Effects of Vitamin D Supplementation on Prevention of Type 2 Diabetes in Patients With Prediabetes: A Systematic Review and Meta-analysis

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META-ANALYSIS

BACKGROUND

While observational studies have shown an association between vitamin D insufficiency and diabetes, it is unclear whether intervention with vitamin D supplements can lower the risk of type 2 diabetes mellitus (T2DM).

PURPOSE

To assess whether vitamin D supplementation reduces the risk of T2DM in people with prediabetes.

DATA SOURCES

We searched MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 5 July 2019.

STUDY SELECTION

We included randomized controlled trials assessing vitamin D supplementation versus placebo in relation to new-onset T2DM in people with prediabetes.

DATA EXTRACTION

We screened studies and extracted data from published trials independently.

DATA SYNTHESIS

We identified eight eligible trials with a total of 4,896 subjects. Vitamin D supplementation significantly reduced the risk of T2DM (risk ratio [RR] 0.89 [95% CI 0.80–0.99]; $I^2 = 0\%$). Benefit was found in nonobese subjects (RR 0.73 [95% CI 0.57–0.92]) but not in obese subjects (RR 0.95 [95% CI 0.84–1.08]) ($P_{interaction} = 0.048$). The reversion of prediabetes to normoglycemia occurred in 116 of 548 (21.2%) participants in the vitamin D group and 75 of 532 (14.1%) in the control group. Vitamin D supplementation increased reversion rate of prediabetes to normoglycemia (RR 1.48 [95% CI 1.14–1.92]; $I^2 = 0\%$.)

LIMITATIONS

Definitions of prediabetes and new-onset diabetes in eligible studies were different, and long-term data on outcomes of T2DM prevention were lacking.

CONCLUSIONS

In persons with prediabetes, vitamin D supplementation reduces the risk of T2DM and increases the reversion rate of prediabetes to normoglycemia. The benefit of the prevention of T2DM could be limited to nonobese subjects. Individual participant data meta-analyses are needed to confirm these findings.

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Observational studies have suggested that low serum 25-hydroxy vitamin D [25(OH)D] is inversely associated with the incidence of type 2 diabetes mellitus (T2DM) (1–3). The hypothesis that vitamin D status may influence the risk of T2DM is biologically plausible because in vivo and in vitro studies have proposed potential roles of vitamin D in impaired pancreatic β-cell function and insulin sensitivity (4,5). However, evidence from interventional trials evaluating the efficacy of vitamin D supplementation for diabetes prevention at a population level has been inconclusive. Published systematic reviews and meta-analyses have suggested that vitamin D supplementation does not lower the risk of developing T2DM among people with prediabetes (6–10). They included mostly small trials and thus were insufficiently powered. Some reviews included mixed interventions (e.g., Vitamin D + calcium versus placebo), which makes it hard to assess the effects of vitamin D alone. Further, increased cardiovascular risk with calcium as well as vitamin D is suspected; this has been under debate and has recently been challenged (11–14).

Recently, the results of two large trials—Vitamin D and Type 2 Diabetes (D2d) (15) and Diabetes Prevention with active Vitamin D (DPVD) (16)—were made available. Both trials individually showed that the risk of new-onset T2DM was trending lower in the vitamin D group than in the placebo group, but the findings were not statistically significant. We sought to determine whether an effect could be observed when pooled across trials. Therefore, we conducted a meta-analysis to evaluate the effect of vitamin D supplementation on the risk of T2DM among people with prediabetes.

METHODS

Protocol and Guidance

This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17). The protocol of this study was registered with PROSPERO (reg. no. CRD42019139881).

Selection Criteria

Inclusion Criteria

1) Population: adults (age ≥18 years) with prediabetes. Prediabetes was defined as impaired fasting glucose (World Health Organization [WHO] criteria [18], 6.1–6.9 mmol/L, or the American Diabetes Association definition [19], 5.6–6.9 mmol/L), impaired glucose tolerance (2-h plasma glucose 7.8–11.0 mmol/L during an oral glucose tolerance test) (18), or raised glycosylated hemoglobin (HbA_{1c}) (American Diabetes Association criteria [19], 39–47 mmol/mol, or National Institute for Health and Care Excellence criteria [20], 42–47 mmol/mol).
2) Intervention: vitamin D supplements, regardless of the type, dose, duration, or route of administration.
3) Comparison intervention: placebo. Trials with multiple interventions (e.g., co-administered vitamin D and calcium) were eligible if the study groups differed only by the use of vitamin D.
4) Outcome(s): the primary outcome was new-onset T2DM. Secondary outcome was reversion of prediabetes to normal.
5) Randomized controlled trial (including both quasi-randomized and cluster-randomized trials**).**

Exclusion Criteria

1) Case reports, case series, and observational studies.
2) Trials of participants with diabetes.
3) Trials with duration <6 months.

