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Vitamin D and Risk for Type 2 Diabetes in People With Prediabetes

A Systematic Review and Meta-analysis of Individual Participant Data From 3 Randomized Clinical Trials

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Background: The role of vitamin D in people who are at risk for type 2 diabetes remains unclear.

Purpose: To evaluate whether administration of vitamin D decreases risk for diabetes among people with prediabetes.

Data Sources: PubMed, Embase, and ClinicalTrials.gov from database inception through 9 December 2022.

Study Selection: Eligible trials that were specifically designed and conducted to test the effects of oral vitamin D versus placebo on new-onset diabetes in adults with prediabetes.

Data Extraction: The primary outcome was time to event for new-onset diabetes. Secondary outcomes were regression to normal glucose regulation and adverse events. Prespecified analyses (both unadjusted and adjusted for key baseline variables) were conducted according to the intention-to-treat principle.

Data Synthesis: Three randomized trials were included, which tested cholecalciferol, 20 000 IU (500 mcg) weekly; cholecalciferol, 4000 IU (100 mcg) daily; or eldecalcitol, 0.75 mcg daily, versus matching placebos. Trials were at low risk of bias. Vitamin D reduced risk for diabetes by 15% (hazard ratio, 0.85 [95% CI, 0.75 to 0.96]) in adjusted analyses, with a 3-year absolute risk reduction of 3.3% (CI, 0.6% to 6.0%). The effect of vitamin D did not differ in prespecified subgroups. Among participants assigned to the vitamin D group who maintained an intratrial mean serum 25-hydroxyvitamin D level of at least 125 nmol/L (≥50 ng/mL) compared with 50 to 74 nmol/L (20 to 29 ng/mL) during follow-up, cholecalciferol reduced risk for diabetes by 76% (hazard ratio, 0.24 [CI, 0.16 to 0.36]), with a 3-year absolute risk reduction of 18.1% (CI, 11.7% to 24.6%). Vitamin D increased the likelihood of regression to normal glucose regulation by 30% (rate ratio, 1.30 [CI, 1.16 to 1.46]). There was no evidence of difference in the rate ratios for adverse events (kidney stones: 1.17 [CI, 0.69 to 1.99]; hypercalcemia: 2.34 [CI, 0.83 to 6.66]; hypercalciuria: 1.65 [CI, 0.83 to 3.28]; death: 0.85 [CI, 0.31 to 2.36]).

Limitations: Studies of people with prediabetes do not apply to the general population. Trials may not have been powered for safety outcomes.

Conclusion: In adults with prediabetes, vitamin D was effective in decreasing risk for diabetes.

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Observational studies provide strong and consistent support for an inverse association between blood 25-hydroxyvitamin D level and risk for type 2 diabetes (1). However, the question of whether vitamin D decreases risk for new-onset diabetes remains unanswered. In trials that were specifically designed to test the hypothesis that vitamin D reduces the rate of progression to diabetes in people with prediabetes (2–4), the risk for developing diabetes was consistently lower in the group assigned to vitamin D than in the placebo group; however, the observed differences were not statistically significant, and the reported relative risk reductions (10% to 13%) were smaller than each trial was powered to detect (25% to 36%).

Two meta-analyses of aggregate data from trials that assessed the effect of vitamin D on diabetes risk reported statistically significant relative risk reductions of 11% to 12% for new-onset diabetes with vitamin D (5, 6). Zhang and colleagues synthesized results from 8 trials (total $n = 4896$; range of sample sizes, 117 to 2423; duration of follow-up, 6 months to 5 years) in persons with prediabetes (6). Three of the included trials had low risk of bias (2–4), and the rest had either unclear or high risk of bias. Barbarawi and colleagues synthesized results from 9 trials (total $n = 43\,559$; range of sample sizes, 109 to 33 951; duration of follow-up, 1 to 7 years) that reported on the effect of taking vitamin D for at least 1 year on new-onset diabetes (5). This meta-analysis included 2 trials (total $n = 38\,780$) that were conducted for nondiabetes outcomes (fracture reduction) in persons with average diabetes risk and reported data on new-onset diabetes in post hoc analyses (7, 8). Data from 1 large vitamin D and diabetes prevention trial that was included in both meta-analyses were derived from an abstract (4). Overall, both meta-analyses included trials that had relatively short durations for assessment of diabetes risk (for example, ≤1 year), had high risk of bias (for example, open-label trials), or were not specifically designed and conducted for primary prevention of type 2 diabetes, potentially undermining the validity of the results. In contrast, a meta-analysis based on individual participant data (IPD) can

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more precisely define participant cohorts, standardize covariate definitions, and harmonize analyses to attenuate methodological heterogeneity and can pursue more elaborate analyses to better explain participant-level treatment effect modifiers and better address clinically relevant questions to inform practice recommendations (9–13).

We conducted a systematic review of the published literature and performed an IPD meta-analysis of randomized, placebo-controlled diabetes prevention trials of vitamin D among adults with prediabetes. We sought to assess whether vitamin D decreases risk for new-onset diabetes, whether the effect differs across prespecified subgroups, whether vitamin D promotes regression to normal glucose regulation, and whether it has adverse effects in this population.

METHODS

This meta-analysis was conducted according to guidelines from the National Academy of Sciences (14) and followed the prespecified analysis plan outlined in the protocol, which was prospectively registered at PROSPERO (CRD42020163522). The study is reported according to the PRISMA-IPD (Preferred Reporting Items for a Systematic review and Meta-analysis of IPD) statement (15).

