple comparison groups were analyzed as a 2-group trial to compare vitamin D treatment versus placebo or no treatment. A random-effects model (DerSimonian and Laird method) was used to estimate combined pooled results. The  $I^2$  statistic (%), calculated as the proportion of total variation attributable to between-study variation, was used to determine statistical heterogeneity between the studies. An  $I^2$  value of more than 75% was considered substantial heterogeneity, although we did not set a priori a cutoff to determine whether to proceed with meta-analytic pooling. We also examined the chi-square test for heterogeneity, and more generally the degree of overlap among study estimated confidence intervals, to evaluate the presence of statistical heterogeneity.

In order to further explore any substantial heterogeneity in the glycemic outcomes between studies, we performed three a priori specified subgroup analyses for glycemic outcomes based on the dose of vitamin D supplementation (  $\leq 2000$  versus  $>2000$  units/day) and length of treatment (  $\leq 12$  versus  $>12$  weeks).

We also performed two sensitivity analyses by including only: (1) the studies with participants whose baseline vitamin D deficiency (serum 25(OH) vitamin D levels  $<50$  nmol/L) corrected to normal ( $>75$  nmol/L) and (2) studies with low risk of bias (absence of high and/or more than 2 unclear biases in our risk of biases assessment).<sup>4,15</sup> Using meta-regression, we tested the influence of vitamin dose and treatment duration on the pooled treatment effect. We evaluated publication bias using funnel plots as well as Eggers test and Begg-Mazumdar test, when ten or more studies were eligible for inclusion. Data were analyzed using STATA version 12.1 (College Station, Texas).

### 3. Results

We identified a total of 2341 articles from PubMed and Cochrane Central prior to July 1st 2016. After excluding 216 duplicates and studies that did not fulfill the inclusion criteria, 29 articles remained for our systematic review, of which 22 articles had sufficient baseline and outcome data for meta-analysis (Fig. 1).<sup>16-44</sup> We also searched the [clinicaltrials.gov](http://clinicaltrials.gov) database and performed hand searches and did not find any additional studies for this review.

#### 3.1. Study characteristics

Characteristics of all 29 studies are shown in Table 1. A total of 3324 participants with type 2 diabetes were included in these studies. Among different types of oral vitamin D formulations, 28 studies used cholecalciferol and 1 study used ergocalciferol. Study duration ranged from 8 weeks to 5.5 years with a median duration of 12 weeks. The most common dosing schedule for vitamin D supplementation was daily, while some studies used weekly or one time bolus schedules. The dose of vitamin D used ranged from 400 IU daily to 450,000 IU once. Nine studies were conducted in Iran, nine in Europe, six in Asia, one in Australia, one in the United Arab Emirates, one in Africa, one in South America and one was a multinational study. Fifteen studies recruited those with vitamin D deficiency as defined by vitamin D25-OH of less than 50 nmol/L. Twelve studies reported how they handled diabetes medications in enrolled participants during the study observation period. Three studies had a treatment group of calcium and vitamin D versus a placebo group that received calcium (instead of no treatment).<sup>33,36,38</sup> One study was funded by a pharmaceutical company.<sup>34</sup> Among the 29 studies included in this systematic review, 22 were included in the meta-analysis while 7 studies were excluded because they did not report the change in the primary outcomes as means and/or did not report the variance estimates for between-group differences.

#### 3.2. Quality assessment

The risk of bias assessment was conducted using the Cochrane Collaboration's tool (Supplementary Fig. 1). Overall, a total of 15 of the 22 studies included in the meta-analysis were deemed poor quality based on having one or more characteristic that was considered high risk or more than two characteristics of unclear risks among the six categories of risks of bias. Among the 22 studies, 15 studies reported adequate details of their randomization method or adequate information to confirm appropriate allocation concealment and masking of participants and personnel; only 8 studies described in sufficient detail whether the outcome assessors were blinded to each participant's treatment assignment; 17 studies reported adequate details of the degrees of missing data and reasons for attrition; 14 studies were deemed low-risk for reporting bias. Among the six categories of biases mentioned above, attrition bias was detected most frequently at high risk (8 studies).

#### 3.3. Meta-analysis: hemoglobin A1C

We included a total of 19 studies for HbA1c and 16 studies for FBG based on the outcome measure reported in the study.

The pooled analysis for HbA1c significantly favored vitamin D treatment with reduction of 0.32% after treatment compared to placebo (WMD  $-0.32\%$  [ $-0.53$  to  $-0.10$ ],  $P = 0.022$ ) albeit with substantial heterogeneity between studies ( $I^2 = 91.9\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ , Fig. 2A).

In dose-stratified analysis (Fig. 2B), studies that used higher doses of vitamin D showed no treatment effect in the absence of statistical heterogeneity between studies (WMD  $0.06\%$  [ $-0.43$  to  $0.32$ ],  $I^2 = 87.2\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ ) whereas the studies using lower doses of vitamin D favored vitamin D supplementation with substantial heterogeneity (WMD  $-0.49\%$  [ $-0.82$  to  $-0.16$ ],  $I^2 = 93.1\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ ). In treatment duration subgroup analysis (Fig. 2C), the studies with shorter treatment lengths showed a trend towards improvement in HbA1c, though the heterogeneity remained substantial (WMD  $-0.30\%$  [ $-0.52$  to  $-0.08$ ]  $I^2 = 85.5\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ ). In contrast, the studies with longer treatment lengths showed no difference in HbA1c (WMD  $-0.34\%$  mg/dl [ $-0.89$  to  $0.2$ ]  $I^2 = 94.9\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ , Fig. 2C).