Data Sources and Searches

Searches were conducted by an experienced research librarian (P.X.) in the databases MEDLINE (Ovid), Embase (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 5 July 2019, without language restrictions. We also searched the WHO International Clinical Trials Registry Platform to identify ongoing or unpublished potentially eligible trials. To maximize our search for relevant articles, we manually reviewed the reference lists of identified trials and systematic reviews. The search strategy is presented in Supplementary Table 1.

Study Selection

After removal of duplicates, two reviewers (Y.Z. and H.T.) independently screened all titles and abstracts for potential relevance, with full texts obtained for those deemed relevant. Disagreements were resolved by consensus or with input from a third independent reviewer (F.F.).

Data Extraction and Quality Assessment

Data Collection Process

Two reviewers (Y.Z. and H.T.) independently extracted data from the included trials using a standard data extraction form (Supplementary Table 2). We contacted the corresponding authors for missing or unreported data. Disagreements were resolved by consensus or with input from a third independent reviewer (F.F.).

Assessment of Risk of Bias and Quality of Evidence

Two reviewers (Y.Z. and H.T.) independently performed risk-of-bias assessment using the Cochrane Collaboration risk of bias (RoB) tool across seven domains: random sequence generation; allocation concealment; blinding of study participants, health care providers, and outcome assessors; incomplete outcome data; and other potential sources of bias (21). Each domain was assessed as low, unclear, or high risk of bias. The trials were judged as low risk of bias when all domains were judged as low risk of bias. Conversely, trials were judged as high risk of bias when one or more domains were judged as unclear or high risk of bias. If data of risk estimates were unavailable from published reports, we collected relevant data by protocol, corresponding with the authors, and abstracting from previous systematic reviews. Two reviewers (Y.Z. and Y.F.) independently rated their confidence in the effect estimates of each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (22).

Data Synthesis and Analysis

We performed statistical analyses using Review Manager (5.3.3; the Cochrane Collaboration) and the meta package in R (version 3.4.3; R Project for Statistical Computing). Continuous variables were pooled using the inverse variance random-effects model and were presented as mean differences with 95% CIs. Dichotomous variables were pooled using the Mantel-Haenszel method and presented as risk ratios (RRs) with 95% CI. We conducted a secondary analysis for the primary outcomes of interest using hazard ratios (HRs) and 95% CI in order to account for the variation in follow-up between the included trials and to assess the impact of censoring. We considered a P value of <0.05 statistically significant. We assessed heterogeneity using the I^2 test (23). We used a fixed-effects weighted model to calculate the pooled estimates except where $I^2 > 30\%$, in which case a

random-effects weighted model was used. The possibility of small study effects was assessed qualitatively by a visual estimate of funnel plot and quantitatively by calculation of the Egger test, Begg test, and Harbord test (24).

Subgroup Analysis

Several a priori determined subgroup analyses were performed to test interactions according to dose (≥2,000 IU/day and <2,000 IU/day), type of vitamin D (vitamin D_2 and vitamin D_3), timing of treatment (daily and intermittently), mean BMI ([weight in kilograms divided by the square of the height in meters] ≥30 kg/m^2 and <30 kg/m^2), mean baseline 25(OH)D (≥50 nmol/L and <50 nmol/L), length of maximum follow-up (≥3 years and <3 years), intervention (vitamin D vs. placebo and adjunctive vitamin D to calcium vs. calcium alone), and latitude (≥37° and <37°). We conducted post hoc subgroup analyses based on mean baseline 25(OH)D (≥30 nmol/L and <30 nmol/L) and achieved 25(OH)D in the vitamin D group (≥75 nmol/L and <75 nmol/L).

Sensitivity Analyses

Sensitivity analyses were conducted by *1*) excluding studies with a high risk of bias, *2*) excluding small trials (number of participants <200), *3*) excluding quasi-randomized or cluster-randomized trials, *4*) excluding trials with follow-up <1 year, *5*) using random-effects or fixed-effects model, *6*) excluding trials reported as an abstract, and *7*) excluding the largest trial.

Data and Resource Availability.

Data are available from the corresponding author.