Data Sources and Searches

We searched Medline (via PubMed), Embase, and ClinicalTrials.gov from database inception through 9 December 2022, with no restrictions on language or publication date. The search strategy is provided in **Supplement Methods 1** (available at Annals.org).

Study Selection

We conducted a systematic review of the published literature and performed an IPD meta-analysis of randomized, placebo-controlled trials that were specifically designed and conducted to test whether vitamin D decreases diabetes risk among adults with prediabetes (who are at risk for type 2 diabetes). Eligible trials 1) were randomized, double-blinded, and placebo-controlled; 2) included only adults (aged ≥18 years) with prediabetes as defined by each trial's adaptation of standard glycemic criteria for prediabetes; 3) evaluated oral vitamin D in any formulation (for example, ergocalciferol [vitamin D_2], cholecalciferol [vitamin D_3], or eldecalcitol [a synthetic analogue of calcitriol]); 4) had new-onset diabetes as the primary outcome; and 5) had an intervention duration of at least 2 years (to allow time for the exposure to have an effect and for outcomes to develop and be captured during follow-up). We excluded 1) studies whose target populations were pregnant or lactating women, hospitalized patients (including those in long-term care facilities), patients with end-stage renal disease, patients with known diabetes (any type), or patients with HIV infection; 2) studies in which the intervention included other supplements or ingredients (for example, calcium or yogurt); and 3) studies that included any amount of vitamin D in the comparator.

Data Extraction and Quality Assessment

We established a consortium that included the principal investigator from each eligible trial and subject and method experts. We obtained deidentified data sets of relevant study variables from each trial (**Supplement Methods 2**, available at Annals.org). The data analyst (J.N.) and at least 1 other member of the research team, in collaboration with each individual principal investigator, assessed the integrity of the data by performing internal and external consistency checks with published results. Databases were harmonized with unified coding and by converting variable units to standard units.

Risk-of-Bias Assessment

The methodological quality of each trial was assessed using the revised Cochrane risk-of-bias tool (16). Risk of bias was independently assessed by 2 researchers (E.A. and E.M.B.), with discrepancies resolved by a third reviewer (A.G.P. or T.A.T.). All included trials had ethics approval.

Outcomes

The primary outcome was time to new-onset diabetes as defined in each trial based on predefined glycemic criteria or a diagnosis of diabetes outside the study (**Supplement Methods 3**, available at Annals.org). Glycemic cutoffs for diabetes diagnosis in each trial followed the American Diabetes Association or World Health Organization guidelines. The secondary outcome of regression to normal glucose regulation was met if both blood glucose criteria (fasting glucose level and glucose level 2 hours after a 75-g oral glucose load) were in the normal range at the last study visit (**Supplement Methods 4**, available at Annals.org). Safety outcomes included intervention-specific adverse events of interest (kidney stones, hypercalcemia, and hypercalciuria) and death from any cause (**Supplement Methods 5**, available at Annals.org).

Laboratory Testing

The trials measured serum 25-hydroxyvitamin D by liquid chromatography–tandem mass spectrometry with calibrators that are traceable to the National Institute of Standards and Technology (17). Details are provided in **Supplement Methods 6** (available at Annals.org).

Data Synthesis and Analysis

All analyses were prespecified in the protocol. The intention-to-treat analysis compared all participants randomly assigned to vitamin D versus placebo, regardless of adherence to the trial protocol, to estimate the average treatment assignment effect, which can be interpreted as the treatment effect of a policy for vitamin D (18). We also conducted secondary analyses that censored follow-up when a participant stopped taking the trial pills, started using a diabetes or weight loss medication, or took vitamin D supplements at doses above 1000 IU/d outside the trial. The secondary analysis provides a trial product estimand, which measures an average treatment effect during treatment and before introduction of a "rescue" or "ancillary" medication (diabetes or weight loss medications, or high-dose vitamin D supplements outside the study) (**Supplement Methods 7**, available at Annals.org) (18).

After finding no evidence that the proportional hazards assumption was violated, we estimated the hazard

ratio of new-onset diabetes between the groups with Cox proportional hazards models that were stratified by trial and included group assignment (vitamin D vs. placebo) as the main predictor variable. Follow-up time was the time from randomization until the occurrence of diabetes, death, withdrawal, or the last follow-up encounter where the participant did not have diabetes. Additional models were adjusted for key variables that were preselected by the author group as the most relevant baseline characteristics associated with the primary outcome (age, gender, body mass index [BMI], race, and hemoglobin A_{1c} level) (19, 20). We report all results as unadjusted intention-to-treat analyses (most conservative) unless stated otherwise. For example, for the outcome of regression to normal glucose regulation, we present only the secondary analyses because intention-to-treat analyses would be misleading (for example, when participants began use of diabetes or weight loss medications).

Among trials that administered cholecalciferol, an inactive form of vitamin D that requires activation to 25-hydroxyvitamin D, we conducted an analysis using published methods (21) to examine whether the intratrial cumulative mean blood 25-hydroxyvitamin D level (measured annually in each trial to account for its seasonal variability) predicted the development of diabetes (after adjustment for baseline age, gender, BMI, race, and hemoglobin A_{1c} level) and to assess whether achieving a higher intratrial mean blood 25-hydroxyvitamin D level among participants assigned to vitamin D versus placebo affected risk for diabetes differentially. Trials that used other forms of vitamin D (such as eldecalcitol) that do not change blood 25-hydroxyvitamin D level were not included in this analysis.