In the two sensitivity analyses, we found a similar tendency to favor vitamin D treatment when including only participants with baseline vitamin D deficiency (WMD  $-0.45$  [ $-1.09$  to  $0.20$ ]  $I^2 = 94.0\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ ) (Fig. 4) whereas the studies with low risk of bias no longer showed a difference in HbA1c after treatment (WMD  $-0.07\%$  [ $-0.32$  to  $0.17$ ]  $I^2 = 77.5\%$ ,  $P_{\text{for heterogeneity}} < 0.001$ ).

### 3.4. Meta-analysis: fasting blood glucose

In contrast to HbA1c, pooled analysis for FBG showed no overall difference after vitamin D supplementation compared with no vitamin D supplementation (weighted mean difference (WMD)  $-2.33$  mg/dl [ $-6.62$  to  $1.95$ ],  $P = 0.542$ ,  $I^2 = 59.2\%$ , Fig. 3A).

To further explore the heterogeneity in the pooled analysis, we performed three subgroup analyses (by vitamin D dose, treatment length, and country) and two sensitivity analyses (studies with vitamin D deficient participants at baseline, studies with low risk of bias). With respect to treatment effect on FBG, we stratified the studies by vitamin D dose equal or less than 2000 IU versus greater than 2000 IU daily. The studies that used higher doses of vitamin D showed a greater tendency to favor vitamin D supplementation with less heterogeneity between studies though differences were non-significant (WMD  $-9.65$  mg/dl [ $-19.56$  to  $0.26$ ]  $I^2 = 36.8\%$ ,  $P_{\text{for heterogeneity}} = 0.148$ , Fig. 3B) compared to studies using lower doses of vitamin D (WMD  $-0.12$  mg/dl [ $-4.97$  to  $4.72$ ]  $I^2 = 69.4\%$ ,  $P_{\text{for heterogeneity}} = 0.002$ , Fig. 3B). Upon stratifying the studies by the length of intervention (equal or less than 12 weeks versus greater than 12 weeks in duration) the studies with shorter treatment lengths showed a tendency to favor vitamin D supplementation though differences were non-significant (WMD  $-6.53$  mg/dl [ $-13.74$  to  $0.67$ ],  $I^2 = 62\%$ ,  $P_{\text{for heterogeneity}} = 0.005$ , Fig. 3C). In contrast, the studies with longer treatment lengths showed no difference in FBG after treatment without any heterogeneity across studies (WMD  $1.46$  mg/dl [ $-1.78$  to  $4.70$ ]  $I^2 = 0\%$ ,  $P_{\text{for heterogeneity}} = 0.480$ , Fig. 3C).

We performed two sensitivity analyses and found a tendency to favor vitamin D treatment in contrast to the overall pooled analysis when we only included: (1) studies with participants

with vitamin D deficiency at baseline (WMD  $-7.64$  mg/dl [ $-16.25$  to  $0.97$ ]  $I^2=49.6\%$ ,  $P_{\text{for heterogeneity}} = 0.064$ ) (Fig. 4) and no difference in FBG and moderate heterogeneity between (2) studies with low risks of bias (WMD  $-0.61$  mg/dl [ $-5.51$  to  $4.29$ ]  $I^2 = 67.6\%$ ,  $P_{\text{for heterogeneity}} = 0.026$ ).

### 3.5. Meta-regression

The results of meta-regression showed no significant differences between subgroups categorized by vitamin D dose or treatment duration on the pooled difference of FBG and HbA1c (all  $P > 0.05$ ).

### 3.6. Publication bias

There was no evidence of publication bias with HbA1C according to the Eggers test ( $P = 0.78$ ) and Begg–Mazumdar test ( $P = 0.19$ ) (Supplementary Fig. 2A). However the funnel plot for HbA1c appeared slightly asymmetric with a few studies falling beyond the funnel, which is consistent with the substantial heterogeneity seen among studies reporting HbA1c.

Similarly, there was no evidence of publication bias with FBG based on the symmetry in the funnel plot and the results of Eggers test ( $P = 0.93$ ) and the Begg–Mazumdar test ( $P = 0.5$ ), both of which were non-significant (Supplementary Fig. 2B).

## 4. Discussion

In this systematic review and meta-analysis, we found a modest but significant reduction in HbA1c of 0.32% after vitamin D supplementation, although with substantial heterogeneity likely from varying treatment doses and lengths across studies. In contrast, we found no benefit of vitamin D supplementation in improving the FBG among individuals with type 2 diabetes. Separate analyses by vitamin D dose, treatment duration, baseline vitamin D status (i.e., insufficient/deficient vs. replete), and risk of study bias (i.e., excluding studies with high risk of bias) confirmed the null finding in the pooled analysis.

