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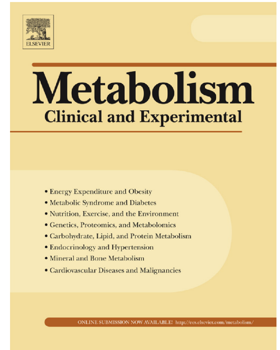

Mini-review. Vitamin D for the prevention of type 2 diabetes: Evidence and implications

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Title: **Mini-Review. Vitamin D for the Prevention of Type 2 Diabetes: Evidence and Implications**
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- Table 1. Trials that were not designed for diabetes prevention but have reported on the effect of vitamin D and new-onset diabetes or regression to normal glucose regulation.
- Table 2. Key characteristics of the randomized, double-blind, placebo-controlled clinical trials with vitamin D for the prevention of diabetes among adults at risk for type 2 diabetes (prediabetes).
- Table 3. Interventions for prevention of Type 2 diabetes: comparative summary

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Box: Future Research

Optimize efficacy by maintaining a target blood 25(OH)D level

- Treat-to-target trials to test whether achieving and maintaining serum 25(OH)D concentrations above 50 ng/mL (125 nmol/L) further reduces diabetes risk.

Cost-Effectiveness

- Comprehensive analyses to quantify the cost-effectiveness of vitamin D supplementation for the prevention of type 2 diabetes, particularly in comparison with intensive lifestyle interventions, metformin, or modern agents such as GLP-1 receptor agonists and GIP/GLP-1 dual agonists.

Vitamin D Metabolites

- Compare the efficacy of active vitamin D analogs (e.g., calcitriol; no BMI interaction observed in the DPVD trial) and calcifediol [25(OH)D], the hydroxylated metabolite with a faster onset of action.

Bone Health Interactions

- Explore potential links between vitamin D-related improvements in bone metabolism and glycemic outcomes in individuals with prediabetes.

Ethnic and Population Differences

- Equity-focused investigations in populations at highest risk of both vitamin D deficiency and T2D—such as individuals with darker skin pigmentation, limited sun exposure, or socioeconomic barriers—to ensure global relevance and accessibility.

Type 1 Diabetes

- Given the frequent coexistence of insulin resistance and weight gain in individuals with T1D, vitamin D may offer additional metabolic benefits that warrant targeted investigation.

Figures: 2

HIGHLIGHTS

1. Vitamin D supplementation reduces type 2 diabetes risk by approximately 15% in adults with prediabetes.
2. Vitamin D increases the likelihood of regression from prediabetes to normal glucose regulation by about 30%.
3. Benefits are greater among those with a low baseline 25(OH)D or a BMI below 30 kg/m^2.
4. Vitamin D provides a practical diabetes-prevention strategy, especially for low-resource settings.

ABSTRACT

Prediabetes is common worldwide and offers a critical opportunity for interventions to prevent type 2 diabetes. Vitamin D has biologically plausible effects on beta cell function, insulin sensitivity, and the immune system, and observational studies consistently associate higher 25-hydroxyvitamin D (25[OH]D) levels with a lower risk of diabetes. Three randomized, double-blind, placebo-controlled trials designed specifically for adults with prediabetes tested moderate-to-high doses of vitamin D_3 (Tromsø, D2d) or an active analog (DPVD). Each study showed a modest reduction in progression to type 2 diabetes. An individual participant data meta-analysis of these trials (n=4,190) demonstrated a 15% relative risk reduction, with greater benefit among those with low baseline 25(OH)D levels and BMI <30 kg/m^2. Vitamin D also increased the likelihood of regression to normal glucose regulation. These findings are further supported by multiple aggregate-data meta-analyses showing consistent, homogeneous benefit of vitamin D in adults with prediabetes. Compared with lifestyle interventions, metformin, and incretin-based therapies, vitamin D is inexpensive, safe, accessible, and easy to implement, with an estimated number needed to treat of ~30. The 2024 Endocrine Society Guideline now recommends vitamin D supplementation for adults with prediabetes at doses above the recommended dietary allowance without requiring routine 25(OH)D testing. Achieving and maintaining a blood 25(OH)D level above 40 ng/mL may confer additional benefit, but the hypothesis needs to be tested in clinical trials.

Introduction

The prevalence of diabetes continues to rise worldwide, creating a significant burden for individuals and healthcare systems. In the United States, over 40 million adults (12% of all adults) live with diabetes [1]. Diabetes is also a significant public health problem worldwide, affecting more than 589 million adults (aged 20 to 70 years), a number projected to reach 853 million by 2050 [2]. Beyond its human toll, diabetes imposes enormous costs, exceeding 1 trillion dollars worldwide – an increase of 338% over the last 17 years [2].