The variability of the effect of vitamin D on new-onset diabetes was assessed by each trial and in prespecified subgroups based on the following key baseline variables: serum 25-hydroxyvitamin D level, age, gender, BMI, self-defined race, glycemic risk (meeting 2 or 3 prediabetes criteria), and total calcium intake from supplements. To test whether overweight or obesity (which are associated with decreased vitamin D bioactivation to 25-hydroxyvitamin D by CYP2R1) modified the effect of cholecalciferol, we performed BMI-based subgroup analyses using data from trials that administered cholecalciferol. Each subgroup analysis included a test for interaction, and effect modification was claimed if the test reached statistical significance.

Rate ratios for regression to normal glucose regulation and for prespecified adverse events (kidney stones, hypercalcemia, hypercalciuria, and death from any cause) were compared between groups using Poisson regression.

Results are presented as means and 95% CIs. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute). No adjustments were made for multiple comparisons.

Role of the Funding Source

The funding agencies of the included trials had no role in the design of the study; collection, analysis, synthesis, or interpretation of the data; writing of the report; or the decision to submit the manuscript for publication.

RESULTS

Study Selection

The literature searches yielded 3835 citations from PubMed and Embase and 270 records in ClinicalTrials.gov. Of these, 44 full-text articles and all 270 ClinicalTrials.gov records were further screened (**Appendix Figure**, available at Annals.org). Three trials met the eligibility criteria: the Tromsø study (3), the vitamin D and type 2 diabetes (D2d) study (2), and the Diabetes Prevention with active Vitamin D (DPVD) study (4). We obtained IPD from all 3 eligible trials, and all randomly assigned participants were included in the meta-analysis.

Each study enrolled adults with prediabetes according to trial-specific criteria that were nearly identical among the trials (**Supplement Methods 3**). Detailed characteristics of each trial are shown in the **Supplement Table** (available at Annals.org). The Tromsø study randomly assigned 511 participants recruited during 2008 to 2010 in Norway, the D2d study randomly assigned 2423 participants recruited during 2013 to 2016 in the United States, and the DPVD study randomly assigned 1256 participants recruited during 2013 to 2015 in Japan. The intervention was cholecalciferol (vitamin D_3) in the Tromsø (20 000 IU/wk) and D2d (4000 IU/d) studies and eldecalcitol (0.75 mcg/d), a synthetic analogue of calcitriol, in the DPVD study. All 3 trials were assessed as being at low risk of bias (**Supplement Figure 1**, available at Annals.org).

All 4190 participants from the 3 trials contributed data to the meta-analysis. Participants were randomly assigned to receive vitamin D (n = 2097) or placebo (n = 2093) (**Table 1**). Forty-four percent of participants were women, 51% self-identified as White or European, 33% self-identified as Asian, and 15% self-identified as Black. At baseline, the mean age of participants was 61 years, mean BMI was 30 kg/m^2, and mean serum 25-hydroxyvitamin D level was 63 nmol/L (25 ng/mL).

Primary Analysis

Over a median follow-up of 3.0 years (IQR, 2.0 to 3.2 years), new-onset diabetes occurred in 475 of 2097 (22.7%) participants in the vitamin D group and 524 of 2093 (25.0%) in the placebo group (8.42 and 9.50 events per 100 person-years, respectively). In the unadjusted intention-to-treat analysis, the hazard ratio for vitamin D was 0.88 (95% CI, 0.77 to 0.99) (**Figures 1** and **2**). After adjustment for baseline age, gender, BMI, race, and hemoglobin A_{1c} level, the hazard ratio for vitamin D was 0.85 (CI, 0.75 to 0.96). The absolute risk reduction for vitamin D compared with placebo was 3.3% (CI, 0.6% to 6.0%), and the number needed to treat was 30.

In the secondary analysis, which censored follow-up when a participant stopped taking the trial pills, started using a diabetes or weight loss medication, or took supplemental vitamin D at a dose above 1000 IU/d outside the trial, the primary outcome occurred in 447 participants in the vitamin D group and 505 in the placebo group (8.26 and 9.61 events per 100 person-years, respectively). The unadjusted hazard ratio for vitamin D was 0.85 (CI, 0.75 to 0.97), and the adjusted hazard ratio was 0.83 (CI, 0.73 to 0.94) (**Figure 1**).

