

Vitamin D Supplementation, Glycemic Control, and Insulin Resistance in Prediabetics: A Meta-Analysis

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Diabetes prevention is a public health priority. Vitamin D supplementation may help prevent the development of diabetes in persons at increased risk. We performed a meta-analysis of controlled clinical trials that assessed glycemic outcome measures among adults at risk for type 2 diabetes, including prediabetes, overweight, or obesity. We searched PUBMED/ MEDLINE, CINAHL, and Google Scholar databases for trials published prior to April 2017. Placebo-controlled clinical trials with random allocation to vitamin D with or without calcium supplementation were selected. Data collection included country, study design, inclusion criteria, sample size, form, and dose of vitamin D, supplementation interval, control group, duration, participant characteristics, comorbidities, baseline and follow-up serum 25-hydroxyvitamin D [25(OH)D] concentration, and available outcome measures [glycosylated hemoglobin (HbA1c), fasting plasma glucose, plasma glucose after 2-hour oral glucose tolerance test, and homeostatic model assessment of insulin resistance (HOMA-IR)]. Data synthesis was conducted using random-effect models (PROSPERO registration no. CRD42017055326). Twenty-eight trials, representing 3848 participants, met the eligibility criteria. Compared with the control group, vitamin D supplementation significantly reduced HbA1c level by -0.48% (95% CI, -0.79 to -0.18), fasting plasma glucose level by -0.46 mmol/L (95% CI, -0.74 to -0.19), and HOMA-IR level by -0.39 (95% CI, -0.68 to -0.11). Subgroup analysis revealed that the effects of vitamin D supplementation on different glycemic measures were influenced by age, calcium coadministration, vitamin D deficiency, serum 25(OH)D level after supplementation, and duration of supplementation. Vitamin D supplementation and improved vitamin D status improved glycemic measures and insulin sensitivity and may be useful as part of a preventive strategy for type 2 diabetes.

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Freeform/Key Words: 25-hydroxyvitamin D, cholecalciferol, diabetes, hemoglobin A1c, prediabetes, vitamin D

Every 3 minutes, a Canadian is diagnosed with type 2 diabetes or prediabetes [1]. Currently, more than 5.7 million Canadians have prediabetes [1]. Prediabetes refers to impaired fasting glucose or impaired glucose tolerance, with fasting blood glucose levels above normal but not elevated enough to be diagnosed as type 2 diabetes mellitus [2]. People with prediabetes are at a 50% higher risk of developing type 2 diabetes [3, 4]. Yet, even if these people at high risk do not progress to type 2 diabetes, prediabetics are still prone to some of the long-term

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 2HPG, plasma glucose after 2-hour oral glucose tolerance test; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; PTH, parathyroid hormone; RCT, randomized controlled trial; SE, standard error.

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complications associated with diabetes, such as heart disease, stroke, and nerve damage [5]. The pathogenesis of prediabetes involves the development of insulin resistance and later impaired insulin secretion [6], often associated with chronic inflammation, an indicator in the development of type 2 diabetes [7, 8].

In parallel with the increased prevalence of prediabetes, there has been an increasing trend in the prevalence of vitamin D deficiency [9, 10]. Individuals with prediabetes commonly have lower serum 25-hydroxyvitamin D [25(OH)D] concentrations than those with normal glucose control [11–14]. Further, the risk of developing diabetes is much greater for prediabetics who are vitamin D deficient [15, 16]. Low vitamin D status in patients with prediabetes can predict future macrovascular complications by contributing to blood pressure dysregulation, renin-angiotensin activity impairments, endothelial dysfunction, and chronic inflammation [17–19]. Calcium might be beneficial for decreasing the risk of diabetes through its effect on insulin release and its indirect effect on weight loss [20–24]. Given this background, as well as its safety, reasonable price, and accessibility [25], vitamin D supplementation during the prediabetic stage, either taken alone or in combination with calcium, has the potential to halt the progression to diabetes has been investigated [21, 26, 27].

Several probable mechanisms of action may explain a possible role for vitamin D to help improve glucose metabolism, including its anti-inflammatory and immunomodulatory effects [28], the induction of insulin secretion by pancreatic β -cells [29], its indirect effect on regulating calcium concentration in pancreatic β -cells, and subsequent insulin secretion [30]. Further, vitamin D receptors are expressed on various insulin-dependent tissues (including the liver, skeletal muscle, and adipose tissue), suggesting a role for vitamin D in glucose utilization and insulin sensitivity [31]. The influence of vitamin D on genes regulating cellular proliferation, differentiation, and apoptosis in metabolic pathways may also play a role [32, 33]. Moreover, in vitamin D-deficient individuals, moderate elevation of parathyroid hormone (PTH) may impair insulin release from pancreatic β -cells [34, 35].

Observational studies, several randomized controlled trials (RCTs), and meta-analyses [36, 37] have been conducted to investigate the effect of vitamin D supplementation on glycemic measures and insulin sensitivity in prediabetes populations. However, no decisive conclusions can yet be drawn from these existing reports [38, 39]. Some of the conflicting results from these studies are due to limitations, including studies not primarily designed for glycemic outcomes, relatively small sample sizes, limited reports on serum 25(OH)D concentrations, inappropriate or infrequent doses of vitamin D (monthly or large bolus doses), and relatively short duration of supplementation that does not account for physiology (*i.e.*, shorter than the turnover of HbA1c) [40–43]. To address these issues, we undertook a systematic review and meta-analysis of RCTs to delineate the impact of vitamin D supplementation on glycemic control and insulin resistance in prediabetic or overweight/obese adult populations. We restricted our analysis to clinical trials with daily or weekly supplementation, which provides a sustained serum 25(OH)D concentration over time, intervention periods of greater than 2 months or long enough for HbA1c turnover, a measurable impact of vitamin D supplementation on 25(OH)D concentrations, meaning the dose was high enough to impact vitamin D status, and the measurement of different parameters associated with prediabetes [HbA1c, FPG, HOMA-IR, and plasma glucose after 2-hour oral glucose tolerance test (2HPG)].

1. Materials and Methods

A. Literature Search Strategy

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [44]. The study protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (registration no. CRD42017055326). The primary outcome of interest was to systematically review the effect of vitamin D supplementation on glycemic control and insulin resistance as measured by HbA1c, FPG, fasting

HOMA-IR, and 2HPG in adult populations with prediabetes, overweight, or obesity. We also evaluated the impact of coadministration of calcium with vitamin D, obesity, serum 25(OH)D status at the beginning and the end of intervention, and the duration of vitamin D supplementation on the abovementioned glycemic measures.

Search terms included [vitamin D; vitamin D3; cholecalciferol; 25(OH)D] AND/OR [prediabetes; insulin resistance; at risk for diabetes; hyperglycemia; HbA1c; glucose] in the title and/or abstract. Studies published in English and those conducted on adults (age ≥ 18 years old) were selected. Calcium was permitted as a combined supplement with vitamin D or as a supplement provided to both treated and control groups.

B. Data Sources

We searched multiple databases including PUBMED/Medline (Medical Literature Analyses and Retrieval System Online), Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane library, and Google Scholar (as the gray literature suggested by the Cochrane guideline). The reference lists of all articles that met the selection criteria and systematic reviews already published were also hand searched by two reviewers (N.M. and M.M.). Databases were searched for studies published from January 1999 until April 2017.

C. Study Selection

Two reviewers (N.M. and M.M.) selected the studies for the systematic review, which were approved by a third reviewer (S.M.K.). Studies were included in this systematic review and meta-analysis of RCTs if: (1) they were placebo-controlled trials; (2) the population included persons with prediabetes, impaired fasting glucose, impaired glucose tolerance, overweight, or obese; (3) were conducted in adults (≥ 18 years); (4) intervention was a minimum of 2 months (defined as the minimum time required to assess changes in glucose blood markers) [45]; (5) supplementation was provided on a daily, biweekly, or weekly basis; and (6) reported baseline and end-of-study measures for serum 25(OH)D concentrations and HbA1c or FPG or HOMA-IR or 2HPG, or providing delta values (changes over time).

Studies were excluded if: (1) they were not placebo controlled; (2) the population included subjects with type 2 diabetes, end-stage renal disease, or gestational diabetes or were conducted in children/adolescents; (3) the duration of the trial was less than 2 months; (4) supplementation was provided less frequently than each week (e.g., monthly basis or as a single large bolus dose); (5) serum 25(OH)D concentrations were not reported at baseline and end of study; (6) they were studies in which the mean change or SD of the outcome measures was not reported; or (7) the study had an observational, case control, cross-sectional, or cohort design, or the publication was a narrative review, comment, opinion piece, methodological report, editorial, letter, or conference abstract.

D. Data Extraction and Management

The full-text of each publication that met the inclusion criteria was screened to determine eligibility (N.M. and M.M.). Any disagreement between the researchers regarding the eligibility of particular studies was resolved through discussion with a third reviewer (S.M.K. or H.V.). Following assessment of methodological quality of the trials by the first reviewer (N.M.), data were extracted using a data extraction form and the most important results from each study were summarized by N.M. and M.M. The extracted data were approved by the third and fourth researchers (H.V. and S.M.K.). Data extracted from each study included first author, reference, year of publication, country of study, study design, inclusion criteria, sample size, form of vitamin D, vitamin D dose and supplementation interval, control group, duration of supplementation, participants' characteristics [sex (n, % male), age, weight, body mass index (BMI)], cosupplementation with calcium, comorbidities, baseline and follow-up serum 25(OH)D concentration (nmol/L), and outcome measures. Any necessary calculations

on data were conducted by the first reviewer (N.M.) and checked by the second reviewer (H.V.).