Type 2 diabetes (T2D) accounts for over 95% of diabetes. Prediabetes is an intermediate state between normoglycemia and diabetes based on specific ranges of hemoglobin A1c between 5.7–6.4% (39–47 mmol/mol), fasting plasma glucose between 100 to 125 mg/dL (5.6 to 6.9 mmol/L) known as impaired fasting glucose, or plasma glucose 140 to 199 mg/dL (7.8 to 11.0 mmol) two hours after a 75-gram glucose challenge, known as impaired glucose tolerance [3]. Prediabetes often precedes T2D and increases risk for cardiovascular disease, cancer, fractures, and other complications [4-6]. Adults with prediabetes progress to diabetes at about 5-10% per year. More than 115 million U.S. adults (43% of all adults) have prediabetes, yet only about half are aware that they have prediabetes [1]. Globally, 635 million adults (1 in 8) have impaired glucose tolerance, and 488 million have impaired fasting glucose.

Despite significant advances in T2D treatment, prevention remains a cornerstone of care. Intensive lifestyle interventions—focusing on weight loss, physical activity, and diet—are effective in trials,[3] but real-world adherence and long-term weight maintenance remain challenging in an increasingly obesogenic environment [7]. Even after successful weight loss, a residual high risk of T2D persists. Pharmacologic options, such as metformin, offer modest benefit for select subgroups but are underutilized.

Over the past decade, vitamin D supplementation has emerged as a promising, affordable, and scalable preventive approach for T2D. Interest grew from consistent observational data linking higher serum 25-hydroxyvitamin D [25(OH)D] levels with lower risk of developing diabetes. Experimental studies support biological plausibility through effects on pancreatic beta cell function, insulin sensitivity, and the immune system. These findings led to randomized controlled trials testing vitamin D supplementation in adults with prediabetes. Results from meta-analyses, including one using individual-participant data (IPD) from the three large, vitamin D and diabetes prevention trials, have confirmed a protective effect of vitamin D against progression to diabetes, especially when target 25(OH)D levels are achieved and maintained.

This review synthesizes the current evidence on vitamin D for T2D prevention, highlighting biological mechanisms, findings from observational studies, results of trials and meta-analyses, and implications for clinical practice and future research.

Mechanisms linking vitamin D and type 2 diabetes

Vitamin D influences T2D pathogenesis through multiple biologically plausible mechanisms, primarily involving effects on pancreatic beta-cell function, insulin action, and the immune system.

The vitamin D receptor is expressed in pancreatic beta cells, and active vitamin D [1,25(OH)$_2$D] enhances insulin secretion in both animal and cell culture models [8, 9]. Mice lacking the vitamin D receptor exhibit impaired insulin secretion in response to glucose [10]. Alternatively, activation of vitamin D also occurs within the pancreatic beta cell by the 25-hydroxyvitamin D-1α-hydroxylase enzyme (CYP27B1), which is expressed in pancreatic beta cells [11]. Vitamin D may also exert indirect effects on beta-cell function by regulating calcium flux—critical for insulin exocytosis—and by modulating the local renin-angiotensin system and inflammatory pathways within pancreatic islets [12-17]. Data from trials suggests that vitamin D supplementation improves beta-cell function, particularly in those with low blood 25(OH)D levels [18, 19].

Vitamin D may enhance insulin action in peripheral tissues through both genomic and non-genomic pathways. Vitamin D receptors are present in skeletal muscle and adipose tissue, where vitamin D upregulates insulin receptor expression and modulates intracellular signaling [20-29]. Vitamin D also influences calcium homeostasis, which plays a key role in insulin-mediated glucose uptake. Vitamin D deficiency leads to higher parathyroid hormone levels, which may impair insulin sensitivity [30, 31]. Observational studies support a link between low vitamin D status and insulin resistance, although intervention trials have shown variable results, potentially due to heterogeneity in study populations and dosing regimens [18, 19].

Low-grade chronic inflammation is increasingly recognized as a contributor to insulin resistance and beta-cell dysfunction. Vitamin D exhibits anti-inflammatory properties by downregulating pro-inflammatory cytokines and inhibiting NF-κB signaling. These effects may help preserve insulin sensitivity and beta-cell viability in the context of metabolic stress.

Experimental data also support a causal role of vitamin D deficiency in the pathogenesis of T2D early in life. For example, in a sophisticated mouse model, vitamin D deficiency during fetal development caused long-lasting changes in immune cell precursors that promote inflammation and insulin resistance, increasing the risk of T2D later in life [32].

Together, these mechanistic pathways support a biologically plausible role for vitamin D in the pathophysiology of T2D. While no single mechanism is likely sufficient to explain the observed clinical effects, the convergence of evidence across multiple domains supports vitamin D as a potential modifiable factor in the development of T2D (**Figure 1**).