Table 1. Participant Characteristics at Baseline*

Characteristic	Overall (*n* = 4190)	Vitamin D (*n* = 2097)	Placebo (*n* = 2093)
Mean age (SD), *y*	60.6 (9.5)	60.4 (9.4)	60.9 (9.6)
Women, *n (%)*	1854 (44.2)	924 (44.1)	930 (44.4)
Race, *n (%)*†			
White/European	2125 (50.7)	1065 (50.8)	1060 (50.6)
Black/African American	616 (14.7)	301 (14.4)	315 (15.1)
Asian	1388 (33.1)	697 (33.2)	691 (33.0)
Other	61 (1.5)	34 (1.6)	27 (1.3)
Current smoking, *n (%)*	260 (8.9)	133 (9.1)	127 (8.7)
Dietary supplement use‡			
Vitamin D			
Participants taking vitamin D supplements, *n (%)*	1216 (29.1)	595 (28.4)	621 (29.8)
Mean intake from supplements among all participants (SD), *IU/d*§	195.8 (340.8)	192.4 (341.1)	199.3 (340.5)
Mean intake among participants using supplements (SD), *IU/d*	331.2 (389.3)	328.9 (392.4)	333.5 (386.4)
Participants taking >1000 IU/d, *n (%)*	3 (0.1)	2 (0.1)	1 (0.0)
Calcium			
Participants taking calcium supplements, *n (%)*	860 (20.6)	407 (19.4)	453 (21.7)
Mean intake from supplements among all participants (SD), *mg/d*§	67.8 (158.0)	64.1 (153.1)	71.5 (162.8)
Mean intake among participants using supplements (SD), *mg/d*	134.0 (201.3)	129.5 (197.2)	138.3 (205.1)
Mean body mass index (SD), kg/m^2	29.5 (5.2)	29.3 (5.3)	29.6 (5.1)
Body mass index category, *n (%)*			
<30 kg/m^2	2365 (56.4)	1188 (56.7)	1177 (56.2)
30 to <35 kg/m^2	1119 (26.7)	562 (26.8)	557 (26.6)
≥35 kg/m^2	706 (16.8)	347 (16.5)	359 (17.2)
Laboratory values			
Mean serum 25-hydroxyvitamin D level (SD)			
nmol/L	63.4 (23.7)	63.0 (23.7)	63.7 (23.7)
ng/mL	25.4 (9.5)	25.2 (9.5)	25.5 (9.5)
Serum 25-hydroxyvitamin D category, *n (%)*‖			
<30 nmol/L (<12 ng/mL)	224 (5.3)	123 (5.9)	101 (4.8)
30 to <50 nmol/L (12 to <20 ng/mL)	1019 (24.3)	510 (24.3)	509 (24.3)
50 to <75 nmol/L (20 to <30 ng/mL)	1726 (41.2)	890 (42.5)	836 (40.0)
≥75 nmol/L (≥30 ng/mL)	1218 (29.1)	573 (27.3)	645 (30.8)
Mean fasting glucose level (SD)			
mmol/L	6.0 (0.5)	6.0 (0.5)	6.0 (0.5)
mg/dL	108.7 (8.2)	108.9 (8.2)	108.6 (8.2)
Mean glucose level 2 h after a 75-g oral glucose load (SD)			
mmol/L	8.1 (1.9)	8.1 (1.9)	8.1 (1.8)
mg/dL	146.0 (33.9)	145.8 (34.8)	146.1 (33.0)
Mean hemoglobin A_{1c} level (SD), %	5.9 (0.2)	5.9 (0.2)	5.9 (0.2)
Prediabetes category, *n (%)*¶			
Met all 3 prediabetes glycemic criteria (IGT + iA1c + IFG)	2011 (48.0)	981 (46.8)	1030 (49.2)
Met 1 or 2 prediabetes glycemic criteria	2179 (52.0)	1116 (53.2)	1063 (50.8)
Mean serum calcium level (SD)			
mmol/L	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)
mg/dL	9.2 (0.4)	9.2 (0.4)	9.2 (0.4)

D2d = vitamin D and type 2 diabetes study; DPVD = Diabetes Prevention with active Vitamin D study; iA1c = impaired A1c; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

* The individual participant data meta-analysis cohort comprises all participants from the 3 included trials (the Tromsø study [*n* = 511], the D2d study [*n* = 2423], and the DPVD study [*n* = 1256]). Percentages may not sum to 100 because of rounding. The *P* value for all statistical comparisons between the vitamin D and placebo groups was greater than 0.05 except for serum 25-hydroxyvitamin D level (*P* = 0.044).

† Race was reported by participants. "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other race (all from the D2d study). Asian includes Asian American (*n* = 130 from the D2d study); Asian, not specified (*n* = 2 from the Tromsø study); or Japanese (*n* = 1256 from the DPVD study).

‡ Data on vitamin D and calcium intake are derived from a question about consumption of dietary supplements, including multivitamins.

§ Value shown is among all participants, regardless of whether they reported use of supplements.

‖ Based on 2011 Institute of Medicine Dietary Reference Intakes for Calcium and Vitamin D.

¶ Definitions are from the 2010 American Diabetes Association Standards of Care guidelines. IFG is defined as fasting glucose level of 100 to 125 mg/dL (5.6 to 6.9 mmol/L). IGT is defined as 2-hour postload glucose level after a 75-g oral glucose load of 140 to 199 mg/dL (7.8 to 11.0 mmol/L). iA1c is defined as hemoglobin A_{1c} level of 5.7% to 6.4%.

Subgroup Analyses

The effect of vitamin D on new-onset diabetes did not differ by baseline age, gender, BMI, race, glycemic risk, or total calcium intake from supplements (**Supplement Figure 2**, available at Annals.org). Among the 224 participants with a baseline serum 25-hydroxyvitamin D level less than 30 nmol/L (<12 ng/mL), the hazard ratio in the vitamin D group was 0.58 (CI, 0.35 to 0.97) (**Supplement Figure 2**).

When we examined data from the 2 trials (Tromsø and D2d [2, 3]) that administered cholecalciferol, which requires activation to 25-hydroxyvitamin D in the liver and elsewhere by CYP2R1, there was a significant interaction by baseline BMI. Supplementation with cholecalciferol

reduced risk for diabetes in participants with a baseline BMI below the median of 31.3 kg/m^2 but not in those with a BMI at or above the median (hazard ratios, 0.74 [CI, 0.60 to 0.90] and 1.01 [CI, 0.84 to 1.22], respectively; *P* for interaction = 0.023) (**Supplement Figure 3**, available at Annals.org). In contrast, in the trial that used eldecalcitol, an active analogue of vitamin D that does not require hydroxylation by CYP2R1, there was no effect modification by baseline BMI (*P* for interaction = 0.82).