E. Quality Assessment

Study quality and the risk of bias in the eligible RCTs were systematically assessed using the Cochrane criteria checklist [46]. The items used for the assessment of each study were: (1) adequacy of random sequence generation; (2) allocation concealment; (3) sample size and power of study; (4) quality of blinding (both participants and personnel); (5) intention-to-treat analysis (incomplete data); (6) compatibility of groups; (7) clear definition of inclusion and exclusion criteria; and (8) the description of withdrawal and dropout. A judgment of “adequate” (✓) indicated low risk of bias, whereas “inadequate” (–) indicated a high risk of bias, taking into account the recommendations of the Cochrane Handbook. We labeled uncertain or unknown risk of bias as “unclear.” Quality assessment was performed by one reviewer (N.M.) and approved by the other reviewers (S.M.K. and H.V.).

F. Statistical Analysis and Data Synthesis

To calculate the effect size, we followed the Cochrane Handbook and used the mean change from baseline to the end of the intervention in the levels and SD of the outcome measures for both control and intervention groups [46]. A meta-analysis was conducted to combine the individual study results. Meta-analysis of RCTs was conducted using Comprehensive Meta-Analysis version 3 software (Biostat 2014, Englewood, NJ) [47]. A *P* value <0.05 was considered to be statistically significant. We based the meta-analysis on calculating net changes from baseline to the endpoint, when the mean and SDs of the changes were reported, as: [(measure at endpoint in the treatment group – measure at baseline in the treatment group) – (measure at endpoint in the control group – measure at baseline in the control group)]. Effect sizes were expressed as the between-group weighted (standardized) mean difference and 95% CI.

Serum 25(OH)D levels were collated in nmol/L, and we used a multiplication factor of 2.496 to convert 25(OH)D levels respectively from ng/mL to nmol/L [48]. Plasma glucose levels (FPG and 2HPG) were collated in mmol/L, and a multiplication factor of 0.0555 was used to convert glucose levels respectively from mg/dL to mmol/L as appropriate [49].

Data were analyzed using a random-effects model (DerSimonian-Laird method) and the generic inverse variance method to compensate for the heterogeneity of studies due to the broad demographic characteristics of populations being studied [47, 49, 50]. Heterogeneity was assessed using the I^2 index with values $\geq 50\%$ determining the use of the random-effects model. The effect size was determined using weighted mean difference with a 95% CI. For treatment effect, a negative value represents a reduction in the outcome in the intervention group relative to the change in the placebo group. When more than one dose of vitamin D was examined in the same study, data from the highest dose was compared with placebo. Studies with more than two intervention groups (e.g., vitamin D alone and in combination with calcium) were used in subgroup analysis as multiple studies and both compared with the placebo.

We conducted a sensitivity analysis using the leave-one-out method (removing one study each time and repeating the analysis). This analysis allowed us to determine the impact of each study on the overall effect size [51].

G. Publication Bias

We explored publication bias using a visual inspection of Begg’s funnel plot asymmetry, supplemented with Egger’s weighted regression tests [49, 52]. Funnel plots were derived separately from changes in FPG, HbA1c, HOMA-IR, 2HPG, and 25(OH)D depicted as weighted mean difference vs its standard error (SE). This step was followed by adjusting the analysis for the effect of publication bias using the Duval and Tweedie “trim and fill” method [53].

H. Subgroup Analysis

In addition to running a sensitivity analysis and using random-effect models, we addressed heterogeneity using subgroup analyses. Subgroup analyses were performed for the following: (1) population was comprised of individuals with prediabetes vs overweight or obese (prediabetes was diagnosed by having HbA1c measured in the range of 5.8% to 6.4%, and any participant with BMI ≥ 25 kg/m² was considered overweight/obese); (2) whether calcium was used in combination with vitamin D; (3) age group (≤ 45 years vs > 45 years); (4) vitamin D deficiency at baseline [serum 25(OH)D level < 50 nmol/L vs ≥ 50 nmol/L]; (5) serum 25(OH)D level at follow-up; (6) body weight status (overweight and obese with BMI ≥ 25 kg/m² vs BMI < 25 kg/m²); and (7) duration of the intervention (< 6 months vs ≥ 6 months).

For each outcome, the effect size for subgroups (two subgroups) was calculated as the weighted mean difference between treatment and placebo groups using Comprehensive Meta-Analysis software (Biostat 2014). Then a between-subgroup comparison for each outcome was conducted with a simple *t* test, and the *P* values were adjusted by Bonferroni correction. Subgroup analyses were determined *a priori* according to established cutoff points such as vitamin D deficiency, defined as a serum 25(OH)D level of less than 50 nmol/L, or based on the distribution of study populations such as median for age or serum 25(OH)D levels at follow-up.

2. Results

A. Search Results and Study Selection Process

We identified a total of 1553 citations using the search keywords. After removing duplicates, 230 records remained. After screening via titles and abstracts, 123 articles remained for further evaluation. We excluded 95 articles for the following reasons: the population included persons with diabetes, children, or adolescents, or occurred during pregnancy; the duration of supplementation was less than 2 months; supplementation was provided on a monthly basis or as a large bolus dose; and studies were not placebo controlled. Studies with insufficient information, after unsuccessful attempt to obtain the information through communication with the authors, were excluded [54–59]. Twenty-eight RCTs met our eligibility criteria and were included in the meta-analysis. Details of the search process and study selection are illustrated in Fig. 1.

B. Risk of Bias Assessment

There was no risk of selection bias because all included studies were reported to be randomized and the allocation was sufficiently concealed. There was a lack of information on blinding of patients and personnel (*n* = 2) and blinding of outcome assessment (*n* = 2). However, all evaluated studies had a low risk of bias according to random allocation concealment, comparability of intervention groups, clear definition of inclusion/exclusion criteria, and the description of dropout/withdrawal. Bias due to attrition was a concern in one trial [60]. Intention-to-treat analyses were conducted in 15 studies. An overview of the quality of bias assessment for each study is presented in Table 1.

C. Characteristics of the Included Studies

The characteristics of the included studies are provided in Table 2. Included studies were published between 2007 and 2017 from different countries, including the United States (seven studies), Norway (three studies), Iran (six studies), and one study each from Canada, the Netherlands, Japan, Finland, Scotland, India, Malaysia, the United Kingdom, Australia, Austria, Denmark, and Germany. The sample size varied from 23 [60] to 511 [61]. Participants in six studies were females only [62–66] and males only in one study [67]. The mean age of participants ranged from 26 years [60] to 71 years [21]. The duration of follow-up across studies ranged from 2 months [64] to 5 years [68], with a median follow-up of 22 weeks [interquartile range (IQR): 14 to 48 weeks].

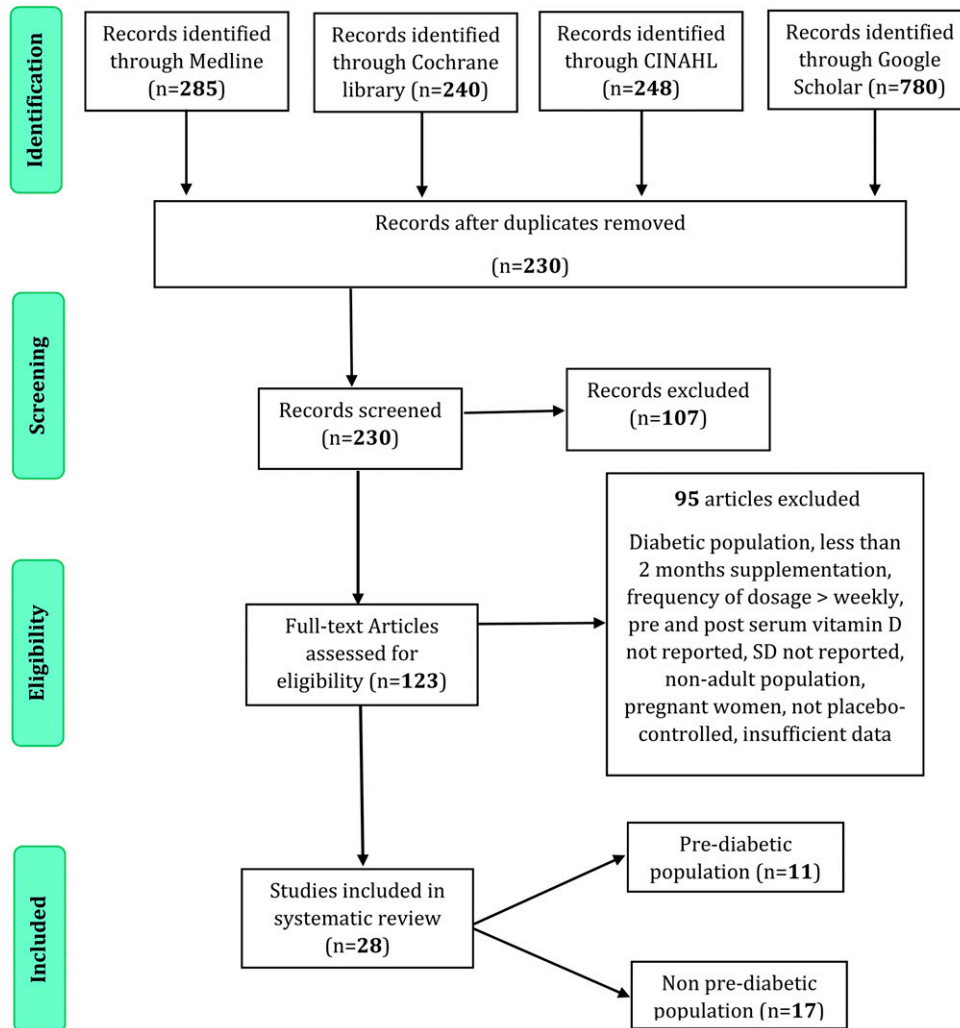


Figure 1. Study selection flow diagram. PRISMA flow diagram of search results following study section procedure assessing vitamin D supplementation and glycemic control among RCTs of adult population.