Observational studies

Numerous observational studies have examined the relationship between vitamin D status and T2D. The most reliable evidence comes from longitudinal cohort studies, showing that individuals with higher blood 25(OH)D levels are less likely to develop T2D. In a pooled analysis of 21 longitudinal cohorts (76,220 participants from North America, Europe, and Asia), baseline 25(OH)D levels in the highest category (as defined in each study, range 18 to 57 ng/mL [46 to 142 nmol/L) were associated with a 38% lower risk of incident T2D when compared to 25(OH)D levels in the lowest category (as defined in each study, range 12 to 20 ng/mL [29 to 49 nmol/L]), even after adjusting for BMI and other potential confounders [33]. A spline regression model showed that higher 25(OH)D levels were monotonically associated with a lower risk of diabetes. Specifically, each 4 ng/mL (10 nmol/L) increment in 25(OH)D level was associated with a 4% lower risk of developing diabetes; data beyond 40 ng/mL (100 nmol/L) remain limited, as few participants in the observational studies had such levels at baseline [33]. Subsequent meta-analyses have confirmed these results [34-36].

Observational studies typically include participants without diabetes at baseline, covering both normoglycemia and prediabetes without specifying the participants' glycemic status. A recent large prospective cohort study showed inverse associations between 25(OH)D levels and incident diabetes across the glycemic spectrum, with similar relative risk reductions in individuals with normoglycemia and prediabetes [37]. These findings suggest that maintaining optimal vitamin D status may be relevant earlier in the natural history of dysglycemia.

Observational cohort studies typically rely on a single 25(OH)D measurement at baseline to define vitamin D status; however, this may not reflect long-term vitamin D status during follow-up. A longitudinal observational study within the Diabetes Prevention Program (DPP) examined the association between blood 25(OH)D levels, measured annually, and the risk of incident T2D among participants with prediabetes who were randomized to the intensive lifestyle or placebo arms of the DPP [38]. By measuring 25(OH)D at multiple time points, the authors constructed an integrated measure of intra-study vitamin D status for each participant, rather than relying on a single baseline value. After multivariate adjustment, including for the DPP lifestyle intervention, there was an inverse association between the integrated intra-study blood 25(OH)D level and incident T2D. Specifically, there was a 28% lower risk of diabetes for participants in the top vs. bottom tertile (mean 30 ng/mL [12 mol/L] vs. 13 ng/mL [5 nmol/L], respectively). No clear 25(OH)D threshold for benefit was observed. Risk declined more steeply when 25(OH)D was higher than 50 ng/mL (125 nmol/L); however, few participants achieved that level during the trial.

Collectively, longitudinal data show a consistent inverse association between vitamin D status – as measured by blood 25(OH)D level – and T2D risk, supporting the rationale for randomized trials to test causality, especially among individuals at high risk, such as those with prediabetes.

Clinical trials and meta-analyses

Fifteen randomized controlled trials published between 2008 and 2025 have reported on the effect of vitamin D supplementation on new-onset T2D (Table 1 and Table 2) [19, 39-50]. The strongest evidence of benefit comes from large, well-designed trials conducted in adults with prediabetes, and meta-analyses integrating results across studies. Next, we summarize the key trials in adults with prediabetes and the meta-analyses that have shaped our current understanding of the role of vitamin D supplementation in preventing T2D.

Vitamin D supplementation in adults at average risk for type 2 diabetes

Two early large trials - the *Women's Health Initiative* (WHI) and the *Randomized Evaluation of Calcium Of vitamin D* (RECORD) - were designed to assess non-diabetes outcomes and later reported on new-onset diabetes in ancillary or post-hoc analyses [39, 40]. Both trials enrolled generally healthy older adults (50-79 years old in WHI; ≥70 years old in RECORD) at low to average risk for T2D (~6.5% incident diabetes over 7 years in WHI; ~2.5% incident diabetes over 5 years in RECORD) and tested low daily doses of vitamin D_3 (400 IU in WHI and 800 IU in RECORD), which are considered too low to influence glucose metabolism meaningfully [51, 52]. Diabetes was self-reported by participants. Neither trial showed a difference in diabetes incidence between the vitamin and placebo groups. These results suggest that low-dose vitamin D supplementation does not prevent diabetes in generally healthy adults at low risk.

More recently, two large trials – the *Vitamin D and Omega-3 Trial* (VITAL, United States) and the *Finnish Vitamin D Trial* (FIND, Finland) - also designed for non-diabetes outcomes - enrolled healthy adults at low to average risk for T2D (~2% incident diabetes over 5 years in VITAL; ~5% incident diabetes over 54 years in FIND) and tested higher vitamin D doses [53, 54]. In VITAL, 25,871 participants (mean baseline 25[OH]D 31 ng/mL) were randomized to 2,000 IU/day of vitamin D_3 or placebo and followed for 5.3 years; the hazard ratio for incident diabetes was 0.91 (95% CI, 0.76–1.09). In FIND, 2,271 participants (mean baseline 25[OH]D 30 ng/mL [75 nmol/L]) were randomized to 1,600 or 3,200 IU/day of vitamin D_3 or placebo; after a mean follow up of 4.2 years, the hazard ratio was 0.86 (95% CI, 0.58–1.29), with a favorable trend toward benefit in those with BMI <25 kg/m^2. Although the results were not statistically significant, the VITAL and FIND trials suggest that higher doses of vitamin D may lower the risk of diabetes in adults at low to average risk.