Intratrial 25-Hydroxyvitamin D Level and Diabetes Risk

In the 2 trials that administered cholecalciferol (Tromsø and D2d [2, 3]), there was a statistically significant interaction between intratrial cumulative mean serum 25-hydroxyvitamin D level and treatment assignment (cholecalciferol or placebo) on risk for diabetes ($P < 0.001$); therefore, we present results by treatment (cholecalciferol vs. placebo). Among participants assigned to cholecalciferol, the hazard ratios for diabetes among those who maintained intratrial mean serum 25-hydroxyvitamin D levels of 100 to 124 nmol/L (40 to 50 ng/mL) ($n = 400$) and 125 nmol/L or higher (≥50 ng/mL) ($n = 472$) during follow-up were 0.38 (CI, 0.27 to 0.55) and 0.24 (CI, 0.16 to 0.36), respectively, compared with participants who maintained levels of 50 to 74 nmol/L (20 to 29 ng/mL) ($n = 114$) (**Figure 3**). Absolute risk reductions at 3 years were 11.4% (CI, 4.6% to 18.3%) and 18.1% (CI, 11.7% to 24.6%), respectively. Among participants assigned to placebo, the hazard ratios for diabetes by intratrial cumulative mean serum 25-hydroxyvitamin D group were not statistically significant (**Figure 3**).

Regression to Normal Glucose Regulation

At the last study visit, 271 of 1881 participants (14.4%) in the vitamin D group had experienced regression to normal glucose regulation compared with 209 of 1889 (11.1%) in the placebo group. The rate ratio for regression to normal glucose regulation in the vitamin D group compared with placebo at the last visit was 1.30 (CI, 1.16 to 1.46) (**Supplement Figure 4**, available at Annals.org).

Safety

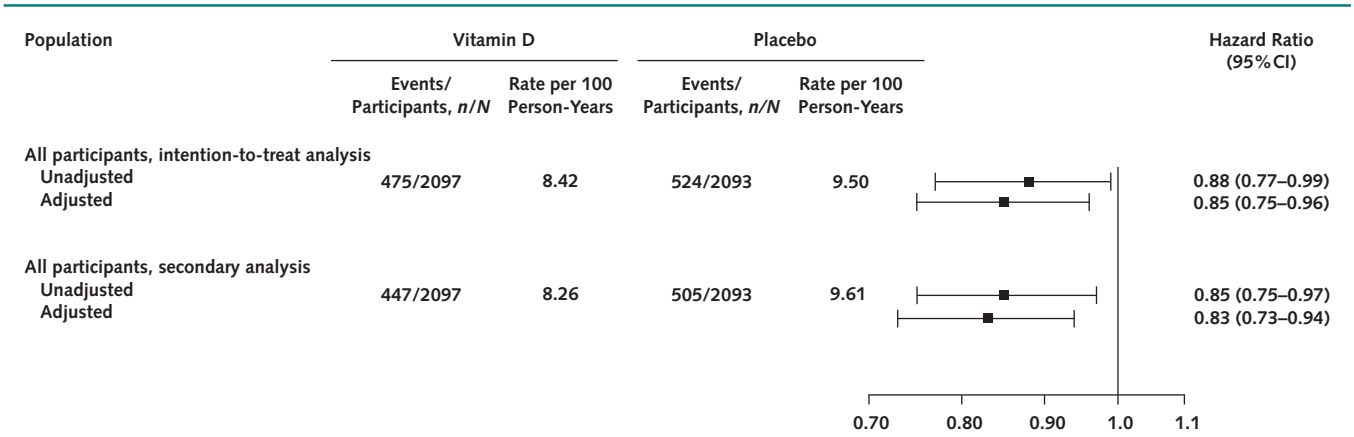
The frequency of the prespecified adverse events of interest (kidney stones, hypercalcemia, and hypercalciuria) was low. Rate ratios were 1.17 (CI, 0.69 to 1.99) for kidney stones, 2.34 (CI, 0.83 to 6.66) for hypercalcemia, and 1.65 (CI, 0.83 to 3.28) for hypercalciuria (**Table 2**). Seven participants (0.3%) in the vitamin D group and 8 (0.4%) in the placebo group died (rate ratio, 0.85 [CI, 0.31 to 2.36]).

DISCUSSION

This IPD meta-analysis of 3 randomized, double-blinded, placebo-controlled trials specifically designed for diabetes prevention found that vitamin D in people with prediabetes was beneficial in decreasing risk for diabetes and increasing the likelihood of regression to normal glucose regulation, with no offsetting safety signals. Among participants treated with cholecalciferol, achieving and sustaining higher serum 25-hydroxyvitamin D levels conferred progressively lower risk for diabetes.