Oral daily doses of vitamin D₃ ranged from 10.5 µg/d (420 IU/d) [69] to 175 µg/d (7000 IU/d) [70], with 10 studies providing daily doses over 100 µg/d (4000 IU/d) [60, 63, 64, 70–76]. In 12 studies, vitamin D supplementation was provided on a weekly basis with a dose range of 500 to 2222 µg/wk (20,000 to 88,880 IU/wk), roughly equivalent to a daily dose of 72 to 318 µg (2860 to 12,700 IU/d) [43, 61, 63, 64, 68, 71, 73–78]. The average serum 25(OH)D concentrations at baseline varied from 25 nmol/L [79, 80] to 76 nmol/L [65], with a median of 38 nmol/L (IQR: 31 to 54 nmol/L) in vitamin D-supplemented groups and 41 nmol/L (IQR: 34 to 56 nmol/L) in the placebo groups. Thirteen studies recruited subjects who were vitamin D deficient [serum 25(OH)D <50 nmol/L] or insufficient [serum 25(OH)D <75 nmol/L] at the beginning of the trial [42, 43, 63, 64, 67, 70, 71, 73, 74, 76, 79–81]. Cosupplementation of vitamin D and calcium occurred in four studies, which assessed vitamin D plus calcium against placebo [21, 72, 73, 79]. A determination of prediabetes was an inclusion criterion in 11 RCTs [15, 61, 67, 68, 71–74, 79, 81, 82]. Being overweight or obese (BMI ≥25 kg/m²) was one of the inclusion criteria in 15 RCTs [21, 42, 60–62, 64, 67, 70–73, 75, 79, 81, 82].

There were 26 studies with acceptable methodological quality and low dropout rate (<20%). These studies included a large number of participants in the intervention groups (n = 1924), an average vitamin D supplementation dose of 88 µg/d (3500 IU/d), and a median of 22 weeks (around 6 months) for the length of supplementation, a duration long enough to detect changes in measured

Table 1. Quality Assessment of Included Studies

Authors	Quality of Random Allocation Concealment	Sample Size Large Enough to Detect Difference	Intention to Treat	Blinding Patients/ Personnel	Blinding Outcome Assessment	Comparability of Groups	Clear Definition of Inclusion Exclusion Criteria	Description of Withdrawal and Dropout
Barengolts <i>et al.</i> 2015	✓	—	✓	✓	✓	✓	✓	✓
Davidson <i>et al.</i> 2013	✓	✓	✓	✓	✓	✓	✓	✓
Oosterwerff <i>et al.</i> 2014	✓	✓	✓	✓	✓	✓	✓	✓
Mitri <i>et al.</i> 2011	✓	U	✓	✓	✓	✓	✓	✓
Harris <i>et al.</i> 2012	✓	✓	U	U	U	✓	✓	✓
Tuomainen <i>et al.</i> 2015	✓	✓	—	✓	✓	✓	✓	✓
Sollid <i>et al.</i> 2014	✓	✓	✓	✓	✓	✓	✓	✓
Dutta <i>et al.</i> 2014	✓	U	U	—	—	✓	✓	✓
Forouhi <i>et al.</i> 2016	✓	✓	✓	✓	✓	✓	✓	✓
Jorde <i>et al.</i> 2016	✓	✓	✓	U	U	✓	✓	✓
Moreira-Lucas <i>et al.</i> 2016	✓	—	✓	✓	✓	✓	✓	✓
Salehpour <i>et al.</i> 2013	✓	U	U	✓	✓	✓	✓	✓
Pittas <i>et al.</i> 2007	✓	U	U	✓	✓	✓	✓	✓
Ramly <i>et al.</i> 2014	✓	✓	✓	✓	✓	✓	✓	✓
Carrillo <i>et al.</i> 2013	✓	✓	U	✓	✓	✓	✓	—
Wamberg <i>et al.</i> 2013	✓	✓	✓	✓	✓	✓	✓	✓
Zittermann <i>et al.</i> 2009	✓	U	U	✓	✓	✓	✓	✓
Gepner <i>et al.</i> 2012	✓	✓	U	✓	✓	✓	✓	✓
Grimnes <i>et al.</i> 2011	✓	✓	✓	✓	✓	✓	✓	✓
Wood <i>et al.</i> 2012	✓	✓	✓	✓	✓	✓	✓	✓
Asemi <i>et al.</i> 2015	✓	✓	✓	✓	✓	✓	✓	✓
Sun <i>et al.</i> 2016	✓	✓	U	✓	✓	✓	✓	✓
Sharifi <i>et al.</i> 2014	✓	✓	U	✓	✓	✓	✓	✓
Mousa <i>et al.</i> 2017	✓	✓	—	✓	✓	✓	✓	✓
Osati <i>et al.</i> 2016	✓	U	U	✓	✓	✓	✓	✓
Grubler <i>et al.</i> 2016	✓	✓	✓	✓	✓	✓	✓	✓
Lorvand Amiri <i>et al.</i> 2016	✓	✓	U	✓	✓	✓	✓	✓
Vahedpoor <i>et al.</i> 2017	✓	✓	✓	✓	✓	✓	✓	✓

Abbreviations: ✓, adequate; —, inadequate; U, unclear.

outcomes. Each of these features improved the statistical strength of this study. Analyzed together, these data provide a diverse population.

D. Pooled Estimate of the Effect of Vitamin D on Serum 25(OH)D Level

All included trials measured the effect of vitamin D supplementation on serum 25(OH)D concentrations. All trials showed a significant increase in serum 25(OH)D levels in vitamin D-supplemented groups, with the overall median serum 25(OH)D concentration ≥ 86 nmol/L at follow-up (mean \pm SD: 91 ± 25 nmol/L), compared with the placebo group (49 ± 20 nmol/L). In seven studies [64, 69, 76, 78–80, 83], follow-up serum 25(OH)D concentrations were below 86 nmol/L, which may be related to low supplementation dose and/or high BMI. The substantial increase of serum 25(OH)D concentration in two studies [43, 71] was likely related to the high dose of supplementation [300 μ g/d (12,000 IU/d) and 143 μ g/d (5700 IU/d)]. Overall, serum 25(OH)D concentrations in the treated arms significantly improved by 45.1 nmol/L (95% CI: 41.3 to 48.9; $P < 0.001$, $I^2 = 97.4\%$; Fig. 2).

E. Pooled Estimate of the Effect of Vitamin D on Glycemic Control

E-1. HbA1c

Sixteen studies examined HbA1c as an outcome. Of the individual studies, seven reported reduced HbA1c with vitamin D supplementation [62, 67, 69, 71, 73, 82, 83], and nine reported null results [15, 42, 43, 61, 68, 72, 74, 79, 81]. Vitamin D supplementation and improved vitamin D status reduced HbA1c significantly, compared with placebo, across all studies by -0.48% (95% CI: -0.79 to -0.18 ; $P = 0.002$, $I^2 = 92.1\%$; Fig. 3).