All four studies used indirect ascertainment of diabetes (self-report or ICD-10 codes), which likely underestimated the number of cases and may have attenuated the true effect of vitamin D on T2D risk.

Vitamin D supplementation in adults with prediabetes

Eleven trials have reported on the effect of vitamin D supplementation and incident diabetes among adults with prediabetes [19, 41-50]. Eight of these trials have limitations, including small sample size (90 to 205 participants) [41-44, 46, 48-50], short duration (≤1 year) [41, 43, 44, 46, 50],open-label study design without placebo [42, 44, 48-50], or not designed for new-onset diabetes as the primary outcome [41-44, 46, 48-50]. Overall, results from these eight trials [41-44, 46, 48-50], are limited in fully informing the clinical question of whether vitamin D supplementation prevents T2D.

Three large, double-blind, placebo-controlled randomized clinical trials were specifically designed to test the hypothesis that vitamin D supplementation lowers the risk of progression from prediabetes to T2D [19, 45, 47, 55, 56]. Collectively, these trials represent the most rigorous evidence available to date (Table 2). In these trials, blood 25(OH)D level was not an eligibility criterion, and participants were allowed to take no vitamin D outside the study (DPVD study) or up to 1,000 IU/day of vitamin D (Tromsø and D2d).

The Tromsø Study (single site, Norway, 2012–2016) enrolled 511 adults with prediabetes randomized to 20,000 IU/week of vitamin D_3 or placebo [45]. After a median follow-up of 2.5 years, diabetes developed in 40.2% of participants in the vitamin D group vs. 43.9% in the placebo group, corresponding to a hazard ratio of 0.90 (95% CI, 0.69 –1.18; intention-to-treat analysis).

The Vitamin D and T2D (D2d) study (22 sites, United States, 2013–2018) enrolled 2,423 adults with prediabetes and overweight or obesity, randomized to 4,000 IU/day of vitamin D_3 or placebo. After a median follow-up of 2.5 years, diabetes developed in 24.2% of participants in the vitamin D group vs. 26.7% in the placebo group, corresponding to a hazard ratio of 0.88 (95% CI, 0.75 to 1.04; intention-to-treat analysis). Among participants with a baseline 25(OH)D level < 12 ng/mL (103 participants), vitamin D supplementation reduced the risk of T2D by 62% (hazard ratio for vitamin D, 0.38; 95% CI, 0.18 to 0.80).

The DPVD trial (3 sites, Japan, 2013–2019) enrolled 1,256 adults with prediabetes randomized to receive 0.75 μg/day of eldecalcitol, an active vitamin D analog, or placebo [19, 55]. After a median follow-up of 3 years, diabetes developed in 12.5% of participants in the vitamin D group vs. 14.2% in the placebo group, corresponding to a hazard ratio of 0.87 (95% CI, 0.67–1.17; intention-to-treat analysis). After adjustment for confounding factors using multivariable fractional polynomial modeling, eldecalcitol reduced the risk of developing diabetes by 31% (hazard ratio 0.69, 0.51 to 0.95).

Individual participant data meta-analysis of the vitamin D and diabetes prevention trials

When the results of the vitamin D and diabetes prevention trials are considered together, pooled analyses provide a clearer picture of the overall efficacy of vitamin D supplementation for diabetes prevention. Pittas et al. conducted an individual participant data (IPD) meta-analysis of the three major randomized clinical trials— Tromsø, D2d, and DPVD [51]. Unlike aggregate-data meta-analyses, which rely on study-level summary statistics, the IPD approach offers several key advantages: greater power to detect modest effects, improved precision of estimates, and robust exploration of effect modifiers.

The IPD meta-analysis included 4,190 adults with prediabetes from the three trials (2,097 randomized to vitamin D and 2,093 to placebo). The combined cohort had a mean age of 61 years; 44% were women, 51% self-identified as White or European, 33% as Asian, and 15% as Black. Mean BMI was 30 kg/m^2, and mean baseline 25(OH)D] was 25 ng/mL (65 nmol/L). During a median follow-up of 3 years, new-onset diabetes occurred in 22.7% of participants in the vitamin D group and 25.0% in the placebo group, corresponding to a 15% relative risk reduction (hazard ratio 0.85; 95% CI, 0.75–0.96) in intention-to-treat analysis (treatment assignment effect) and a 17% reduction (hazard ratio 0.83; 95% CI 0.73-0.94) in per-protocol analysis (trial product estimand). Subgroup analyses revealed that the preventive effect of vitamin D was most pronounced among individuals with baseline 25(OH)D less than 12 ng/mL (30 nmol/L) (n= 224; hazard ratio of 0.58; 95% CI 0.35 to 0.97) and those with a BMI below the median of 30 kg/m^2 (n=2,365; hazard ratio of 0.79; 95% CI 0.66 to 0.95). The beneficial effect did not differ by age, sex, race, glycemic risk category, or calcium intake. Vitamin D was safe and well-tolerated. Hypercalcemia and nephrolithiasis were rare and similar across groups.