RESULTS

Eligible Studies and Study Characteristics

The PRISMA flow diagram of the meta-analysis is shown in Fig. 1. Our systematic electronic literature search initially identified 4,265 studies. After application of exclusion criteria, eight trials (15,16,25–30) were deemed eligible and included in the meta-analysis. The excluded trials and reasons for exclusion are listed in Supplementary Table 3.

The summary characteristics of the included trials are shown in Table 1, and the inclusion criteria of those trials are shown in Supplementary Table 4. All studies were published from 2013 to 2019. A total of 4,896 participants were included, with sample sizes ranging from 147 to 2,423, and two trials (15,16) included >1,000 participants. Five trials recruited participants with prediabetes (15,16,28–32), two trials recruited participants with prediabetes and vitamin D deficiency (25,26), and one trial recruited participants with prediabetes, vitamin D deficiency, and obesity (27). The duration of follow-up of the included trials ranged from 6 months to 5 years.

The risk of bias is shown in Supplementary Figs. 1 and 2. Three trials (15,16,29) had a low risk of bias, one (25) had unclear risk, and trials (26–28,30) had a high risk. Most trials that were assigned a high risk of bias had insufficient or nonblinding of participants. The quality of evidence was rated following the GRADE approach. The quality of the primary outcome is moderate (Supplementary Table 5).

New-Onset T2DM

All eight trials (15,16,25–30) measured and reported the development of new-onset diabetes. In total, 1,022 (20.9%) of 4,896 trial participants were diagnosed with new-onset diabetes during the trial. Combining data from all eight trials (15,16,25–30) reporting a RR, we found that vitamin D supplementation reduced the incidence of new-onset diabetes by 11% (RR 0.89 [95% CI 0.80–0.99]; $I^2 = 0\%$ [Fig. 2*A*]). When combining data from the three trials (15,16,29) that reported an HR, we also found a similar decrease in new-onset diabetes in those with vitamin D supplementation compared with control subjects (HR 0.88 [95% CI 0.78–0.99]; $I^2 = 0\%$ [Fig. 2*B*]).

Funnel plot analysis showed no asymmetry (Supplementary Fig. 3). The Egger test ($P = 0.11$), Begg test ($P = 0.72$), and Harbord test ($P = 0.16$) did not detect any significant small study effects.

For each of our sensitivity analyses, the point estimates for most outcomes changed minimally (Table 2). Five of 16 sensitivity analyses changed in statistical significance. When we excluded studies with a high risk of bias, the pooled HR showed a significant reduction in diabetes (HR 0.88 [95% CI 0.78–0.99]), although the pooled RR did not (RR 0.91 [95% CI 0.81–1.01]). With small trials excluded, the pooled HR was significant (HR 0.88 [95% CI 0.78–0.99]), but the pooled RR was not (RR 0.90 [95% CI 0.81–1.01]). With exclusion of the largest trial, both the pooled HR (0.88 [95% CI 0.74–1.05]) and the pooled RR (0.87 [95% CI 0.73–1.02]) were nonsignificant. When excluding we excluded trials only available as an abstract, the pooled RR showed a significant reduction in diabetes (RR 0.89 [95% CI 0.80–1.00], $P = 0.04$), although the pooled HR did not (HR 0.89 [95% CI 0.77–1.02]). The results of other sensitivity analyses were robust (Table 2).

Subgroup analyses found that vitamin D did not lower the risk of new-onset diabetes among obese patients (mean BMI ≥30 kg/m^2, RR 0.95 [95% CI 0.84–1.08]; $I^2 = 0\%$). However, vitamin D reduced the risk of new-onset diabetes in nonobese patients by 27% (mean BMI <30 kg/m^2, RR 0.73 [95% CI 0.57–0.92]; $I^2 = 4\%$; $P_{\text{interaction}} = 0.048$ [Table 3 and Supplementary Fig. 4]). However, we did not find any interaction according to mean baseline 25(OH)D, achieved 25(OH)D in vitamin D group, dose, length of follow-up, intervention, or latitude. Similarly, meta-regression examining the effect of dose and duration of vitamin D on diabetes risk did not reveal a statistically significant effect (Supplementary Figs. 5 and 6).

Reversion of Prediabetes to Normal

Five trials (25–27,29,30) totaling 1,080 participants reported the rate of reversion of prediabetes to normal. The reversion of prediabetes to normoglycemia occurred in 116 of 548 (21.2%) participants in the vitamin D group and 75 of 532 (14.1%) in the control group. Comparing the two groups, we find that the rate of reversion from prediabetes to normoglycemia was significantly increased by vitamin D supplementation (RR 1.48 [95% CI 1.14–1.92]; $I^2 = 0\%$ [Fig. 3]). The results were consistent among different subgroups, and there was no statistical evidence of interaction (Supplementary Table 6). However, the RR for reversion of prediabetes to normal in obese patients (1.93 [95% CI 1.00–3.71]) was trending higher than that in nonobese patients (1.41 [95% CI 1.06–1.86]), although the interaction was not statistically significant ($P = 0.38$).