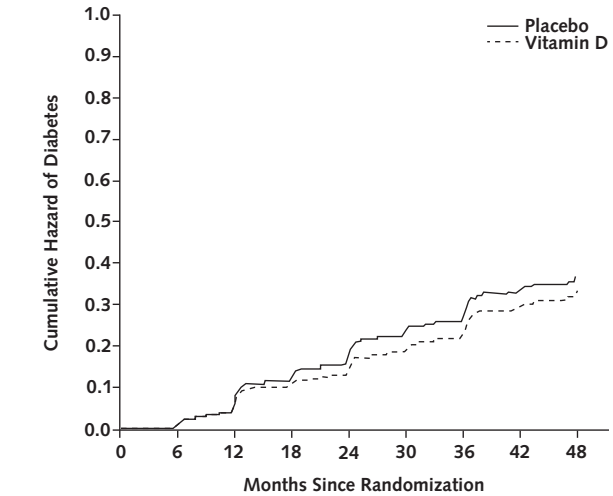
The individual trials included in this meta-analysis, which were powered to detect diabetes risk reductions no lower than 25%, reported nearly identical, non–statistically significant risk reductions of 10% (Tromsø), 12% (D2d), and 13% (DPVD) (2–4). When we combined IPD, vitamin D reduced risk for diabetes by 12% and 15% in the unadjusted and adjusted intention-to-treat analyses, respectively, a benefit that the original trials were underpowered to detect. We found no statistically significant effect modification in any subgroup defined by key baseline characteristics. Although the degree of relative reduction in risk for diabetes with vitamin D is small (15%) compared with other diabetes prevention strategies (58% with intensive lifestyle modification and 31% with metformin in the Diabetes Prevention Program study) (22), the 3-year absolute risk reduction was 3.3%,

Figure 1. Effect of vitamin D on new-onset diabetes among adults with prediabetes.



Secondary analyses censored follow-up when a participant stopped taking the trial pills, started using a diabetes or weight loss medication, or took vitamin D supplements at a dose above 1000 IU/d outside the study.

Figure 2. Incidence curves for new-onset diabetes among adults with prediabetes: intention-to-treat analysis.



At risk, *n*

Vitamin D	2097	2040	1908	1745	1527	1298	1105	429	281
Placebo	2093	2032	1900	1714	1488	1239	1050	397	255

translating to a number of persons with prediabetes needed to treat of 30 (compared with 7 with intensive lifestyle modification and 14 with metformin in the Diabetes Prevention Program study). Extrapolating to the more than 374 million adults worldwide who have prediabetes suggests that inexpensive vitamin D supplementation could delay the development of diabetes in more than 10 million people.

In participants treated with cholecalciferol (Tromsø and D2d), those who maintained higher intratrial serum 25-hydroxyvitamin D levels had lower risk for diabetes, with the greatest risk reduction (76%) occurring at intratrial serum 25-hydroxyvitamin D levels of 125 nmol/L or higher compared with those who maintained an intratrial mean serum 25-hydroxyvitamin D level of 50 to 74 nmol/L. These findings confirm results from the D2d study, which used identical methods (21), and are consistent with reports from aggregate meta-analyses that higher cholecalciferol doses were more effective than lower doses in reducing diabetes risk (5). These results from the present study are also consistent with results from longitudinal observational studies that have reported a larger decrease in diabetes risk for participants who have blood 25-hydroxyvitamin D levels above 125 nmol/L (1, 23).

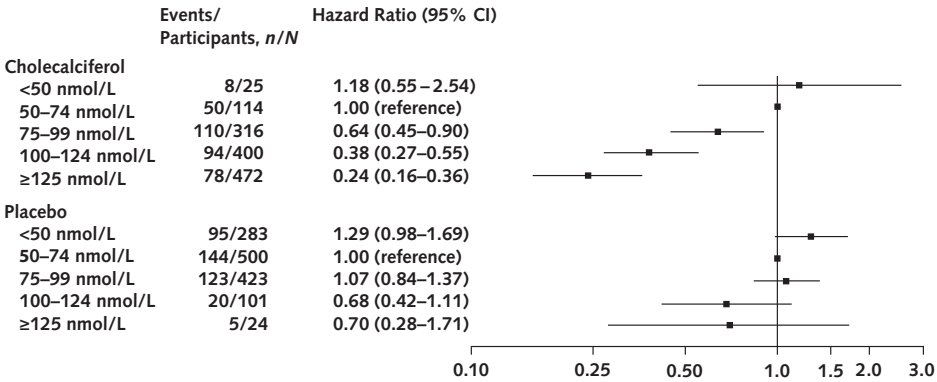
These results suggest that the blood 25-hydroxyvitamin D level needed to optimally reduce diabetes risk may be near and possibly above the range of 125 to 150 nmol/L (50 to 60 ng/mL) that the 2011 Institute of Medicine Committee to Review Dietary Reference Intakes for Calcium and Vitamin D provided as the range corresponding to the tolerable upper intake level (UL) of 4000 IU/d for vitamin D (24). The report stated that this UL is purposefully conservative because of the unavailability of adequate safety data. A carefully designed and monitored trial of treatment to a 25-hydroxyvitamin D target is needed to test our finding that higher levels are required to optimize reduction in diabetes risk. Such a "treat-to-target" trial would also provide important evidence related to the UL for vitamin D.

Clinically relevant adverse events, such as kidney stones, hypercalcemia, and hypercalciuria, were reported in each of the 3 included trials. These events were rare (1.3% for kidney stones, 0.4% for hypercalcemia, and 0.8% for hypercalciuria), and, in the combined analysis, there were no statistically significant differences between the vitamin D and placebo groups. Detailed analyses from the D2d study showed that cholecalciferol at 4000 IU/d was well tolerated and overall adverse events were less frequent in the vitamin D group compared with placebo (25). However, trials are not designed or powered to evaluate safety, especially because they exclude people who may be at risk for adverse events. Although IPD meta-analyses improve the power to detect differences in adverse events, they cannot fully assess safety (26–28). Observational studies can provide clinically useful information on safety. Longitudinal observational studies that have reported on blood 25-hydroxyvitamin D level and diabetes risk have not reported adverse outcomes with higher levels of 25-hydroxyvitamin D. However, the benefit and safety of vitamin D are population-specific, and the balance of benefit and safety requires constant assessment as evidence evolves.