The key strength of this IPD meta-analysis lies in the high quality and homogeneity of the included trials, all of which were double-blind, placebo-controlled, and at low risk of bias. Importantly, in contrast to other meta-analyses that combined trials with heterogeneous designs (see below), the Tromsø, D2d, and DPVD trials were specifically designed for diabetes prevention, enrolled participants using modern definitions of prediabetes, maintained adequate long-term follow-up, and ascertained new-onset diabetes using standardized glycemic criteria as defined by the American Diabetes Association or the World Health Organization.

Aggregate data meta-analyses of vitamin D trials reporting on new-onset diabetes
Several aggregate data (i.e., study-level) meta-analyses have examined the effect of vitamin D supplementation on new-onset T2D by combining results from randomized controlled trials, including the three high-quality vitamin D and diabetes prevention trials (**Figure 2**). Zhang et al. synthesized data from eight trials (total n = 4,896; follow-up 6 months–5 years) in adults with prediabetes, including three high-quality studies (Tromsø, D2d, and DPVD) and several smaller trials with potentially high risk of bias [57]. Vitamin D supplementation lowered the risk of T2D by 11% (risk ratio 0.89; 95% CI, 0.80–0.99). In subgroup analyses, the benefit appeared limited to studies enrolling participants with a mean BMI < 30 kg/m^2 (RR 0.73; 95% CI, 0.75–0.92).

Barbarawi et al. included nine trials (n = 43,559; follow-up 1–7 years) that reported diabetes incidence after at least one year of supplementation [58]. Two large trials—WHI and RECORD (n = 39,243)—tested low-dose vitamin D (defined as <1,000 IU/day) in populations at low to moderate diabetes risk, while the remaining seven trials (n = 4,316) enrolled adults with prediabetes who received moderate-to-high doses (defined as ≥1,000 IU/day; doses ranged from 2857 to 12,695 IU/day). Vitamin D supplementation lowered diabetes risk in the moderate-to-high dose trials among adults with prediabetes (risk ratio 0.88; 95% CI, 0.79–0.99), but not in the low-dose trials among adults in the general population at low risk for diabetes (risk ratio 1.02; 95% CI, 0.94–1.10; p for interaction = 0.04). Consistent with Zhang et al., benefit was confined to studies with a mean baseline BMI < 30 kg/m^2 (RR 0.68; 95% CI, 0.53–0.89), suggesting obesity may blunt responsiveness to vitamin D.

A systematic review by Shah et al. that was undertaken to support the 2024 Endocrine Society Guideline on Vitamin D concluded that vitamin D supplementation reduced the risk of developing diabetes compared with control when data from ten trials that tested vitamin D_2 or D_3 were synthesized (relative risk 0.90, 95% CI 0.81–1.00; I^2 = 0%; moderate certainty) [59]. When the DPVD study was included, the result did not change (relative risk 0.90, 95% CI 0.81 to 0.99; I^2 = 0%).

More recently, Tobias et al. performed a meta-analysis restricted to four high-quality trials that tested cholecalciferol (vitamin D_3)— Tromsø, D2d, VITAL, and FIND [53], and reported an 11% relative risk reduction in diabetes incidence with vitamin D_3 supplementation compared with placebo (pooled hazard ratio 0.89; 95% CI 0.80 to 0.99; I^2 = 0%).

In the review by Shah et al., vitamin D produced improvements in glycemic measures: fasting plasma glucose: mean difference −5.29 mg/dL (95% CI −7.90 to −2.68); glucose 2-hours after a 75-gram oral glucose challenge: mean difference −7.61 mg/dL (95% CI −12.55 to −2.66); HbA1c: small, nonsignificant reduction (−0.05%; 95% CI −0.10 to 0.01). Although these glycemic improvements observed with vitamin D supplementation in adults with prediabetes may appear small, they are clinically meaningful when placed in context. For example, in the DPP, small reductions in glycemia—within the range of 5 to 10 mg/dL—were associated with substantially lower diabetes incidence (31 to 58% relative risk reduction). These findings underscore that interventions producing even minor shifts toward normoglycemia translate into meaningful preventive effects over time.