The present systematic review provides an update to an index review by Krul-Poel et al. with 11 additional studies with 1746 participants. Our findings are similar to the previous systematic reviews and meta-analyses confirming a lack of a strong evidence to support vitamin D treatment to improve glycemic outcomes.<sup>8–10,45</sup> In contrast to the previous systematic reviews, we only included RCTs and used a more comprehensive database search strategy and more stringent selection criteria to focus on studies with adults with type 2 diabetes receiving oral vitamin D (cholecalciferol or ergocalciferol) compared against a clearly defined placebo group, thus enhancing our ability to more precisely evaluate the effect of vitamin D treatment on glycemic control. Furthermore, we performed additional subgroup and sensitivity analyses based on vitamin D dose, treatment length, baseline vitamin D status and study quality in order to better understand the differences in glycemic outcomes after vitamin D treatment across studies.

While most of the studies showed little difference in HbA1C, two studies deviated from the rest by showing a significant benefit in HbA1C reduction related to vitamin D supplementation with a mean difference of  $-1.7$  (95% CI  $-2.66$  to  $-0.74$ ) and  $-1.82$  (95%

CI  $-2.14$  to  $-1.5$ ), respectively.<sup>25,33</sup> In contrast to stable HbA1Cs in the placebo groups in most included studies, the placebo group in the study by Nikooyeh et al. showed worsening of HbA1C from 7.5% to 8.7%, thus making its treatment group appear superior in comparison. The study by Ghavamzadeh et al. also showed a significant benefit but had a large dropout rate which led to a substantial attrition bias: among 984 randomized participants, only 52 remained in the final analysis.

In order to further explore the substantial heterogeneity in HbA1C results across studies, we performed subgroup analyses and found that more beneficial effects were observed by studies using lower doses of vitamin D. The positive association between a lower dose vitamin D treatment and HbA1C improvement is unanticipated but appears partly due to the longer mean treatment length compared to the studies using a higher dose of vitamin D (50.8 versus 11.6 weeks). Indeed, a subgroup analysis by vitamin D treatment length suggests a more favorable HbA1C reduction with longer treatment duration ( $-0.34$  versus  $-0.30\%$ ), although not statistically significant. In fact the association between a lower dose of vitamin D treatment and HbA1C improvement may be a reflection of a nonlinear relationship between vitamin D status and glucose metabolism. One study showed a threshold effect of 25-hydroxyvitamin D on glucose-insulin metabolism such that 25-hydroxyvitamin D level above 65 nmol/L supported normal glucose metabolism.<sup>46</sup> Therefore, it is possible that a higher dose of vitamin D treatment may not necessarily result in any further improvement in glucose metabolism beyond a certain cutoff.

Therefore, we evaluated a subgroup of studies of adults whose vitamin D status was corrected from deficient to normal after the intervention and found that they overall tended to show a greater mean reduction in HbA1C, although this did not achieve statistical significance. The lack of statistical significance here may be attributable to the relatively smaller number of studies that restricted the intervention to those with baseline vitamin D deficiency. Together, these findings support the need to further explore the impact of vitamin D treatment in evaluating the glycemic outcomes after vitamin D treatment in those who are vitamin D deficient at baseline.

The lack of overall effect on FBG was similarly driven by two studies that showed a marked beneficial effect of vitamin D supplementation on FBG.<sup>18,33</sup> Specifically, the study by Nikooyeh et al. showed a mean difference of  $-32.10$  mg/dl (95% CI  $-63.40$  to  $-0.80$ ) in FBG, suggesting a clinically significant improvement in glycemic control among adults with diabetes after vitamin D supplementation for 12 weeks. However, this finding is again weakened by the fact that the placebo group had a significant worsening in glycemic control during this time (187.5 mg/dl at baseline, 203.3 mg/dl at the end of the study) in contrast to the placebo groups in other studies, which had largely stable FBG measurements during the study period. Interestingly, there was an absence of heterogeneity across studies in our subgroup analysis whose treatment length was 12 weeks or greater, which underscores the importance of the treatment length of vitamin D in affecting glucose metabolism, specifically fasting blood glucose. Moreover, we found a tendency to favor vitamin D treatment in studies that corrected vitamin D deficiency in their participants, which suggests that treating the vitamin D deficiency may be needed to observe glycemic benefits.



The strengths of our systematic review are inclusion of studies with a randomized controlled design, inclusion of two complementary short and long-term glycemic outcome measures that are laboratory derived and well defined with minimum detection bias (i.e., HbA1c and FBG), well-defined treatment (i.e., vitamin D supplementation) compared to placebo and an updated search with the addition of 11 new studies in this systematic review compared to the index systematic review by Krul-Poel et al.<sup>8</sup> Furthermore, we explored the role of treatment dose and duration in subgroup analyses to understand the role of these factors in overall results and the heterogeneity across studies. Additionally, we performed subgroup analyses of studies whose participants' baseline vitamin D deficiency corrected to normal upon intervention. We also conducted a thorough review of the quality of the included studies and risk of bias using the Cochrane Collaboration tool, which was not performed in previous meta-analyses.<sup>13</sup> Another strength of our study is the relative uniformity of the formulation of vitamin D used in the included studies: 28 out of 29 studies used oral cholecalciferol while one study used oral ergocalciferol. By excluding studies using calcitriol or intramuscular injections of vitamin D or studies with patients who have tuberculosis, we reduced the potential for varying pharmaco-dynamic profiles among these formulations, which could differentially affect treatment outcomes.