DISCUSSION

In this meta-analysis of eight randomized controlled trials involving patients with prediabetes, vitamin D supplementation reduced the risk of new-onset T2DM. Similarly, our meta-analysis suggested

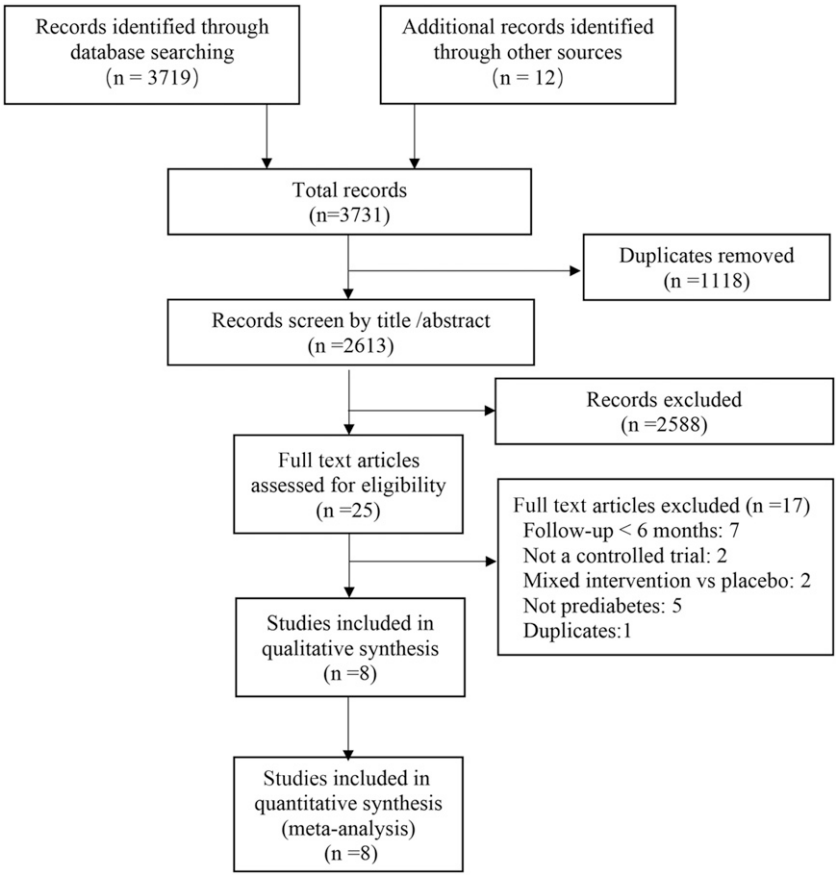

Figure 1—PRISMA flow diagram.

that vitamin D supplementation may lead to increased reversion of prediabetes to normal.

Two major mechanisms potentially explain how vitamin D supplementation may reduce T2DM risk. First, vitamin D modulates insulin synthesis and secretion. The pancreatic islet cells contain all components of the vitamin D endocrine system, including the vitamin D receptor (33), 1α-hydroxylase (34), and vitamin D–binding protein (35). In animal studies, vitamin D deficiency is associated with decreased insulin synthesis and secretion (36), whereas vitamin D supplementation restored insulin secretion (37). Moreover, vitamin D modulates the local pancreatic islet renin-angiotensin system while improving islet β-cell secretory function (38). Second, in peripheral insulin-target cells, vitamin D may reduce insulin resistance in several ways, including presence of the vitamin D receptor in adipocytes (39), muscle (40), and hepatocytes (41); facilitation of the expression of insulin receptor and insulin responsiveness for glucose transport (42); and indirectly via the regulation of calcium metabolism, which is essential for insulin-mediated intracellular processes (40). These mechanisms support the continued interest among clinical researchers in using vitamin D supplementation to reduce T2DM risk.