Table 2. Characteristics of Included Studies

Study	Place of Study	n	Study Population	Mean Age	% Male	Vitamin D μg (IU)
Barengolts <i>et al.</i> 2015	US	173	Prediabetes and hypovitaminosis D (12–73 nmol/L) overweight	60	100	10 $\mu\text{g}/\text{d}$ (400 IU/d)
Davidson <i>et al.</i> 2013	US	109	Prediabetes and 25(OH)D <75, obese and HTN	55	NA	Mean 2221 $\mu\text{g}/\text{wk}$ (88,865 IU/wk) adjusted based on BMI and baseline D
Oosterwerff <i>et al.</i> 2014	Netherlands	130	Prediabetes and vitamin D deficiency (<50) and obese	42	61	30 $\mu\text{g}/\text{d}$ (1200 IU/d)
Mitri <i>et al.</i> 2011	US	92	Prediabetes and overweight	57	49	50 $\mu\text{g}/\text{d}$ (2000 IU/d)
Harris <i>et al.</i> 2012	US	89	Prediabetes and obese	55	35	100 $\mu\text{g}/\text{d}$ (4000 IU/d)
Tuomainen <i>et al.</i> 2015	Finland	73	Prediabetes and vitamin D deficiency (<75) and overweight	70	NA	First arm: 40 $\mu\text{g}/\text{d}$ (1600 IU/d); second arm: 80 $\mu\text{g}/\text{d}$ (3200 IU/d)
Sollid <i>et al.</i> 2014	Norway	511	Prediabetes and obese	50	61	500 $\mu\text{g}/\text{wk}$ (20,000 IU/wk)
Dutta <i>et al.</i> 2014	India	136	Prediabetes and 25(OH)D <75 overweight	55	NA	A; 1500 $\mu\text{g}/\text{wk}$ (60,000 IU/wk) for 8 wk then monthly
Forouhi <i>et al.</i> 2016	UK	340	Prediabetes	52	NA	83 $\mu\text{g}/\text{d}$ (3300 IU/d) D3
Jorde <i>et al.</i> 2016	Norway	226	Prediabetes	62	64	500 $\mu\text{g}/\text{wk}$ (20,000 IU/wk)
Moreira-Lucas <i>et al.</i> 2016	Canada	63	Prediabetes and vitamin D deficient	46	52	700 $\mu\text{g}/\text{wk}$ (28,000 IU/wk)
Salehpour <i>et al.</i> 2013	Iran	77	Premenopausal women and obese	34	0	25 $\mu\text{g}/\text{d}$ (1000 IU/d)
Pittas <i>et al.</i> 2007	US	92	Overweight	71	52	18 $\mu\text{g}/\text{d}$ (700 IU/d)
Ramly <i>et al.</i> 2014	Malaysia	171	Premenopausal women and D deficient (<50)	50	0	1250 $\mu\text{g}/\text{wk}$ (50,000 IU/wk) for 2 mo then monthly
Carrillo <i>et al.</i> 2013	US	23	Overweight and obese	26	48	100 $\mu\text{g}/\text{d}$ (4000 IU/d)
Wamberg <i>et al.</i> 2013	Denmark	52	Obese and D deficient (<50)	34	29	175 $\mu\text{g}/\text{d}$ (7000 IU/d)
Zittermann <i>et al.</i> 2009	Germany	165	Overweight and average 25(OH)D = 30	44	33	83 $\mu\text{g}/\text{d}$ (3332 IU/d)
Asemi <i>et al.</i> 2015	Iran	104	Women with PCOS and vitamin D deficiency (<50) and obese	29	0	1250 $\mu\text{g}/\text{wk}$ (50,000 IU/wk)
Gepner <i>et al.</i> 2012	US	109	Postmenopausal women and 25 \leq 25(OH)D \leq 150	64	0	63 $\mu\text{g}/\text{d}$ (2500 IU/d)
Grimnes <i>et al.</i> 2011	Norway	94	Vitamin D deficient	53	52	500 μg biweekly (20,000 IU biweekly)
Wood <i>et al.</i> 2012	Scotland	305	Postmenopausal women	65	0	25 $\mu\text{g}/\text{d}$ (1000 IU/d) or 10 $\mu\text{g}/\text{d}$ (400 IU/d)
Sun <i>et al.</i> 2016	Japan	81	Healthy	45	6	11 $\mu\text{g}/\text{d}$ (420 IU/d)
Sharifi <i>et al.</i> 2014	Iran	53	Adults with NAFLD	42	49	1250 μg biweekly (50,000 IU/biweekly)
Mousa <i>et al.</i> 2017	Australia	54	Overweight and obese	30	65	2500 μg (100,000 IU bolus) then 100 $\mu\text{g}/\text{d}$ (4000 IU/d)
Osati <i>et al.</i> 2016	Iran	210	Vitamin D deficient	38	23	1250 $\mu\text{g}/\text{wk}$ (50,000 IU/wk)
Grubler <i>et al.</i> 2016	Austria	185	People with arterial HTN	60	53	70 $\mu\text{g}/\text{d}$ (2800 IU/d)
Lorvand Amir <i>et al.</i> 2016	Iran	73	Patients with NAFLD	42	62	25 $\mu\text{g}/\text{d}$ (1000 IU/d)
Vahedpoor <i>et al.</i> 2017	Iran	58	Patients with cervical intraepithelial neoplasia	37	NA	1250 μg biweekly (50,000 IU biweekly)

(Continued)

E-2. FPG

The effect of vitamin D on FPG was reported in 25 RCTs. Of these studies, eight reported reduced FPG with vitamin D supplementation [21, 61, 63, 69, 72, 73, 78, 82], four found an increase [42, 43, 62, 70], and 13 studies reported no change in FPG at follow-up [60, 64–66, 68, 71, 74–77, 80, 81, 83]. The combined data show vitamin D supplementation reduced FPG by -0.46 mmol/L (95% CI: -0.74 to -0.19 ; $P = 0.001$, $I^2 = 92.4\%$; Fig. 4).

F. Pooled Estimate of the Effect of Vitamin D on Insulin Resistance and Glucose Tolerance

F-1. Fasting HOMA-IR

The influence of vitamin D supplementation on insulin resistance (using HOMA-IR) was evaluated in 20 studies. In the individual studies, eight reported a lowering effect of vitamin D on HOMA-IR [21, 63, 64, 68, 74, 76, 78, 80], one study found an increase [72], and 11 found no effect in the vitamin D-supplemented group [43, 60–62, 66, 69–71, 73, 79, 81]. Vitamin D

Table 2. Characteristics of Included Studies (Continued)

Other Treatments	Control Group	Duration of Trial	Outcomes Measured	Treated Group		Control Group	
				Baseline 25(OH)D (nmol/L) Cases	Mean Change (nmol/L) Cases	Baseline 25(OH)D (nmol/L) Controls	Mean Change (nmol/L) Controls
500 mg/d CaCO ₃	Placebo	12 mo	HbA1c ^a	36	84	35	50
	Placebo	12 mo	HbA1c ^a , FPG, 2HPG, HOMA-IR	55	107	55	55
	Placebo plus CaCO ₃	16 wk	HbA1c, HOMA-IR, 2HPG ^a	25	35	22	23
	Placebo	16 wk	HbA1c ^a , 2HPG ^a , FPG ^a	61	25	60	−18
Calcium 600 mg/d	Placebo	12 wk	HbA1c, HOMA-IR ^a , FPG ^a , 2HPG	40	41	38	−1
	Placebo	5 mo	HbA1c, FPG, 2HPG ^a , HOMA-IR	57	45 (80 µg/d)	57	4
Calcium 500mg/d C; vitamin D-sufficient group got Ca	Placebo	1 y	HbA1c, FPG ^a , 2HPG, HOMA-IR	60	46	61	3
	Placebo	1 y	HbA1c, FPG ^a , 2HPG ^a , HOMA-IR	42	47 (A)	95	−73 (C)
	Placebo	4 mo	HbA1c	46	40	46	0
	Placebo	5 y	HbA1c, FPG, 2HPG, HOMA-IR ^a	60	62	61	6
Calcium 500 mg/d	Placebo	24 wk	FPG, HbA1c, HOMA-IR ^a	48	51	48	−2
	Placebo	12 wk	HbA1c ^a , FPG ^a , 2HPG, HOMA-IR	37	38	47	4
	Placebo	3 y	HOMA-IR ^a , FPG ^a	71	31	81	−8
	Placebo	12 mo	FPG ^a , HOMA-IR ^a	30	56	30	6
	Placebo	12 wk	FPG, 2HPG, HOMA-IR	48	36	45	14
	Placebo	26 wk	FPG ^a , HOMA-IR	34	76	34	13
	Placebo	12 mo	HbA1c, FPG	30	56	30	12
	Placebo	12 mo	FPG, HOMA-IR ^a	29	30	35	1
Plus Ca placebo	Calcium placebo + vitamin D placebo	2 mo	FPG, HOMA-IR ^a	29	30	35	1
	Placebo	4 mo	FPG	76	39	81	−0.5
	Placebo	6 mo	FPG ^a , HbA1c, HOMA-IR	42	100	39	3
	Placebo	12 mo	FPG, HOMA-IR	32	43 (25 µg/d)	36	−3
Hypocaloric diet	Placebo	1 y	FPG ^a , HOMA-IR, HbA1c ^a	33	28	32	−1
	Placebo	4 mo	FPG	37	46	44	6
	Placebo	4 mo	FPG	31	57	34	2
	Placebo	2 mo	FPG, HOMA-IR ^a	34	35	35	2
	Placebo	2 mo	FPG, HbA1c ^a	54	11	51	0
	Placebo	3 mo	FPG, HOMA-IR ^a	25	43	25	2
	Placebo	6 mo	FPG ^a , HOMA-IR ^a	27	40	28	−2
	Placebo	6 mo	FPG ^a , HOMA-IR ^a	27	40	28	−2

Abbreviations: HTN, hypertension; NA, not available; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

^aSignificant difference between intervention and placebo groups ($P < 0.05$).

supplementation was found to reduce HOMA-IR across all studies by -0.39 (95% CI: -0.68 to -0.11 ; $P = 0.007$, $I^2 = 91.3\%$; Fig. 5).