The limitations of our review are the relatively short treatment length and small sample size of some but not all studies, which may limit our ability to draw conclusions on the effects of longer-term vitamin D supplementation, and moderate to substantial heterogeneity across studies in some of our results. In addition, our review is not generalizable to individuals with normal glucose metabolism and many of the included studies did not provide enough details to allow accurate qualitative assessment of how each study handled randomization, allocation, missing data and type of analysis. Furthermore, the glycemic outcomes reported in many of the included studies may have been affected by adjustments in diabetes medications during intervention given that only 9 out of 22 studies included in the meta-analysis reported avoiding diabetes medication adjustment during the observation period. As with all meta-analyses, this meta-analysis is subject to publication bias, whereby null results of completed but unpublished trials result in systematically unrepresentative treatment effects in the published literature. However, we found little evidence for publication bias on visual inspection of funnel plots and in the results of Eggers test and the Begg–Mazumdar test.

Another factor that may pose a challenge to interpreting the study results include questionable power calculations given that most studies that reported the number of participants needed for sufficient power did not achieve these recruitment targets. Additionally, lack of data on ethnic composition of participants in each study, which may be particularly important given the evidence for differing levels of available circulating vitamin D for a given total vitamin D measurement.<sup>47</sup> Although vitamin D deficiency is widely prevalent, individuals with darker skin color are at an increased risk of vitamin D deficiency and cultural preferences dictating that the amount of skin exposure to the sun may play a role in sunscreen use and overall vitamin D metabolism in individuals.<sup>48,49</sup> We did not incorporate in our analyses country latitude or season(s) during which study was conducted as indicators of overall ultraviolet light exposure.<sup>50</sup> Also, there were differences across the included studies with regard to the method of serum 25(OH) vitamin measurement, thus

adding to the challenge of comparing the baseline vitamin D status of participants across studies.

## 5. Conclusion

In this meta-analysis, we found a modest reduction of 0.32% in HbA1C after vitamin D treatment in individuals with type 2 diabetes, although the HbA1C results are limited by the presence of substantial heterogeneity between studies likely related to varying lengths of treatments across studies and to small sample size in some studies. On the other hand, we found no difference in FBG levels among adults with type 2 diabetes treated with versus without vitamin D. Additionally, in a subset of studies reporting vitamin D levels before and after the intervention, we found that the normalization of vitamin D levels may be needed to observe beneficial effects of vitamin D supplementation on glycemic outcomes. Ultimately, larger studies are needed to further investigate the effect of vitamin D treatment on glucose metabolism among individuals with type 2 diabetes and to identify subpopulations such as those with vitamin D deficiency that may accrue the greatest benefit.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jdiacomp.2017.04.019>.