Comparison With Other Studies

Published systematic reviews have also evaluated the effect of vitamin D supplementation on glycemic control and diabetes prevention in people with and people without prediabetes (6–10). Characteristics and included trials of those reviews are presented in Supplementary Tables 7 and 8. Those reviews mostly found that vitamin D supplementation was not associated with a lower incidence of diabetes (6–8). In 2014, a meta-analysis of four trials by Seida et al. (6) found that vitamin D_3 supplementation had no preventive effect on diabetes in patients with prediabetes (odds ratio 1.02 [95% CI 0.94–1.10]). For populations without diabetes, a review in 2018 by Tang et al. (8) found that vitamin D supplementation did not affect the risk of T2DM (RR 1.01 [95% CI 0.93–1.08]). In the same year, an additional systematic review by He et al. (7) suggested that vitamin D supplementation did not reduce the incidence of T2DM in the adults without diabetes (RR 0.86 [95% CI 0.74–1.01]), but the incidence of T2DM was decreased in a subgroup analysis of people with prediabetes (RR 0.84 [95% CI 0.70–1.00]; $P = 0.047$). However, that meta-analysis incorrectly included two reports (29,43) of the same trial with different follow-up durations, and that trial contributed the most participants to that analysis. With exclusion of that one study alone, the subgroup analysis was no longer significant.

The major difference between the current study and previous reviews was the inclusion of three large, relatively long-term (3–5 years) trials, accounting for 78.5% (3,762 of 4,788) of the total number of participants in this analysis. The data from these trials were not previously available and provide improved statistical power concerning the effects of vitamin D supplementation on T2DM prevention. Further, the two largest trials (D2d and DDVP) (15,16) had nonsignificant findings on their own, and it was stated that D2d was powered to detect 25% risk reduction, but the true effect was lower (15).

Effects of BMI in Modulating the Benefits of Vitamin D

An interesting finding of the subgroup analysis is that the benefit of vitamin D supplementation on prevention of diabetes was only seen in nonobese patients and not in obese patients. Several theories may explain the observed finding. First, vitamin D is fat soluble and is more easily sequestered into fat cells and stored until needed for further metabolism. Studies have shown that obese patients need higher loading doses of vitamin D than normal-weight patients to achieve a similar increase in serum 25(OH)D concentration (44). Second, there is increasing evidence that obesity influences 25(OH)D metabolism (45). Obesity decreases hepatic 25-hydroxylase activity, which in turn reduces serum 25(OH)D (46).

However, without individual patient data, subgroup analysis of mean baseline BMI is not reliable. Trials with mean baseline BMI <30 kg/m^2 may include participants with BMI ≥ 30 kg/m^2 in both

Table 1—Summary characteristics of included studies

First author, year (reference no.)	Country	Study population	No. of patients	% female	Mean age (years)	Mean BMI (kg/m^2)	Treatment	Control	Duration	Baseline 25(OH)D for vitamin D/control groups (nmol/L)	Achieved 25(OH)D for vitamin D/control groups (nmol/L)
Davidson, 2013 (25)	U.S.	Prediabetes and vitamin D deficient	117	67.9	52.4	32.5	Vitamin D_3 88,865 IU/week	Placebo	1 year	52.5/52.5	162.5/50.5
Dutta, 2014 (26)	India	Prediabetes and vitamin D deficient	170	59.2	47.9	26.6	Vitamin D_3 60,000 IU/week for 8 weeks, then 60,000 IU/month + calcium 500 mg/day	Calcium 500 mg/day	1 year	42.5/45	88.4/43.8
Barengolts, 2015 (27)	U.S.	Prediabetes, vitamin D deficiency, and overweight	173	0	59.0	31.9	Vitamin D_2 50,000 IU/week	Placebo	1 year	36.7/35	120/50
Kuchay, 2015 (28)	India	Prediabetes	147	NA	48.1	25.5	Vitamin D_3 60,000 IU/week for 4 weeks, then 60,000 IU/month	Placebo	1 year	49.4/47.1	108/55.9
Jorde, 2016 (29)	Norway	Prediabetes	511	38.6	62	30.0	Vitamin D_3 20,000 IU/week	Placebo	5 years	59.9/61.1	122.3/66.7
Kawahara, 2018 (16)	Japan	Prediabetes	1,256	NA	NA	NA	Eldecalcitol 0.75 μg/day	Placebo	3 years	NA	NA
Niroomand, 2019 (30)	Iran	Prediabetes	162	76.5	46.5	31.5	Vitamin D_3 50,000 IU/week for 3 months, then 50,000 IU/month	Placebo	6 months	30.7/31.7	89.9/39.9
Pittas, 2019 (15)	U.S.	Prediabetes	2,423	44.8	60	32.1	Vitamin D_3 4,000 IU/day	Placebo	5 years	69.2/70.5	135.8/72.0

Data are presented as mean unless otherwise indicated. To convert vitamin D IU to μg, multiply by 0.0025. NA, not available.

vitamin D–treated and –untreated groups. Likewise, the converse (i.e., trials with mean baseline BMI ≥30 kg/m^2 may include participants with BMI <30 kg/m^2) could occur. Moreover, the finding from the subgroup analysis should be interpreted with caution because the analysis was influenced by one large multisite study, D2d.