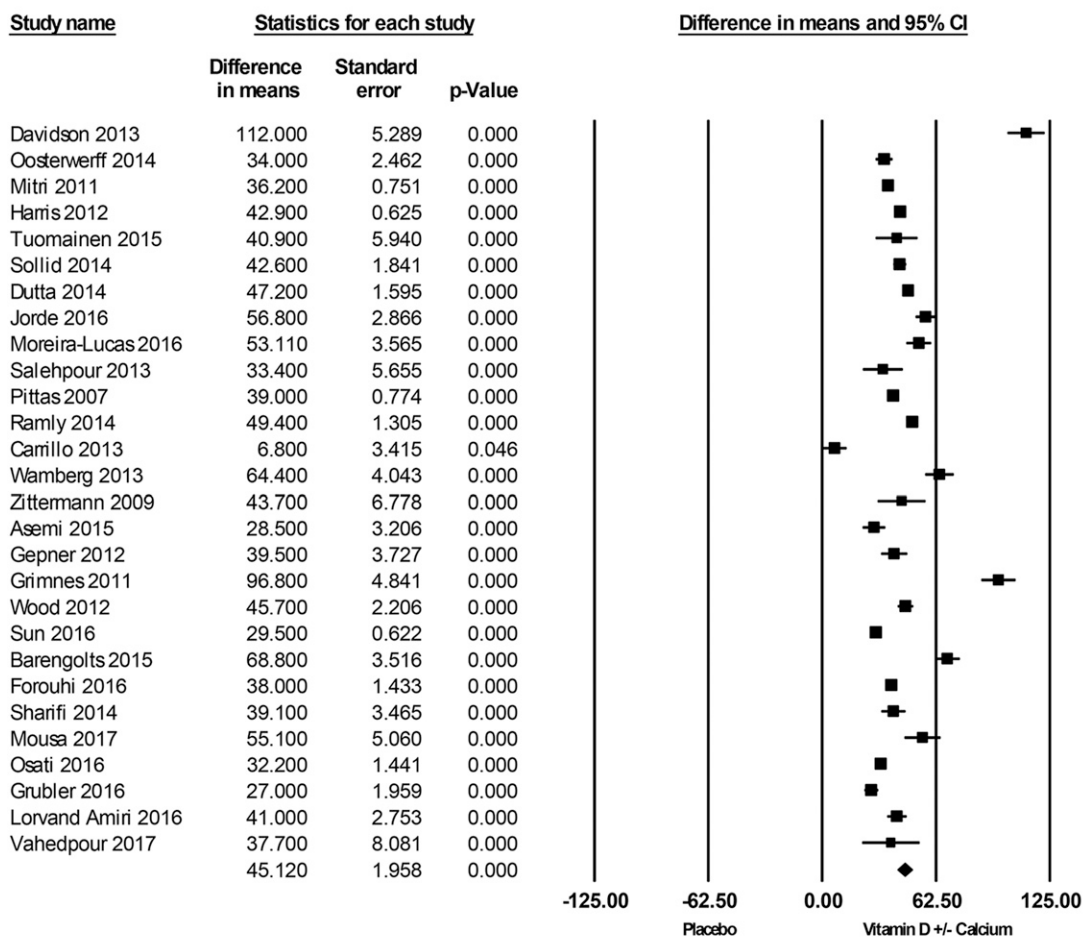
F-2. 2HPG

Ten studies contributed data on the effect of vitamin D supplementation on 2HPG. Of these studies, two reported positive effects of vitamin D supplementation [73, 82], one reported negative effects [81], and seven reported null results [60–62, 68, 71, 72, 79]. Combined data demonstrate that vitamin D supplementation did not significantly effect 2HPG, but a nonsignificant trend was found for decreased 2HPG by -0.13 mmol/L (95% CI: -0.34 to 0.08 ; $P = 0.2$, $I^2 = 69.1\%$; Fig. 6).

F-3. Sensitivity analysis

In the leave-one-out sensitivity analyses, the pooled effect estimates remained similar across all studies for HOMA-IR, 2HPG, and serum 25(OH)D concentration. These results confirm that the significant difference between the studied groups reflects the overall effect of all included studies. For HbA1c, after excluding one study [62], the effect size decreased from -0.48% ($P = 0.002$, $I^2 = 92\%$) to -0.31% ($P = 0.01$, $I^2 = 86\%$), and the effect of vitamin D supplementation on HbA1c was significant. For FPG, after excluding the study by Sun *et al.*

Effect of vitamin D supplementation on serum 25(OH)D level (nmol/L)



Meta Analysis

Figure 2. Forest plot of mean change from baseline in serum 25(OH)D concentrations (nmol/L) between vitamin D supplementation and control.

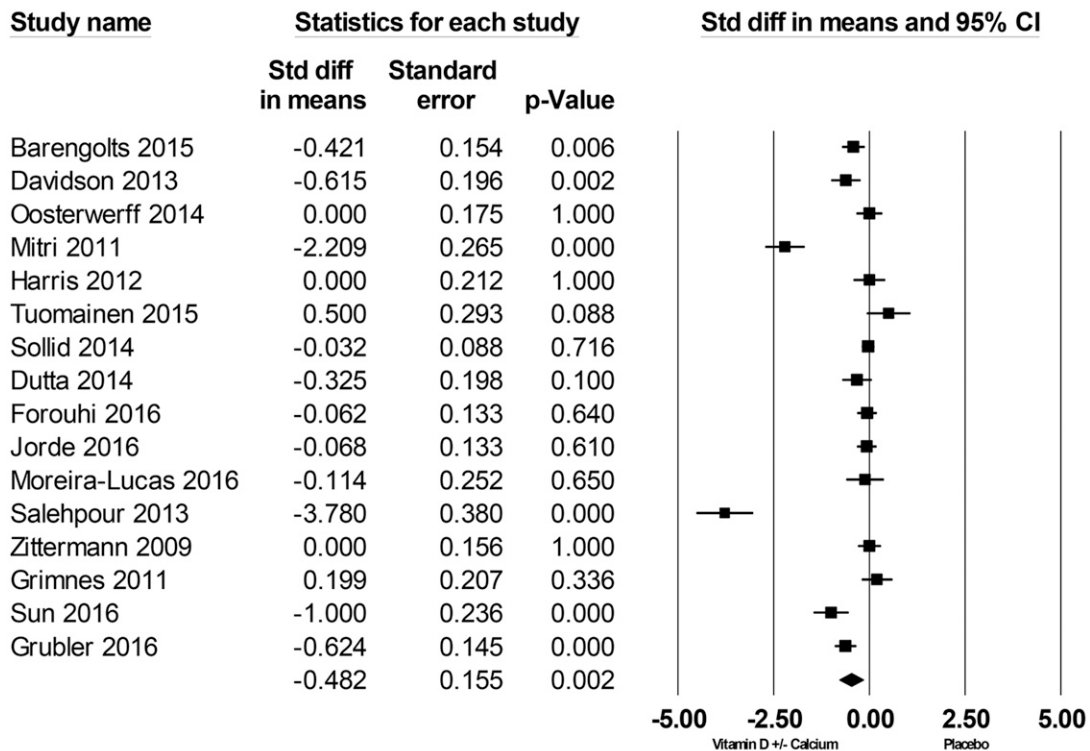
[69], the effect size decreased from -0.46 mmol/L ($P = 0.001$, $I^2 = 92\%$) to -0.36 mmol/L ($P = 0.005$, $I^2 = 90\%$), and after excluding the study by Pittas *et al.* [21], the effect size decreased to -0.36 mmol/L ($P = 0.004$, $I^2 = 89\%$). In both situations, the effect of vitamin D supplementation on reduced FPG remained significant.

F-4. Publication bias

For HbA1c, visual inspection of funnel plot asymmetry demonstrated a potential publication bias for the comparison of HbA1c percentage between vitamin D-administered groups and placebo groups [Fig. 7(a)]. The presence of a publication bias also was suggested by Egger's linear regression (intercept = -5.13 , SE = 2.33 ; 95% CI = -10.15 to -0.12 , $t = -2.2$, two-tailed $P = 0.04$). After adjusting the effect size for potential publication bias using the "trim and fill" method, four potentially missing studies were imputed in the funnel plot and the effect size increased from -0.48% (95% CI: -0.79 to -0.18) to -0.71% (95% CI: -1.02 to -0.39) [Fig. 7(b)].

For FPG, the funnel plot was asymmetric [Supplemental Fig. 1(a)] though Egger's linear regression (intercept = -3.74 , SE = 1.88 ; 95% CI = -7.64 to 0.15 , $t = -1.99$, two-tailed $P = 0.059$) did not indicate a potential bias. Using the "trim and fill" correction method, the effect size was adjusted for potential publication bias and six potentially missing studies were imputed

Effect of vitamin D supplementation on HbA1c (%)



Meta Analysis

Figure 3. Forest plot of mean change from baseline in HbA1c (%) between vitamin D supplementation and control.

in the funnel plot. The effect size increased from -0.46 mmol/L (95% CI: -0.74 to -0.19) to -0.72 mmol/L (95% CI: -1.02 to -0.42) [Supplemental Fig. 1(b)].

For HOMA-IR, funnel plot asymmetry indicated a potential publication bias in determining the effect size of vitamin D supplementation on HOMA-IR changes, compared with placebo group [Supplemental Fig. 2(a)]. The presence of a publication bias was not confirmed by Egger's linear regression (intercept = -1.09 , SE = 2.18 ; 95% CI = -5.67 to 3.49 , $t = -0.5$, two-tailed $P = 0.6$). Using the "trim and fill" method to adjust the effect size for potential publication bias, five potentially missing studies were imputed in the funnel plot and the effect size increased from -0.39 (95% CI: -0.68 to -0.11) to -0.62 (95% CI: -0.92 to -0.32) [Supplemental Fig. 2(b)].

Visually inspected funnel plot symmetry did not indicate any potential publication bias for the comparison of 2HPG levels between the vitamin D-supplemented group and placebo groups [Supplemental Fig. 3(a)]. Moreover, the Egger's linear regression (intercept = -1.19 , SE = 1.48 ; 95% CI: -4.6 to 2.2 , $t = -0.81$, two-tailed $P = 0.4$) did not detect any publication bias. Using the "trim and fill" correction and adjusting the effect size for potential publication bias, no potentially missing study was imputed in the funnel plot and the effect size remained the same (effect size: -0.13 mmol/L, 95% CI: -0.34 to 0.08) [Supplemental Fig. 3(b)].

For serum 25(OH)D levels, the funnel plot was asymmetric [Supplemental Fig. 4(a)] and Egger's linear regression (intercept = 3.61 , SE = 1.76 ; 95% CI = -0.005 to 7.23 , $t = 2.05$, two-tailed $P = 0.05$) indicated a potential bias. Using the "trim and fill" correction method, the effect size was adjusted for potential publication bias and no potentially missing studies were imputed in the funnel plot. The effect size remained the same at 45.1 nmol/L (95% CI: 41.3 to 48.9) [Supplemental Fig. 4(b)].