Collectively, these aggregate data meta-analyses and the individual participant data meta-analyses described above demonstrate a consistent protective effect of vitamin D supplementation on diabetes risk

Vitamin D and regression to normal glucose regulation

While diabetes prevention trials often focus on delaying progression from prediabetes to diabetes, regression to normal glucose regulation (NGR) is also clinically meaningful. Beyond reducing diabetes incidence, vitamin D supplementation appears to promote metabolic recovery toward NGR. Evidence for this comes from the three major vitamin D diabetes-prevention trials—D2d, Tromsø, and DPVD—and several smaller randomized studies across diverse populations.

In the D2d study, vitamin D increased the likelihood of achieving NGR compared to placebo by 31% to 45%, depending on the NGR definition used. Over a median follow-up of 2.5 years, 12.4% vs 9.5% achieved NGR when defined by two or more American Diabetes Association glycemic criteria in the normal range (rate ratio 1.31; 95% CI, 1.02–1.70) and 8.7% vs 6.0% achieved NGR when both fasting and 2-hour glucose were in the normal range (rate ratio 1.45; 95% CI, 1.05–2.00) [60]. The Tromsø and DPVD trials showed similar, though non-statistically significant, trends favoring vitamin D (1.37; 95% CI 0.90 to 2.08 in Tromsø; 1.18; 95% CI 0.92 to 1.53 in DPVD), likely owing to smaller sample sizes [19, 45].Multiple smaller trials from the United States, India, Iran, and Greece also showed higher rates of reversion to normoglycemia with vitamin D [41-43, 46, 48-50].

Consistent results from meta-analyses reinforce these findings: Zhang et al. reported a 48% higher likelihood of regression to NGR (relative risk 1.48; 95% CI, 1.41 to 1.92) [57].The IPD meta-analysis of the three vitamin D and diabetes prevention trials found that 14.4% achieved NGR with vitamin D vs. 11.1% with placebo (rate ratio 1.30; 95% CI, 1.16 to 1.46). A recent meta-analysis of 10 trials (4,478 participants) found a 27% higher likelihood of NGR with vitamin D compared with placebo (rate ratio 1.27; 95% CI, 1.12–1.45), with no heterogeneity (I^2 = 1%) and high-quality evidence [61].

Together, these data indicate that vitamin D not only lowers diabetes risk but also increases the probability of returning to euglycemia.

Effect modification of the effect of vitamin D on diabetes risk by BMI

Evidence from subgroup analyses across vitamin D trials suggests that BMI modifies the preventive effect of vitamin D on diabetes risk**.** In pooled analyses, vitamin D supplementation reduced diabetes incidence most in participants with BMI < 30 kg/m^2 (hazard ratio 0.79; 95% CI 0.66 to 0.95), whereas the effect was markedly attenuated in those with 30 to 34.9 kg/m^2 (hazard ratio 0.90; 95% CI 0.72 to 1.12) [51]. Among those with BMI ≥ 35 kg/m^2, vitamin D did not seem to have an effect (hazard ratio 1.07; 95% CI 0.82 to 1.39). The effect modification by BMI was evident with native vitamin D_3 but not with eldecalcitol [51]. The mechanisms likely involve pharmacologic and biologic factors. In obesity, the expanded adipose compartment serves as a reservoir for vitamin D, leading to greater sequestration and reduced bioavailability. Therefore, the doses used in diabetes prevention trials (~2,000–4,000 IU/day) may be insufficient to raise serum 25(OH)D to target levels in people with obesity. A post hoc analysis in the D2d study showed that even among individuals with BMI up to 40 kg/m^2, those who achieved serum 25(OH)D > 40 ng/mL had a lower risk of developing diabetes [62]. These findings suggest that people with obesity would require higher or weight-adjusted doses of vitamin D to achieve 25(OH)D levels comparable to those of people with lower BMI [63].

Consistent patterns have emerged in other large trials, including VITAL and FIND**,** reinforcing a dose–response gradient for vitamin D_3 in T2D prevention across BMI categories. These findings suggest that while obesity can blunt vitamin D's metabolic effects, sufficient serum concentrations can restore efficacy. Importantly, these results challenge the perception that only obese individuals are at risk for T2D: approximately 20% of individuals with diabetes have a BMI < 25 kg/m^2**,** a group that may have "metabolically obese normal weight" phenotypes with excess visceral adiposity. This phenotype—prevalent in Asian populations [64]—illustrates that normal BMI does not preclude metabolic dysfunction, as low muscle mass, visceral fat accumulation, and inflammation can drive insulin resistance and beta cell stress.

Optimizing blood 25(OH)D levels and the concept of "treat-to-target"

Observational cohort studies consistently show that individuals with higher blood 25(OH)D levels have a lower risk of developing T2D, with no clear threshold for benefit. Meta-analyses of observational studies confirm that higher vitamin D status—particularly above 40 ng/mL—is associated with progressively lower diabetes risk, suggesting that both avoiding deficiency and maintaining higher circulating 25(OH)D levels may help reduce diabetes incidence. For example, D2d study participants with baseline vitamin D deficiency (<12 ng/mL) randomized to vitamin D had a 62% lower risk of diabetes (n=103; hazard ratio 0.38; 95% CI 0.18 to 0.80) and improved beta cell function compared with placebo.