Strengths and Limitations

The strengths of this review included a comprehensive search for evidence, using a priori research protocol, duplicate assessments of eligibility, risk of bias, and data abstraction. The study included a rigorous assessment of the quality of evidence and of the credibility of subgroup analyses.

Several limitations must be considered. First, some trials included in this systematic review differed in their definition of prediabetes and new-onset diabetes. For example, some trials defined impaired plasma glucose, in accordance with WHO criteria, as a fasting blood glucose of 6.1–6.9 mmol/L; others followed the American Diabetes Association guideline, which recommended a cutoff point of 5.6–6.9 mmol/L.

Second, the analysis included only trial-level data. Only the main trial results were considered. Individual patient data were not available. Individual patient data help determine, for example, whether the benefit of vitamin D is restricted to obese subjects. Our subgroup analysis was based on mean baseline BMI, and its reliability would be improved with individual patient data.

Third, while included trials focused on short-term or intermediate outcomes, the prodromal period of prediabetes that proceeds toward T2DM may be as long as a decade (47). Participants enrolled in short-term trials are likely to be at varying stages of β-cell damage for the duration of follow-up, and therefore participants may vary in their degree of response to attempts at β-cell rescue. This inevitably reduces the effect seen in a trial setting, which implies that any reductions in T2DM risk with vitamin D supplementation are likely to be larger in real life than in the context of a trial. Thus, longer-term follow-up is required to examine whether the beneficial effect of vitamin D on prevention of T2DM was sustained, or even increased, with repletion over extended periods.

Fourth, the participants of the included trials were of varying ethnicity, were from different countries, and potentially had