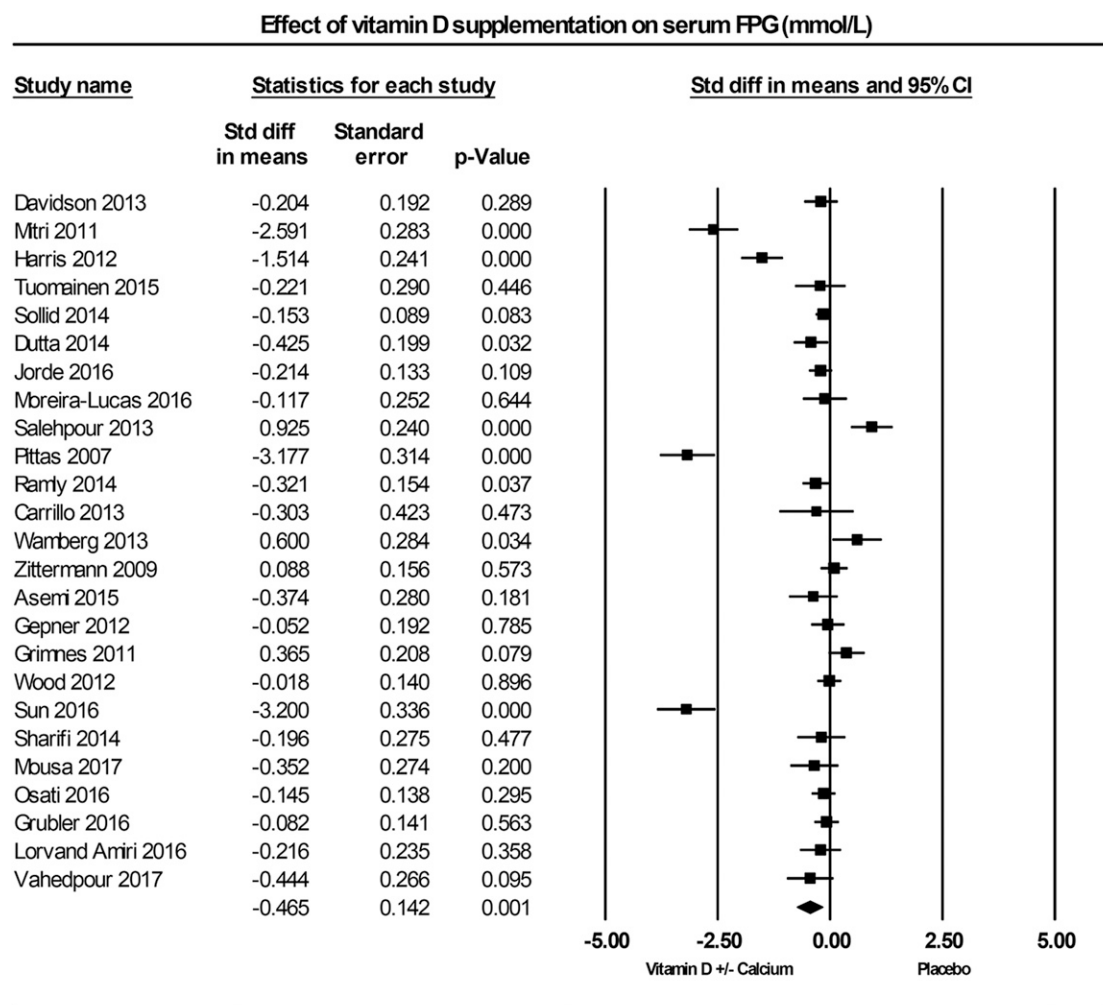
**Meta Analysis**

Figure 4. Forest plot of mean change from baseline in FPG (mmol/L) between vitamin D supplementation and control.

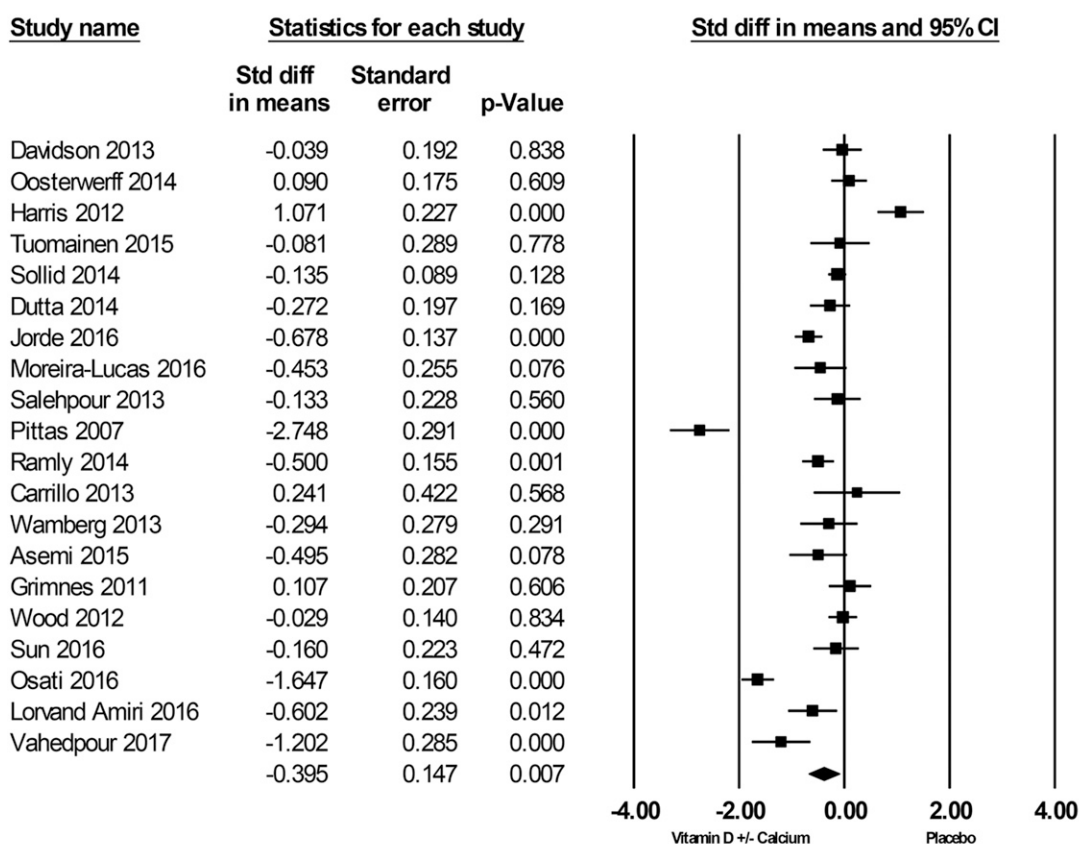
G. Subgroup Analysis**G-1. Effect of population characteristics**

We conducted a subgroup analysis to examine the effect of vitamin D supplementation in pre-diabetes in comparison with populations that were overweight/obese but not prediabetic (Table 3). The lowering effect was observed in both groups with no significant difference in the change of HbA1c and FPG between prediabetics and overweight/obese participants. Both HbA1c and HOMA-IR showed a greater reduction over time among overweight/obese individuals compared with prediabetics (HbA1c: -0.98 ± 0.45 vs -0.29 ± 0.14 , $P = 0.1$; HOMA-IR: -0.62 ± 0.23 vs -0.07 ± 0.16 , $P = 0.05$). There were not enough studies to perform subgroup analyses on 2HPG.

G-2. Effect of combined vitamin D and calcium supplementation

Subgroup analysis was performed to determine if concomitant calcium supplementation influenced the effects of vitamin D (Table 3). There was no significant difference in the change of HbA1c and HOMA-IR when calcium was provided in combination with vitamin D compared with vitamin D alone (HbA1c: -1.05 ± 0.74 vs -0.53 ± 0.18 , $P = 0.2$; HOMA-IR:

Effect of vitamin D supplementation on HOMA-IR



Meta Analysis

Figure 5. Forest plot of mean change from baseline in HOMA-IR between vitamin D supplementation and control.

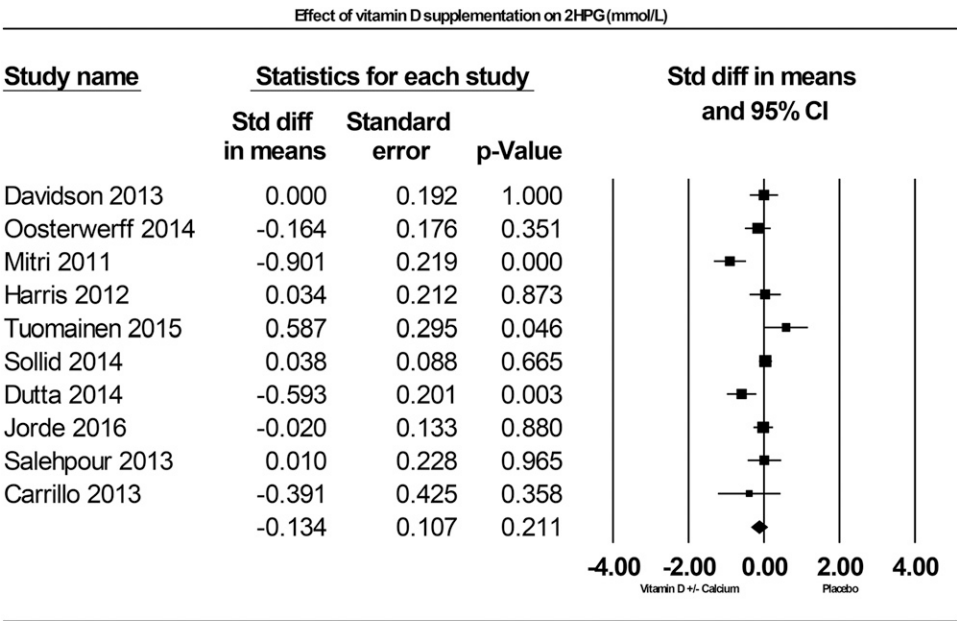
-0.46 ± 0.5 vs -0.38 ± 0.1 , $P = 0.4$), although coadministration of calcium showed greater reduction in HbA1c. However, FPG (-1.67 ± 0.5 vs -0.18 ± 0.1 , $P = 0.002$) and 2HPG (-0.54 ± 0.3 vs 0.03 ± 0.06 , $P = 0.02$) showed a greater reduction when vitamin D was provided in combination with calcium. Overall, combining calcium with vitamin D improved its effect on glycemic control.