Findings from the Tromsø and D2d trials provide additional evidence of a dose-response relationship. For example, among D2d participants in the vitamin D group who maintained mean intra-trial 25(OH)D levels of 40-49 ng/mL (100-124 nmol/L) and ≥50 ng/mL (125 nmol/L) during follow-up were 52% and 71%, respectively, less likely to develop diabetes compared to those who maintained 25(OH)D levels of 20-29 ng/mL (50 to 74 nmol/L), even after accounting for nonadherence and off-protocol vitamin D supplementation. Using the same methodology and individual participant data from D2d and Tromsø, participants treated with vitamin D who maintained intra-trial 25(OH)D levels of 40-49 and ≥50 ng/mL during follow-up were 62% and 76%, respectively, less likely to develop diabetes compared to participants who maintained levels of 20-29 ng/mL.

The DPVD study used an active vitamin D analogue (eldecalcitol), which does not rely on conversion to 25(OH)D and does not alter 25(OH)D levels. As such, a treat-to-target strategy based on 25(OH)D levels is not applicable to active analogues, and dose titration is constrained by safety considerations rather than biochemical targets. For this reason, the DPVD study should be viewed as mechanistically informative but conceptually distinct from a treat-to-target approach using native vitamin D.

Vitamin D formulation and dosing in adults with prediabetes

Cholecalciferol (vitamin D_3) is the most extensively studied formulation for preventing T2D. Daily or weekly dosing provides the most consistent efficacy and safety, supported by the Tromsø and D2d studies, which showed good tolerability without adverse events [45, 47]. Active vitamin D analogs have been tested less widely. In the DPVD trial, eldecalcitol (0.75 μg/day) was used, reflecting its common clinical use in Japan and the investigators' aim to achieve a more uniform biological effect, independent of variability in conversion to 25-hydroxyvitamin [19]. Eldecalcitol reduced diabetes incidence with an effect size similar to that of vitamin D_3, with no safety issues [19]. Unlike trials with vitamin D_3, there was no effect modification of eldecalcitol by BMI, suggesting that active forms may overcome obesity-related impairment in 25(OH)D activation. However, because active vitamin D analogues bypass physiologic control of 1α-hydroxylase, these agents have a narrower therapeutic window and require monitoring for hypercalcemia. Accordingly, while the use of an active analogue may be reasonable in selected individuals under close clinical supervision (e.g., individuals with conditions affecting vitamin D metabolism such as advanced CKD), cholecalciferol remains the preferred and recommended formulation for diabetes prevention at the population level.

Intermittent high-dose ("bolus") regimens—such as monthly or annual dosing—are not recommended, as they have proven ineffective for glycemic outcomes [65] and, in some studies , potentially harmful [66]. The 2024 Endocrine Society Guideline advises against bolus therapy (defined as less frequent than weekly) and recommends doses of 1,000–4,000 IU/day or weekly equivalents, to maintain stable 25(OH)D levels that mimic physiologic exposure.

Current Guidelines on vitamin D supplementation and prevention of type 2 diabetes

The 2024 Endocrine Society Clinical Practice Guideline on Vitamin D for the Prevention of Disease recommends vitamin D supplementation in adults with prediabetes at doses higher than the recommended dietary allowance (RDA), while advising against routine measurement of serum 25(OH)D. This recommendation in favor of supplementation was based on consistent evidence from randomized controlled trials (summarized above). In contrast, the evidence of the need for 25(OH)D testing is incomplete, as the results are from post hoc analyses. According to the Guideline, vitamin D supplementation for diabetes prevention can be implemented without baseline or follow-up testing, lowering cost and simplifying clinical translation. Although recommending empiric (i.e., without 25[OH]D testing) is reasonable and evidence-based, measuring 25(OH)D may be informative in selected populations—such as individuals with obesity—who often require higher or tailored supplementation strategies to achieve target levels, which have been shown to further reduce diabetes risk [67].

The 2025 *ADA Standards of Care in Diabetes* acknowledges vitamin D supplementation as a potential preventive intervention but concludes that it should not be routinely recommended because "the benefit–risk ratio remains uncertain" and "the optimal dose for diabetes prevention is unclear." This justification is not supported by the totality of evidence. The three vitamin D and diabetes prevention trials all demonstrated a consistent reduction in diabetes incidence and a significantly higher likelihood of regression to normoglycemia in adults with prediabetes with vitamin D. Three different meta-analyses with aggregate data (study-level) and an IPD meta-analysis – all by different authorship teams – have confirmed these findings and strengthened confidence in the efficacy and safety of vitamin D for T2D prevention **(Figure 2**). Regarding the optimal dose, daily doses equivalent to ~3,500 IU/day were used in the trials, providing a pragmatic range (2,000–5,000 IU/day) that can be applied in clinical practice, not unlike intensive lifestyle interventions where a range is recommended that fits the patient's needs.