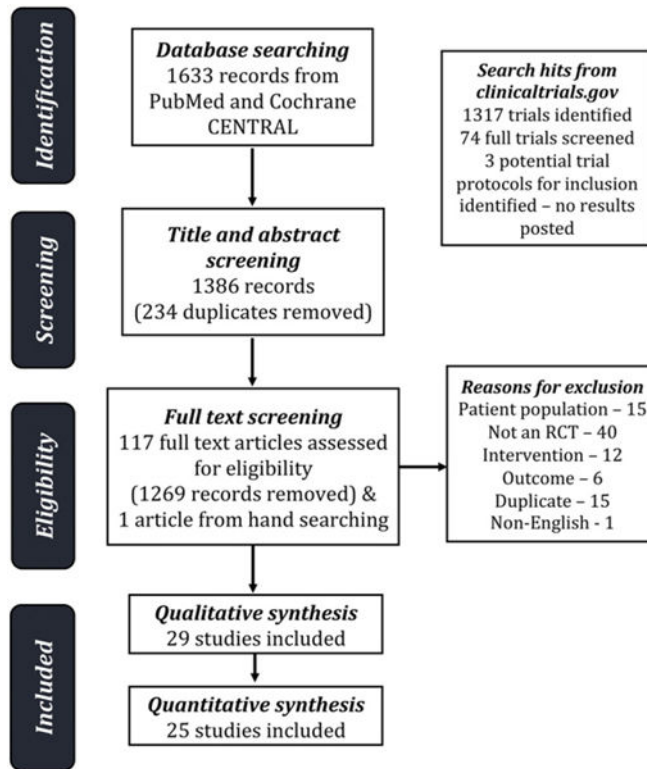
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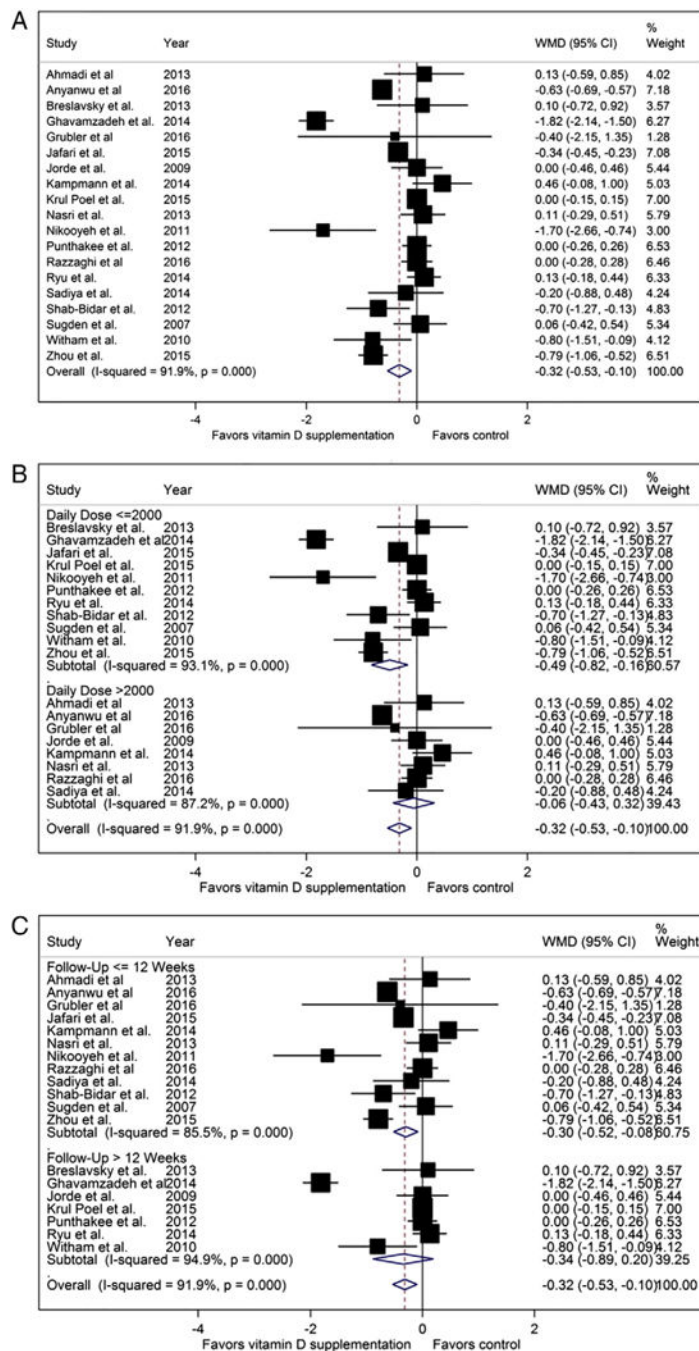
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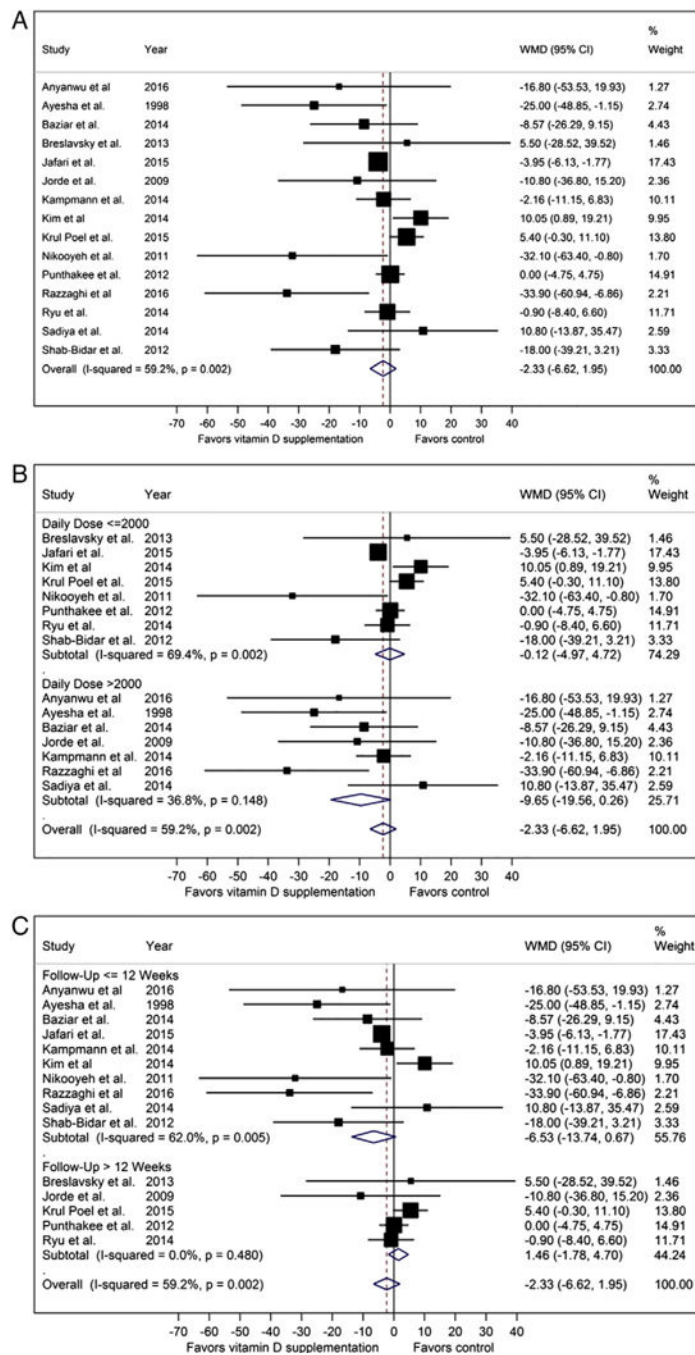
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**Fig. 1.**  
Flow diagram of search and selection processes.