G-3. Influence of age on the effect of vitamin D

Subgroup analysis was conducted to determine if age influenced outcomes by comparing studies in which mean participant age in each study was less or greater than 45 years (Table 3). HbA1c showed greater improvement in populations with a mean age younger than 45 years in comparison with older populations (-1.15 ± 0.6 vs -0.30 ± 0.1 , $P = 0.05$). Greater reduction in FPG for populations older than 45 years was not statistically significant (-0.58 ± 0.20 vs -0.31 ± 0.24 , $P = 0.2$). Changes in HOMA-IR and 2HPG did not differ significantly between the two compared age groups.

G-4. Influence of obesity on the effect of vitamin D

We compared the effect of vitamin D supplementation on glycemic measures between studies conducted in overweight/obese and nonobese populations (Table 3). There was no significant



Meta Analysis

Figure 6. Forest plot of mean change from baseline in plasma glucose after 2HPG (mmol/L) between vitamin D supplementation and control.

difference in the change of HbA1c, FPG, and HOMA-IR between obese and nonobese populations. We were not able to compare 2HPG as it was reported in only one study with a nonobese population in comparison with nine studies on obese populations.

G-5. Effect of baseline vitamin D status

Participants with vitamin D deficiency, mean serum 25(OH)D concentration <50 nmol/L, at the beginning of the intervention were compared with those who had mean serum 25(OH)D concentration ≥50 nmol/L (Table 3). Greater reductions were found within HbA1c and FPG levels when baseline mean serum 25(OH)D concentration was ≥50 nmol/L, whereas the lowering effect was significantly less in the subgroup with baseline mean 25(OH)D <50 nmol/L

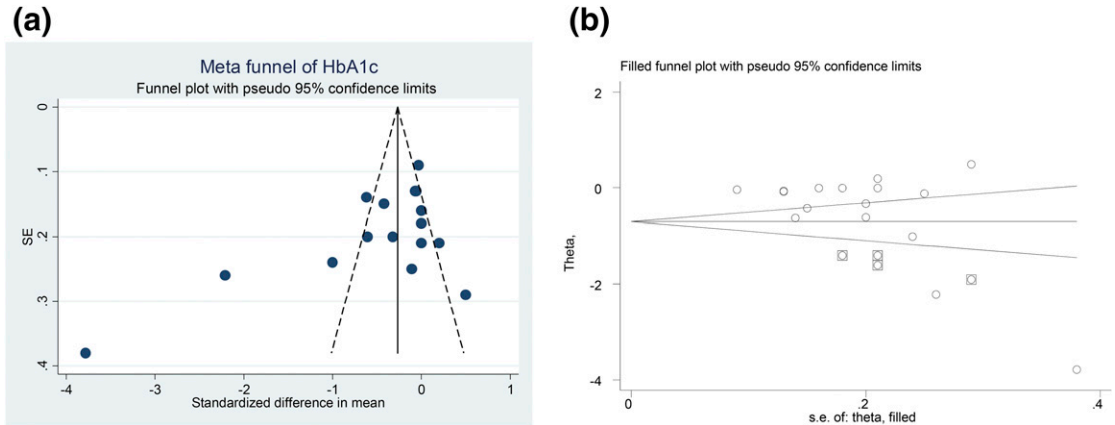


Figure 7. (a) Funnel plot of SE by standardized mean difference for HbA1c, detailing publication bias in the studies selected for analyses. Closed circles represent observed published studies. (b) “Trim and fill” method to impute for potentially missing studies for HbA1c. Four potentially missing studies were imputed in funnel plot. Closed circles represent observed published studies. Squares with circle inside represent imputed studies.

(HbA1c: -0.79 ± 0.25 vs -0.14 ± 0.13 , $P = 0.04$; FPG: -0.69 ± 0.21 vs -0.11 ± 0.10 , $P = 0.05$). The lowering effect of vitamin D on HOMA-IR and 2HPG did not differ based on serum 25(OH)D status at baseline.

G-6. Effect of serum 25(OH)D concentration at follow-up

Subgroup analysis was carried out based on the concentration of serum 25(OH)D achieved at follow-up, either below or above the median level (86 nmol/L) (Table 3). Vitamin D supplementation significantly decreased HbA1c ($P = 0.05$), FPG ($P = 0.05$), and HOMA-IR ($P = 0.1$) to a greater extent when serum 25(OH)D concentration achieved was above 86 nmol/L. In agreement with these results, we also found dose-response effects for all four parameters. With increased vitamin D supplementation dose, there was a greater reduction in HbA1c ($y = -2926.2x + 2741.3$, $R^2 = 0.06$), FPG ($y = -2686.4x + 3414.3$, $r^2 = 0.045$), HOMA-IR ($y = 876.75x + 3437.5$, $r^2 = 0.031$), and 2HPG ($y = -1779x + 3461.3$, $r^2 = 0.153$).

G-7. Effect of length of intervention

We compared the effects of vitamin D in studies of short and long duration (<6 months vs ≥ 6 months, respectively) (Table 3). For HbA1c, we found that vitamin D supplementation for less than 6 months provided a larger effect size on HbA1c in comparison with long durations (-0.75 ± 0.33 vs -0.25 ± 0.11 , $P = 0.1$). However, both FPG and HOMA-IR showed a greater but nonsignificant reduction with supplementation greater than 6 months compared with shorter durations (FPG: -0.64 ± 0.22 vs -0.32 ± 0.19 , $P = 0.1$; HOMA-IR: -0.53 ± 0.18 vs -0.24 ± 0.27 , $P = 0.1$). The duration of supplementation did not affect the reduction in 2HPG. There were three studies included in our meta-analysis with intervention durations of 2 months [64, 76, 83] that found a significant reduction in HbA1c [83], a decreased trend in FPG [64, 76, 83], and significant reduction in HOMA-IR [64, 76] following vitamin D supplementation. Despite a shorter duration of intervention, compared with other trials, these studies provided higher vitamin D supplementation doses (2800 to 7100 IU/d) and included vitamin D-deficient populations at baseline.

3. Discussion

Interest in the protective effects of vitamin D supplementation against the progression of diabetes has heightened in recent years, and the current analysis underscores some of these benefits. We evaluated 28 studies combined, including 11 centered on prediabetics and 16 on populations at high risk, and found significant effects of vitamin D supplementation on insulin resistance and hyperglycemia. Vitamin D supplementation and increased serum 25(OH)D concentrations improved insulin sensitivity (decreased HOMA-IR), glucose metabolism, and glycemic control (reduced HbA1c and FPG). Our findings suggest that a serum 25(OH)D concentration above 86 nmol/L can improve measures of glucose metabolism and response to insulin in prediabetics. Serum 25(OH)D concentrations above 86 nmol/L were achieved with an average vitamin D supplementation of 88 $\mu\text{g/d}$ (3500 IU/d) or more, taking body weight into account; Ekwaru *et al.* [84] previously showed that obese individuals often require two to three times the dose of vitamin D that an individual with a normal BMI requires to achieve the same 25(OH)D response. The greatest benefits were found in populations most at risk for early disease. We also found improvements in those considered vitamin D sufficient when they started vitamin D supplementation.

Subgroup analyses further demonstrated that both FPG and 2-hour postprandial plasma glucose reductions were enhanced with vitamin D taken in combination with calcium supplements, as were insulin resistance and fasting HOMA-IR. Longer duration of supplementation seemed to be more effective at reducing HOMA-IR than those shorter than 6 months. We used fasting HOMA-IR, which detects liver insulin resistance and shows