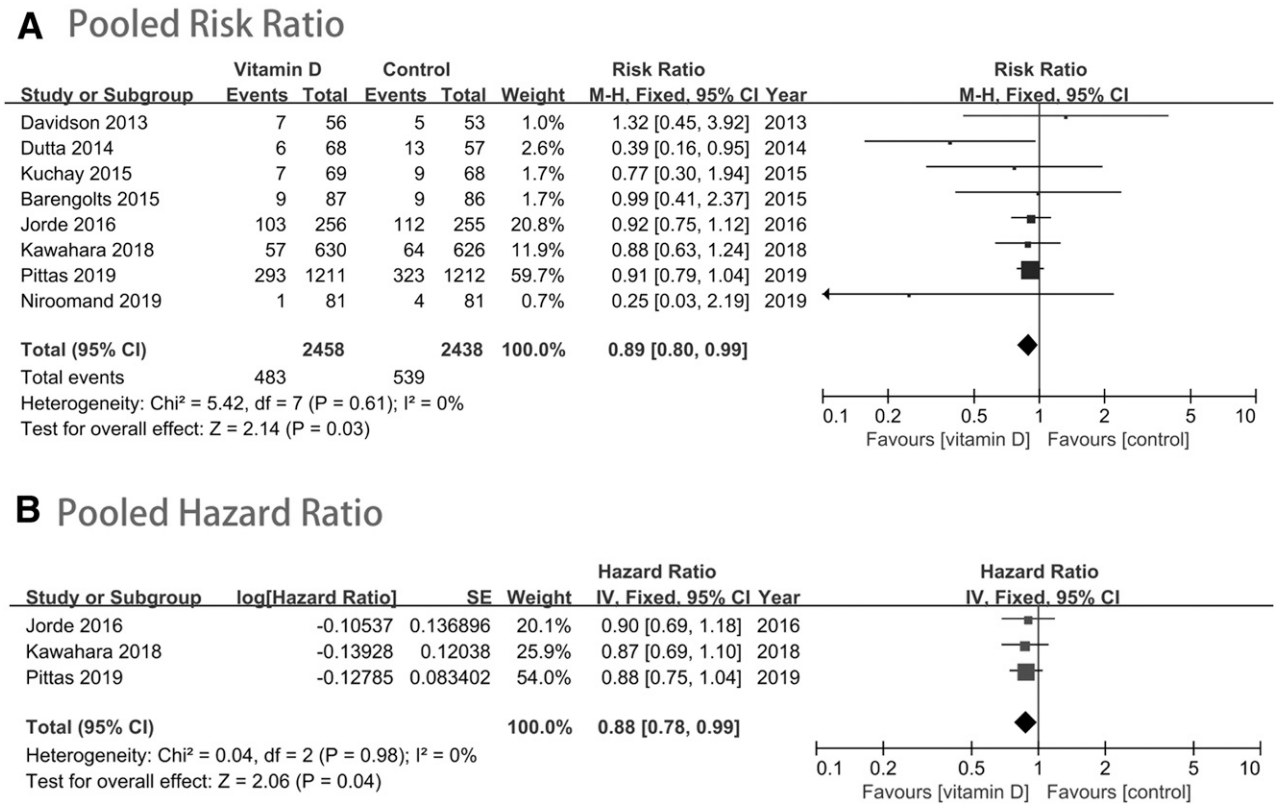

Figure 2—Forest plot of new-onset T2DM for all trials evaluating vitamin D supplementation. *A*: Pooled RR. *B*: Pooled HR. df, degrees of freedom; IV, inverse variance; M-H, Mantel-Haenszel.

different dietary habits; such characteristics may modulate the effects of vitamin D supplementation.

Fifth, there are various methods for assessing vitamin D status serum via 25(OH)D serum levels, including protein-binding assays and liquid chromatography–tandem mass spectrometry. Among the eight included trials, the method of measuring 25(OH)D levels varied across some trials and was not reported in several.

Implications

In 2019, the American Diabetes Association released a position statement of nutrition therapy recommendations for the management of adults with diabetes. The statement does not recommend the routine use of vitamin D or multivitamins for improving glycemia in people with diabetes or prediabetes due to a lack of evidence (48). However, the American Diabetes Association recommends intensive lifestyle intervention and metformin for diabetes prevention. In the Diabetes Prevention Program, lifestyle

Table 2—Sensitivity analyses of the primary outcome

Sensitivity analyses	No. of excluded trials (reference nos.)	No. of included trials (reference nos.)	HR (95% CI)	*P*	No. of included trials (reference nos.)	RR (95% CI)	*P*
Overall analysis	0	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	8 (15,16,25–30)	0.89 (0.80, 0.99)	0.03
Excluding studies with high risk of bias	5 (25–28,30)	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	3 (15,16,29)	0.91 (0.81, 1.01)	0.08
Excluding small trial (participants <200)	5 (25–28,30)	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	3 (15,16,29)	0.91 (0.81, 1.01)	0.08
Excluding quasi/cluster-randomized trials	0	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	8 (15,16,25–30)	0.89 (0.80, 0.99)	0.03
Excluding trials with follow-up <1 year	1 (30)	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	7 (15,16,25–29)	0.90 (0.81, 1.00)	0.04
Using random-effects models	0	3 (15,16,29)	0.88 (0.78, 0.99)	0.04	8 (15,16,25–30)	0.90 (0.81, 1.00)	0.04
Excluding trials reported as abstract	1 (16)	2 (15,29)	0.89 (0.77, 1.02)	0.09	7 (15,25–30)	0.89 (0.80, 1.00)	0.04
Excluding the largest trial	1 (15)	2 (16,29)	0.88 (0.74, 1.05)	0.17	7 (16,25–30)	0.87 (0.73, 1.02)	0.09

Table 3—Subgroup analysis of the effect of vitamin D on new-onset diabetes

	No. of trials	No. of patients	I^2	RR (95% CI)	$P_{interaction}$
Overall	8	4,896	0%	0.89 (0.80, 0.99)	
Baseline 25(OH)D (nmol/L)					
≥50	3	2,517	0%	0.90 (0.80, 1.02)	0.79
<50	5	1,122	26%	0.87 (0.68, 1.11)	
Baseline 25(OH)D (nmol/L)					
≥30	7	3,640	0%	0.89 (0.80, 1.00)	NA
<30	0	0	NA	NA	
Achieved 25(OH)D in vitamin D group (nmol/L)					
≥75	7	4,734	0%	0.90 (0.81, 1.00)	NA
<75	0	0	NA	NA	
Type of vitamin D					
Vitamin D_3	7	4,723	0%	0.89 (0.80, 0.99)	0.81
Vitamin D_2	1	173	NA	0.99 (0.41, 2.37)	
Daily dose equivalent (IU)					
≥2,000	8	4,896	0%	0.89 (0.80, 0.99)	NA
<2,000	0	0	NA	NA	
Mean BMI (kg/m$^{2)}$					
≥30	5	2,514	0%	0.95 (0.84, 1.08)	0.048
<30	3	1,126	4%	0.73 (0.57, 0.92)	
Timing of treatment					
Daily	2	3,679	0%	0.90 (0.80, 1.03)	0.70
Intermittently	6	1,217	8%	0.86 (0.66, 1.10)	
Intervention					
Vitamin D vs. placebo	7	4,771	0%	0.90 (0.81, 1.01)	0.07
Vitamin D + calcium vs. calcium	1	125	NA	0.39 (0.16, 0.95)	
Latitude					
≥37°	3	3,557	0%	0.89 (0.79, 1.00)	0.85
<37°	6	1,339	15%	0.86 (0.63, 1.18)	
Follow-up					
≥3 years	3	4,190	0%	0.91 (0.81, 1.01)	0.28
<3 years	5	706	0%	0.70 (0.45, 1.10)	