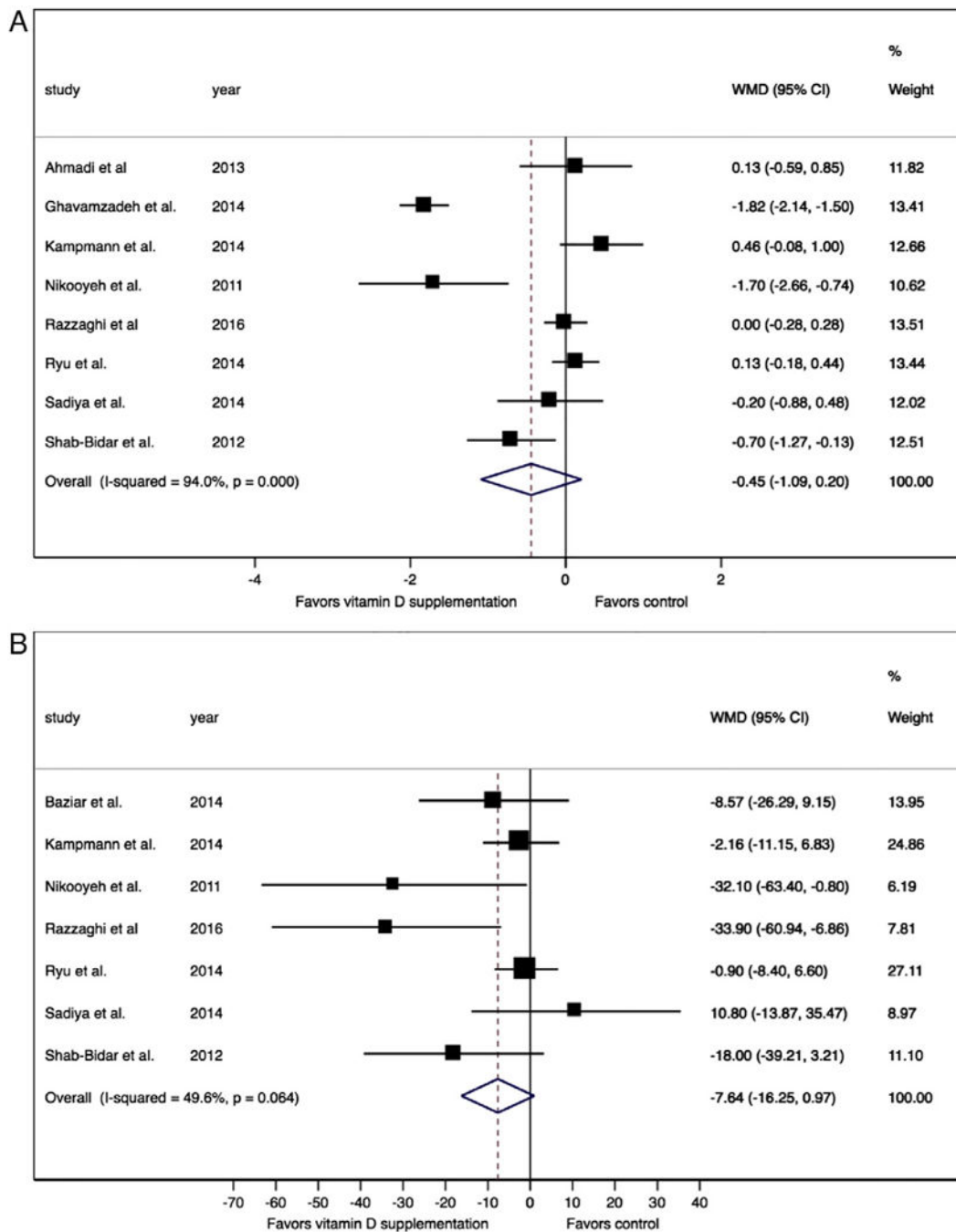


**Fig. 2.** Hemoglobin A1C forest plots (%; A: pooled, B: stratified by dose, C: stratified by treatment length).



**Fig. 3.** Fasting blood glucose forest plots (mg/dl, A: pooled, B: stratified by dose, C: stratified by treatment length).





**Fig. 4.** Studies of individuals whose vitamin D deficiency corrected to normal after intervention (A: hemoglobin A1C, 4B: fasting glucose, vitamin D deficiency defined as vitamin D25OH <50 nmol/L).