The vitamin D formulations in the eligible trials were not identical because of differences in clinical practice between Europe and the United States (cholecalciferol was tested in Tromsø and D2d) and Japan (eldecalcitol was tested in DPVD), which informed the selection of vitamin D for each trial. Eldecalcitol is a synthetic analogue of calcitriol (1,25-dihydroxyvitamin D), which is the active form of vitamin D that binds directly to the vitamin D receptor and is used for prevention and treatment of osteoporosis in Japan (4). Cholecalciferol requires a 2-step hydroxylation process to be converted to calcitriol. Pooling results from these 3 trials is appropriate because the physiologic effects of cholecalciferol and eldecalcitol would not be expected to vary given that the final product of the vitamin D biosynthetic pathway for cholecalciferol is calcitriol. This is supported by the remarkably similar relative risk reduction for new-onset diabetes reported in each trial individually (10% to 13%).

There is evidence that obesity represses vitamin D bioactivation by CYP2R1 (29, 30), leading to reduced production of 25-hydroxyvitamin D, and that weight loss upregulates CYP2R1 expression (30). When we examined data from the 2 trials that administered cholecalciferol (2, 3), which requires activation first by CYP2R1 and subsequently by CYP27B1, there was an interaction by BMI such that participants with baseline BMI below the median (31.3 kg/m^2) had a 26% lower risk for diabetes with cholecalciferol versus placebo, whereas among participants with a BMI at or above the median, there did not seem to be an effect. In contrast, in the DPVD trial, which used an active analogue of vitamin D that does not require hydroxylation by CYP2R1 or CYP27B1 (4), there was no effect modification by baseline BMI. Taken

Figure 3. Effect of cholecalciferol on new-onset diabetes among adults with prediabetes according to intratrial cumulative mean serum 25-hydroxyvitamin D level.



Analyses censored follow-up when a participant stopped taking the trial pills, started using a diabetes or weight loss medication, or took vitamin D supplements at a dose above 1000 IU/d outside the study. Details are provided in Supplement Methods 7 (available at Annals.org).

together, these results suggest that the effect of vitamin D on diabetes risk is mediated via its conversion to 25-hydroxyvitamin D by CYP2R1—which is primarily expressed in the liver but also in multiple other tissues, including in pancreatic β cells (31)—and subsequently to 1,25-dihydroxyvitamin D by CYP27B1 in the kidney and pancreatic β cells and other tissues (32). This can explain why cholecalciferol seems to work in leaner people with prediabetes with intact CYP2R1 bioactivity but less well in those with overweight or obesity who are unable to fully convert vitamin D to 25-hydroxyvitamin D, thereby reducing the exposure of the pancreatic β cell to the beneficial effects of the fully activated vitamin D molecule.

Beyond delaying progression to diabetes, regression to normal glucose regulation is also important because euglycemia is associated with a lower prevalence of microvascular disease, nephropathy, and retinopathy compared with prediabetes, primarily due to lower glycemic exposure over time (33). At the last study visit, participants assigned to vitamin D were 30% more likely than those in the placebo group to have had regression to normal glucose regulation. Hence, when evaluating the overall benefit of vitamin D in prediabetes, the higher likelihood of regression to normal glucose regulation should be added to the lower risk for progression to diabetes.

This IPD meta-analysis has several strengths. In contrast to aggregate data meta-analysis, an IPD meta-analysis increases the statistical power to detect benefits and risks and, through data harmonization, improves the precision of results and allows additional, thorough, and more appropriate analyses, including analyses to establish the robustness of results in important subgroups (9–12). The key strength of our meta-analysis lies in the homogeneity and high quality of the included clinical trials, all of which were randomized, double-blinded, placebo-controlled, and at low risk of bias. Most important, and in contrast to other meta-analyses in this area (5, 6), the eligible trials in this meta-analysis were specifically designed and conducted

Table 2. Occurrence of Prespecified Adverse Events*

Event	Vitamin D (*n* = 2097; 5643 Person-Years)			Placebo (*n* = 2093; 5514 Person-Years)			Incidence Rate Ratio for Vitamin D vs. Placebo (95% CI)
	Events, *n*	Events per 100 Person-Years	Participants With ≥1 Event, *n*	Events, *n*	Events per 100 Person-Years	Participants With ≥1 Event, *n*	
Kidney stone (self-reported)	30	0.53	29	25	0.45	24	1.17 (0.69–1.99)
Within-study laboratory evaluation							
Hypercalcemia	12	0.21	12	5	0.09	5	2.34 (0.83–6.66)
Hypercalciuria	22	0.39	22	13	0.23	13	1.65 (0.83–3.28)
Death due to any cause	7	0.12	7	8	0.15	8	0.85 (0.31–2.36)

D2d = vitamin D and type 2 diabetes study; DPVD = Diabetes Prevention with active Vitamin D study.