To convert Vitamin D IU to μg, multiply by 0.0025. NA, not available.

intervention reduced the risk of progression to diabetes by 58% compared with placebo (49). Our meta-analysis showed that in patients with prediabetes, vitamin D supplementation reduced the risk of T2DM by 11%, and this risk can be further reduced by reversing prediabetes to the normoglycemic state by 48%. Although the magnitude of the effect of vitamin D was smaller than that of lifestyle intervention, achieving and maintaining a lifestyle-modification program (defined as 150 min of physical activity per week and >7% weight loss) is challenging; vitamin D is a safe, economical, and widely available nutrient. Thus, vitamin D may play a role in the prevention of diabetes in these who cannot sustain an intensive lifestyle intervention. Moreover, it remains to be seen whether adjunctive vitamin D in people with prediabetes receiving intensive lifestyle intervention might lower the incidence of T2DM further than lifestyle intervention alone. Additionally, others have observed increased insulin resistance during the

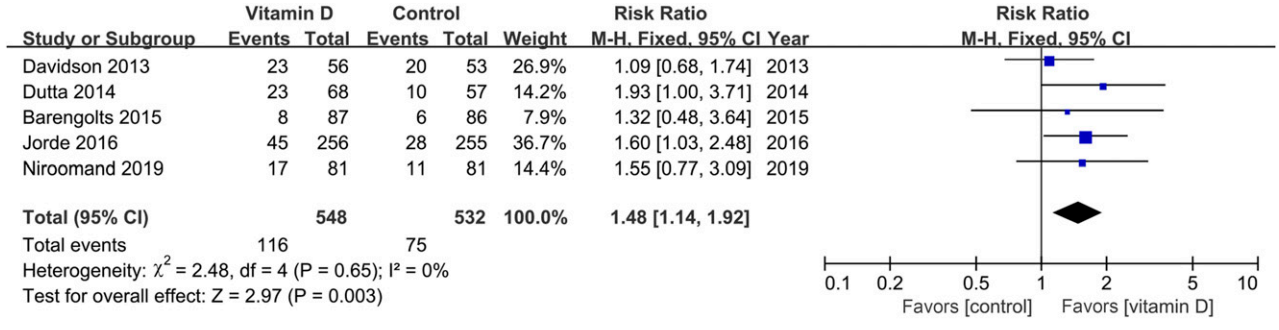

Figure 3—Forest plot of reversion of prediabetes to normal for all trials evaluating vitamin D supplementation. M-H, Mantel-Haenszel.

long run-in period for T2DM development, and that insulin resistance can be reduced by vitamin D supplementation when 25(OH)D values are raised to sufficient levels, at least in persons with vitamin D deficiency (45,50).

Nonetheless, these findings should be interpreted with caution because the overall RR was relatively small and statistically marginal. In particular, sensitivity analyses showed the results were largely driven by the largest trial (D2d).

Conclusion

Results from this meta-analysis show that vitamin D supplementation reduces the risk of T2DM in participants with prediabetes. Reversion of prediabetes to normoglycemia was significantly increased by vitamin D supplementation. The benefit of the prevention of T2DM appears to be confined to nonobese subjects. Individual participant data meta-analyses are needed to confirm the overall result and identify subgroups that benefit the most from supplementation.

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Author Contributions. F.F. and Y.Z. contributed to study concept and design. P.X. performed the literature search. Y.Z. and H.T. selected the studies. Y.Z. and H.T. performed data extraction from relevant studies. J.T., J.L., and Y.Z. prepared initial figures and data analysis. Y.Z. wrote the first draft of the manuscript. Y.Z., H.T., J.T., J.L., W.C., Y.H., Y.F., L.D.L., P.X., D.J., and F.F. critically revised successive drafts of the manuscript and approved the final version. F.F. has affirmed that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. F.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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