**Table 1**  
 Characteristics of the randomized controlled trials included in the systematic review ( $n = 29$ ).

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Ahmadi 2013	30/30	Iran	T: 58 C: 57	T1: 35.2 ± 19.4 T2: 177.7 ± 66.1 C1: 100.1 ± 15.2 C2: 43.9 ± 15.2	D <sub>3</sub> 50,000 IU per week	12	N/A	HbA1c	Yes
Anyanwu 2016	17/16	Nigeria	T: 52.5 C: 51.1	T1: 17.2 ± 2.2 T2: 18.2 ± 2.2 C1: 18.5 ± 5.2 C2: 16.7 ± 1.7	D <sub>3</sub> 3000 IU daily	12	All medications were kept constant	HbA1c FBG	Yes
Aysha 1998	8/8/8	India	N/A	T1: 104.8 ± 5.5 T2: 149.8 ± 2.2 C1: 59.9 ± 15 C2: 82.4 ± 2.2	T1: D <sub>3</sub> 150,000 IU once T2: D <sub>3</sub> 300,000 IU once T3: D <sub>3</sub> 450,000 IU once	12	N/A	FBG	Yes
Barchetta 2016	26/29	Italy	T: 57.4 C: 59.8	Median (IQR) T1: 43.1 (31.1–58.5) T2: 85.8 (73–110) C1: 37.1 (27.3–51.6) C2: 40 (20.8–60.5)	D <sub>3</sub> 2000 IU daily	24	Drug alterations were not allowed	HbA1c FBG	No
Baziar 2014	43/44	Iran	T: 50 C: 53	T1: 35.8 ± 14.6 T2: 112.4 ± 31.4	D <sub>3</sub> 50,000 IU weekly	8	Drug alterations were not allowed	FBG	Yes

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Brevlasky 2013	24/23	Israel	T: 67 C: 66	CI: 38.7 ± 13.9 C2: 42.1 ± 15.6 T1: 32.2 ± 26.7 T2: 43.9 ± 28.4 C1: 26.9 ± 16.4 C2: 34.9 ± 14.7	D <sub>3</sub> 1000 IU daily	52	All medications were kept constant	HbA <sub>1c</sub> FBG	Yes
Cavalcante 2015	Total 38 (did not specify T vs C)	Brazil	T: 62.16 C: 62.32	T1: 55.9 ± 9.9 T2: 57.4 ± 10.6 C1: 57.2 ± 10.5 C2: 57.0 ± 9.7	D <sub>3</sub> 943 IU daily	12	N/A	HbA <sub>1c</sub>	No
Dalan 2016	31/30	Singapore	T: 52.2 C: 54.8	Median T1: 43.25 T2: 79 C1: 46.5 C2: 48.3	D <sub>3</sub> 4000 IU to pts with baseline 25(OH)D < 50 nmol/L D <sub>3</sub> 2000 IU daily to pts with baseline 25(OH)D 50–75 nmol/L Dose reduced by half if 25(OH)D > 50 nmol/L at 8 weeks	16	N/A	HbA <sub>1c</sub>	No
Elkassaby 2014	26/24	Australia	T: 53 C: 51	Median (IQR) T1: 59 (42–75) T2: 128 (111–146) C: 62 (40–80) C2: 61 (45–87)	D <sub>3</sub> 10,000 IU × 2 weeks, then 6000 IU × 22 weeks	24	Medications were increased by family physician if necessary	HbA <sub>1c</sub> FBG	No

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Ghavamzadeh 2014	60/60	Iran	T: 52 C: 49	T1: 31.0 ± 4.9 T2: 104.9 ± 19.0 C1: 34.8 ± 3.8 C2: 32.1 ± 3.4	D <sub>3</sub> 400 IU daily	14	N/A	HbA1c	Yes
Grubler 2016	20/27	Austria	Not specified for this subgroup	T1: 41.6 ± 15.2 T2: N/A C1: not specified C2: N/A	D <sub>3</sub> 2800 IU daily	8	N/A	HbA1c FBG	Yes
Jafari 2015	32/32	Iran	T: 58 C: 57	T1: 62.23 ± 4.52 T2: 86.83 ± 4.87 C1: 62.72 ± 4.27 C2: 56.13 ± 2.89	Fortified yogurt containing 2000 IU D <sub>3</sub> in 100 mg/day	12	Drug alterations were not allowed	HbA1c FBG	Yes
Jorde 2009	20/16	Norway	T: 58 C: 55	T1: 60 ± 14 T2: 118.3 ± 29.8 C1: 58.5 ± 21 C2: 57.2 ± 14.8	D <sub>3</sub> 40,000 IU weekly	24	Participants were advised to keep all medications constant	HbA1c FBG	Yes
Kampmann 2014	8/8	Denmark	T: 62 C: 57	T1: 31 ± 4.9 T2: 104.9 ± 19.0 C1: 34.8 ± 3.8 C2: 32.1 ± 3.4	D <sub>3</sub> 11,200 IU daily × 2 weeks, then 5600 IU daily × 10 weeks	12	Participants were advised to keep all medications constant	HbA1c FBG	Yes
Kim 2014	15/13	Korea	T: 70 C: 69	T1: 11.91 ± 1.66 T2: N/A C1: 13.05 ± 1.43 C2: N/A	D <sub>3</sub> 1200 IU daily	12	N/A	FBG	Yes
Krul Poel 2015	136/138	The Netherlands	T: 67 C: 67	T1: 60.6 ± 23.3	D <sub>3</sub> 50,000 IU per month	104	Drug alterations	HbA1c FBG	Yes