Table 3. Meta-analysis and Subgroup Analysis of Primary and Secondary Outcomes

Subgroup Analysis	No. of Study	No. of Subjects		Standardized Mean Difference (95% CI)	P Value	Between-Group P Value ^a
		Vitamin D	Placebo			
Study population						
HbA1c						
Prediabetes	11	892	880	-0.29 ± 0.14 (-0.57 to -0.01)	0.04	0.1
Overweight/obese (not prediabetes)	5	310	307	-0.98 ± 0.45 (-1.87 to -0.10)	0.02	
FPG						
Prediabetes	8	628	615	-0.65 ± 0.23 (-1.11 to -0.19)	0.005	0.2
Overweight/obese (not prediabetes)	17	883	885	-0.38 ± 0.19 (-0.74 to -0.01)	0.04	
HOMA-IR						
Prediabetes	8	647	634	-0.07 ± 0.16 (-0.39 to 0.24)	0.6	0.05
Overweight/obese (not prediabetes)	12	591	596	-0.62 ± 0.23 (-1.07 to -0.18)	0.006	
Concomitant use of calcium						
HbA1c						
D vs placebo	14	1082	1073	-0.53 ± 0.18 (-0.88 to -0.19)	0.002	0.2
D + Ca vs placebo	3	166	160	-1.05 ± 0.74 (-2.51 to 0.42)	0.1	
FPG						
D vs placebo	20	1296	1286	-0.18 ± 0.1 (-0.389 to 0.032)	0.09	0.002
D + Ca vs placebo	5	215	214	-1.67 ± 0.5 (-2.68 to -0.66)	<0.001	
HOMA-IR						
D vs placebo	15	1004	997	-0.38 ± 0.1 (-0.65 to -0.12)	0.004	0.4
D + Ca vs placebo	5	234	233	-0.46 ± 0.5 (-1.51 to 0.6)	0.4	
2HPG						
D vs placebo	6	501	494	0.03 ± 0.06 (-0.09 to 0.16)	0.6	0.02
D + Ca vs placebo	4	209	206	-0.54 ± 0.3 (-1.15 to 0.07)	0.08	
Age groups						
HbA1c						
≤45 y	4	226	227	-1.15 ± 0.6 (-2.33 to 0.04)	0.06	0.05
>45 y	12	976	960	-0.30 ± 0.1 (-0.57 to -0.03)	0.02	
FPG						
≤45 y	11	449	449	-0.31 ± 0.24 (-0.78 to 0.17)	0.2	0.2
>45 y	14	1062	1051	-0.58 ± 0.20 (-0.94 to -0.23)	0.001	
HOMA-IR						
≤45 y	9	377	379	-0.48 ± 0.24 (-0.96 to -0.008)	0.04	0.3
>45 y	11	861	851	-0.32 ± 0.19 (-0.69 to 0.04)	0.08	
2HPG						
≤45 y	3	114	116	-0.13 ± 0.13 (-0.39 to 0.13)	0.3	0.4
>45 y	7	596	584	-0.13 ± 0.14 (-0.41 to 0.14)	0.3	
Obesity						
HbA1c						
Obese	11	853	845	-0.63 ± 0.21 (-1.05 to -0.20)	0.004	0.2
Normal BMI	5	349	342	-0.19 ± 0.17 (-0.51 to -0.14)	0.2	
FPG						
Obese	17	1006	1002	-0.48 ± 0.18 (-0.84 to -0.12)	0.009	0.4
Normal BMI	8	505	498	-0.44 ± 0.24 (-0.91 to 0.03)	0.06	
HOMA-IR						
Obese	14	816	812	-0.44 ± 0.22 (-0.87 to -0.02)	0.04	0.3
Normal BMI	6	422	418	-0.29 ± 0.14 (-0.56 to -0.03)	0.03	
25(OH)D level at baseline						
HbA1c						
<50 nmol/L	7	368	353	-0.14 ± 0.13 (-0.40 to 0.12)	0.2	0.04
≥50 nmol/L	9	694	693	-0.79 ± 0.25 (-1.27 to -0.30)	0.001	
FPG						
<50 nmol/L	9	456	447	-0.11 ± 0.10 (-0.31 to 0.08)	0.2	0.05
≥50 nmol/L	16	692	693	-0.69 ± 0.21 (-1.10 to -0.27)	0.001	
HOMA-IR						
<50 nmol/L	10	521	512	-0.36 ± 0.19 (-0.75 to 0.02)	0.06	0.4
≥50 nmol/L	10	717	718	-0.43 ± 0.23 (-0.88 to 0.02)	0.06	
2HPG						
<50 nmol/L	4	200	191	-0.08 ± 0.21 (-0.47 to 0.33)	0.7	0.2
≥50 nmol/L	6	461	458	-0.16 ± 0.14 (-0.43 to 0.11)	0.2	
Serum 25(OH)D level at follow-up						
HbA1c						
<86 nmol/L	4	208	211	-0.22 ± 0.20 (-0.66 to 0.22)	0.3	0.05
≥86 nmol/L	10	891	873	-0.33 ± 0.1 (-0.62 to -0.04)	0.02	
FPG						
<86 nmol/L	10	558	562	-0.37 ± 0.23 (-0.83 to 0.08)	0.08	0.05
≥86 nmol/L	14	821	813	-0.46 ± 0.19 (-0.82 to -0.09)	0.01	
HOMA-IR						
<86 nmol/L	10	496	501	-0.29 ± 0.25 (-0.80 to 0.21)	0.2	0.1
≥86 nmol/L	10	742	729	-0.49 ± 0.18 (-0.84 to -0.13)	0.007	
2HPG						
<86 nmol/L	4	157	162	-0.08 ± 0.11 (-0.30 to 0.14)	0.5	0.4
≥86 nmol/L	6	553	538	-0.16 ± 0.16 (-0.47 to 0.16)	0.3	

(Continued)

Table 3. Meta-analysis and Subgroup Analysis of Primary and Secondary Outcomes (Continued)

Subgroup Analysis	No. of Study	No. of Subjects		Standardized Mean Difference (95% CI)	P Value	Between-Group P Value ^a
		Vitamin D	Placebo			
Duration of supplementation						
HbA1c						
<6 months	8	461	464	-0.75 ± 0.33 (-1.41 to -0.08)	0.02	0.1
≥6 mo	8	741	723	-0.25 ± 0.11 (-0.48 to -0.03)	0.02	
FPG						
<6 mo	14	598	597	-0.32 ± 0.19 (-0.71 to 0.06)	0.09	0.1
≥6 mo	10	913	903	-0.64 ± 0.22 (-1.07 to -0.21)	0.003	
HOMA-IR						
<6 mo	10	407	410	-0.24 ± 0.27 (-0.77 to 0.29)	0.3	0.1
≥6 mo	10	831	820	-0.53 ± 0.18 (-0.88 to -0.17)	0.004	
2HPG						
<6 mo	6	227	232	-0.14 ± 0.19 (-0.52 to 0.24)	0.4	0.4
≥6 mo	4	483	468	-0.11 ± 0.12 (-0.34 to 0.13)	0.3	

P value represents within-group comparison. Subgroup analysis was not done for 2HPG and obesity (one study in obese subgroup). Independent *t* test for between-groups comparison.

^aP values were adjusted by Bonferroni correction.

inability of insulin in liver to lower glucose concentration. This is different from the fed-state HOMA-IR representing peripheral insulin resistance or failure of glucose uptake in muscle tissues [85]. Other studies have similarly shown that the combination of vitamin D with calcium may help improve glucose metabolism and significantly lower the risk of diabetes [21, 24, 73] by facilitating glucose transportation into different organs and regulating insulin receptor genes and insulin secretion [86, 87]. Subgroup analyses additionally found that individuals who are obese but not prediabetic and younger than 45 years and/or those considered to be vitamin D sufficient at baseline had the largest improvements. The duration of treatment did not influence the short-term measures of response.

These results are consistent with previous reports that have demonstrated that vitamin D supplementation and the highest quartile of serum 25(OH)D concentration, compared with the lowest quartile, reduced the risk of cardiometabolic disorders, including diabetes, metabolic syndrome, and cardiovascular diseases [21, 82, 88]. Moreover, our results support the findings that individuals whose 25(OH)D concentrations increased by at least 50 nmol/L had a 26% reduction in the risk of HbA1c elevation (≥5.8%) [89]. The findings of the current study are not in agreement with all previous reviews [36–38, 90, 91]; however, it should be noted that our methodology properly accounted for the biology of vitamin D and glucose metabolism. For instance, only studies that were sufficiently long enough to detect changes in HbA1c, a 2- to 3-month measure of glucose control, and long enough for 25(OH)D concentrations to reach a plateau, for individuals across the range of BMIs, were included. We also included various blood measurements used in the diagnosis of diabetes.

There is growing biological and mechanistic evidence that support a role for low vitamin D status as a contributing factor in the development of type 2 diabetes. Reduction in insulin secretion, for instance, has been linked to vitamin D deficiency, and optimization of serum 25(OH)D concentrations following vitamin D supplementation has been shown to restore insulin secretion and improve glucose metabolism, glucose tolerance, and insulin sensitivity [30, 92, 93]. Also, vitamin D indirectly stimulates insulin secretion by altering calcium flux through cell membranes to normalize extracellular calcium [21]. Evidence suggests that elevated PTH may be associated with an increased risk of glucose intolerance and diabetes [94, 95], and the concomitant use of calcium with vitamin D decreases PTH levels significantly [96]. Other potential mechanisms demonstrated *in vitro* and in animal models include improving insulin action through stimulating the expression of the insulin receptor, enhancing insulin responsiveness for glucose transport, gene polymorphism, and the influence of vitamin D on gene expression of metabolic pathways [31, 33], and improving systemic inflammation by a direct effect on cytokines [21].

The current study has several limitations. The trials included in this systematic review were heterogeneous with respect to the outcomes measured, supplemental vitamin D dose

and whether it was given in combination with calcium, the length of the intervention, and the definition of a high-risk population. We used a random-effects model in a meta-analysis to overcome these limitations, but this model can have poor error estimations and, with heterogeneous data such as in the current meta-analysis, might default to an arithmetic mean (equal weights). Some of the studies had comparatively small populations (10 to 30 participants per intervention group) that in isolation are hard to extrapolate, but taken together lend support to the larger trials. Most studies did not describe dietary intake, latitude, season, or sun exposure contributing to vitamin D synthesis. Also, although it is difficult to interpret results based solely on vitamin D supplementation, we included only studies that measured serum 25(OH)D to account for outside factors as well as different doses provided and different responses to supplementation based on BMI. We examined the effect of serum 25(OH)D concentration in addition to vitamin D dose to overcome some of these limitations.

This review is based on a recent and up-to-date literature search representing the available data on the effect of vitamin D supplementation on glycemic control in prediabetics and a high-risk population. We included only placebo-controlled RCTs with appropriate methodological qualities and the least probable chance of bias or dropout and studies that measured several outcome measures of glucose control and insulin response: HbA1c, FPG, HOMA-IR, and 2HPG. We ensured that the studies included provided vitamin D supplements as daily or weekly doses to reduce variation introduced by the differences in response in vitamin D metabolism and only those that measured 25(OH)D concentrations. Most of the included studies had been designed for glycemic outcomes and covered a diverse population that supports the generalizability of the results.

4. Conclusion

Vitamin D deficiency and type 2 diabetes are escalating health problems worldwide. The results presented here provide promising evidence that vitamin D supplementation improves glycemic control and attenuates insulin resistance in prediabetics or individuals at high risk of developing diabetes. The amount of vitamin D most likely to produce a response is $\geq 88 \mu\text{g/d}$ (3500 IU/d), a level that is close to the current upper level of intake recommended by Health Canada, the US Institute of Medicine, and the European Food Safety Authority. Even though the effect size for vitamin D is not comparable to the effect of metformin or other glycemic control medications, over a long period of time and when administered at the population level, vitamin D supplementation may offer an affordable, safe, and accessible preventive measure.

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