* Kidney stone was a prespecified adverse event of interest in all trials; it was based on self-report and confirmed by review of medical records. Hypercalcemia was a prespecified adverse event of interest in all trials; it was based on trial-specific serum calcium thresholds (uncorrected for albumin) and required confirmation by repeated measurement. Hypercalciuria was a prespecified adverse event of interest in 2 trials (D2d and DPVD); it was based on trial-specific urine calcium–creatinine thresholds and required confirmation by repeated measurement. In the Tromsø study, participants were not assessed for hypercalciuria in real time, but primary urine calcium–creatinine data were available. To incorporate the Tromsø study data in the individual participant data meta-analysis, we used the D2d study criterion for hypercalciuria (yes/no), defined as a fasting morning urine calcium–creatinine ratio (mg/dL ÷ mg/dL) above 0.375. Further details on definitions of adverse events are provided in Supplement Methods 5 (available at Annals.org).

for diabetes prevention, used modern definitions of prediabetes (which were nearly identical within trials) to define the study populations that were at risk for diabetes, had adequate long-term follow-up, and ascertained the primary outcome of new-onset diabetes using nearly identical prespecified glycemic criteria.

The search strategy excluded diabetes prevention trials with vitamin D that targeted children, pregnant or lactating women, hospitalized patients, and patients with end-stage renal disease or HIV at enrollment. Therefore, our results may not apply to these populations because the pathophysiology of diabetes and rates of progression to diabetes may differ. The studied population included people at high risk for type 2 diabetes, so the results do not apply to the general healthy population and should not be extrapolated to those who are at average risk for type 2, type 1, or other types of diabetes (such as monogenic diabetes).

This IPD meta-analysis of vitamin D trials, specifically designed and conducted for diabetes prevention, overcame limitations of meta-analyses that used aggregate data from heterogeneous studies and provides evidence supporting the use of vitamin D in people with prediabetes to reduce their risk for progression to type 2 diabetes.

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Note: Dr. Pittas, Ms. Vickery, and Mr. Nelson had full access to all of the data in the study, and all authors had responsibility for the decision to submit the manuscript for publication.

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Reproducible Research Statement: *Study protocol:* Available on PROSPERO (CRD42020163522). *Statistical code:* Available from Ms. Vickery (e-mail, evickery@tuftsmedicalcenter.org). *Data set:* Sharing of data used in this analysis is at the discretion of the principal investigators of the individual trials.

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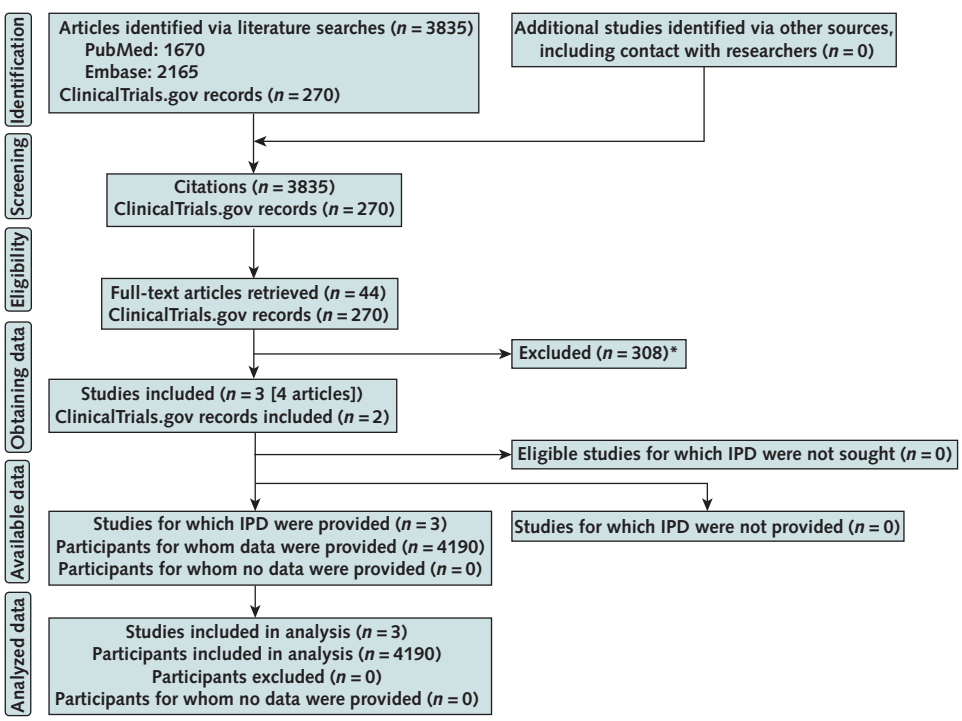
Appendix Figure. PRISMA-IPD (Preferred Reporting Items for a Systematic review and Meta-analysis of IPD) flow diagram.



IPD = individual participant data.
* For reporting purposes, 1 exclusion reason was chosen for each article or record; however, most excluded studies had multiple reasons for exclusion. Excluded published articles (*n* = 40): existing systematic review (*n* = 18), follow-up <2 years (*n* = 9), population not people with prediabetes (*n* = 4), did not study vitamin D supplementation alone (*n* = 2), duplicate publication or no unique data (*n* = 3), not randomized controlled trial (*n* = 2), not double-blinded (*n* = 2). Excluded ClinicalTrials.gov records (*n* = 268): not prediabetes (*n* = 132), not randomized controlled trial (*n* = 64), not double-blinded (*n* = 22), did not study vitamin D supplementation alone (*n* = 20), follow-up <2 years (*n* = 16), not adults (*n* = 12), no outcome of interest (*n* = 1), terminated early and no results available (company chose not to report interim results) (*n* = 1).