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Nasri 2014	30/30	Iran	55	T2: 101.4 ± 27.6 C1: 59.1 ± 23.2 C2: 59.8 ± 27.4 T1: 83.9 ± 52 T2: 164 ± 57 C1: 105.7 ± 64 C2: 115.8 ± 94	D <sub>3</sub> 50,000 IU weekly	12	N/A	HbA <sub>1c</sub>	Yes
Nikooyeh 2011	30/30	Iran	T: 51 C: 51	T1: 44.4 ± 28.7 T2: 77.7 ± 28.6 C1: 41.6 ± 44.5 C2: 37.2 ± 44	D <sub>3</sub> 1000 IU daily (both groups received calcium 300 mg daily)	12	Drug alterations were not allowed	HbA <sub>1c</sub> FBG	Yes
Punthakee 2012	607/614	33 countries	T: 67 C: 67	N/A	D <sub>3</sub> 1000 IU daily	287	N/A	HbA <sub>1c</sub> FBG	Yes
Razzaghi 2016	30/30	Iran	T: 59.6 C: 58.6	T1: 37.9 ± 24.7 T2: 70.1 ± 31.2 C1: 50.4 ± 38.9 C2: 45.9 ± 21.2	D <sub>3</sub> 50,000 IU every 2 weeks	12	N/A	HbA <sub>1c</sub> FBG	Yes
Ryu 2014	79/79	Korea	T: 55 C: 56	T1: 27.0 ± 12.7 T2: 75.4 ± 27.0 C1: 25.2 ± 9.7 C2: 38.9 ± 17.7	D <sub>3</sub> 2000 IU daily + calcium 200 mg daily	24	N/A	HbA <sub>1c</sub> FBG	Yes
Sadiya 2014	45/42	UAE	T: 49 C: 48	T1: 28.5 ± 9.2 T2: 62.3 ± 20.8 C1: 30.5 ± 11.2	D <sub>3</sub> 6000 IU daily × 3 months, then 3000 IU daily × 3 months	12	Advised to maintain usual medical care	HbA <sub>1c</sub> FBG	Yes

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Shab-Bidar 2012	50/50	Iran	T: 53 C: 52	C2: 25.4 ± 11.8 T1: 38.5 ± 20.2 T2: 72.0 ± 23.5 C1: 38 ± 22.8 C2: 33.4 ± 22.8	D <sub>3</sub> 1000 IU daily (both groups received calcium 340 mg daily)	12	N/A	HbA <sub>1c</sub> FBG	Yes
Strobel 2014	43/43	Germany	60	T1: N/A T2: 87.4 (33.9, 143.8) C1: N/A C2: 49.9 (20.0, 95.6)	D <sub>3</sub> 1904 IU daily	24	N/A	HbA <sub>1c</sub> FBG	No
Sugden 2008	34	Scotland	T: 65 C: 64	T1: 40.2 ± 10.3 T2: Change of 22.9 ± 16.6 C1: 36.4 ± 8.5 C2: Change of 7.6 ± 12.5	D2 100,000 IU once	8	Drug alterations were not allowed	HbA <sub>1c</sub>	Yes
Tabesh 2014	30/30	Iran	T: 50 C: 54	T1: 27.8 ± 13.9 T2: N/A C1: 35.7 ± 15.1 C2: N/A	D <sub>3</sub> 50,000 IU weekly + calcium 1000 mg daily	8	N/A	HbA <sub>1c</sub> FBG	No
Witham 2010	22/19/20	Scotland	T1: 65 T2: 63 C: 67	T1: 48 ± 21 T2: 79 ± 21 C1: 45 ± 17 C2: 54 ± 20	T1: D <sub>3</sub> 100,000 IU once T2: D <sub>3</sub> 200,000 IU once	12	N/A	HbA <sub>1c</sub>	Yes
Yiu 2013	50/50	Hong Kong	T: 66 C: 65	T1: 52.7 ± 11.0 T2: 146.3	D <sub>3</sub> 5000 IU daily	12	N/A	HbA <sub>1c</sub> FBG	No

First author, year	Participants (T/C)	Country	Participant's age (mean)	Vitamin D-25OH level (nmol/L)	Intervention vitamin D type, dose, frequency	Duration of observation (weeks)	Diabetes medications during the study period	Outcome measures	In meta-analysis
Zhou 2015	31/31	China	59	C1: 54.7 ± 10.2 C2: 59.4 T1: 30.9 ± 20.9 T2: 48.1 ± 5.8 C1: 33.2 ± 19.4 C2: 29.1 ± 5.9	D <sub>3</sub> 1000 IU	12	N/A	HbA1c	Yes

T1: treatment group before intervention, T2: treatment group after intervention, C1: control group before intervention, C2: control group after intervention, FBG: fasting blood glucose, HbA1c: hemoglobin A1c.