Regarding safety, the risk profile of vitamin D is highly favorable when pharmaceutical-grade products are used within recommended limits (typically ≤10,000 IU/day), and when serum 25(OH)D levels are maintained below 150 ng/mL. Serious adverse effects are exceedingly rare and primarily associated with supraphysiologic dosing or unregulated preparations. No evidence suggests that individuals with prediabetes or diabetes are at higher risk of toxicity with vitamin D compared with the general population. Thus, from both efficacy and safety perspectives, the available data support vitamin D as a low-risk preventive option for adults with prediabetes, warranting its application in clinical and public health contexts.

Comparison with other interventions

Compared with established diabetes-prevention strategies, vitamin D appears competitive in efficacy, number needed to treat (NNT), cost, adherence, and safety (Table 3). In the DPP, intensive lifestyle intervention reduced diabetes incidence by 58% with an NNT of ~7 over 3 years, but required a resource-heavy model: frequent individual and group sessions, tailored diet and activity goals, and continuous coaching, which is difficult to maintain long-term [7]. This level of support is rarely reimbursed, poses practical barriers (time, cost, travel), and for sedentary adults carries some injury risk. In routine practice, lifestyle advice is usually reduced to simplified messages, "eat less / better and exercise more," that seldom reproduce DPP-level outcomes. Metformin reduced diabetes risk by ~31% overall in DPP (NNT ~14), with benefits mainly in people with BMI ≥35 kg/m^2, younger adults, or those with higher fasting glucose. Although inexpensive and safe, metformin is used infrequently for diabetes prevention in routine clinical practice [68].

Injectable incretin receptor agonist-based therapies have recently shown large relative risk reductions in adults with obesity and prediabetes. In SURMOUNT-1, tirzepatide reduced progression to diabetes by ~94% over 3 years (estimated NNT ~9) [69]. Semaglutide 2.4 mg weekly in adults with obesity and prediabetes also markedly improved glycemia and promoted reversion to normoglycemia, and has been interpreted as substantially lowering future diabetes risk, with reported NNT values on the order of ~19 to prevent one diabetes case when modeled over similar horizons [70].These agents are costly, require long-term injections, and have evolving safety data for pure diabetes-prevention populations; real-world adherence may also be lower than in clinical trials [71].

In contrast, vitamin D is inexpensive, orally administered, widely accessible, and has an excellent safety profile, positioning it as a practical and scalable diabetes-prevention option.

Summary

There is now clear and consistent evidence from well-conducted, generalizable randomized controlled trials and meta-analyses that vitamin D supplementation can lower the risk of developing T2D and promote regression to normoglycemia in adults with prediabetes. The three trials designed explicitly for diabetes prevention—the D2d study in the United States, the DPVD study in Japan, and the Tromsø study in Norway—each demonstrated a consistent reduction in diabetes incidence with vitamin D. These large trials and smaller trials, when analyzed together in four recent meta-analyses, including an IPD meta-analysis, show that vitamin D supplementation reduces the risk of diabetes by 11 to 17%, depending on the type of analysis. The trials varied in design and dosage, ranging from 842 to 7543 IU/day (mean ≈ 3500 IU/day), all of which exceeded the current Recommended Dietary Allowance (600–800 IU/day).

A dose–response relationship was evident in the trials that used cholecalciferol: participants who maintained mean intra-trial serum 25(OH)D levels ≥50 ng/mL (125 nmol/L) had a six-fold greater reduction in diabetes risk compared to those with levels of 20–29 ng/mL (50–74 nmol/L). However, because the data on achieved 25(OH)D levels were post hoc, until further data are available, vitamin D supplementation for diabetes prevention can be implemented without testing of vitamin D status.

As experienced clinical trialists, we emphasize that planning and executing large, long-duration randomized controlled trials is far more time-consuming, complex, and costly than most clinicians appreciate—particularly in academic settings where resources are limited and regulatory burdens are high. As of today, we are unaware of other large ongoing or planned randomized controlled trials on this topic. Given these realities, it is unlikely that additional large-scale trials on vitamin D for diabetes prevention will be undertaken in the near future, and recommendations should be developed based on the available evidence. Suggested future research is shown in the **Box.**

Unlike other preventive interventions for T2D that have adherence, safety, or cost limitations, vitamin D is a safe, inexpensive, and globally scalable intervention that modestly but meaningfully reduces the risk of T2D —an opportunity too important for clinicians and public health systems to overlook. This is especially true in lower-resource countries [72], given that over 80% of adults with diabetes live in low- and middle-income countries, where the cost and logistics of pharmacologic or lifestyle interventions are significant barriers.

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Figure 1 legend. An overview of vitamin D and the prevention of type 2 diabetes

Figure 2 legend. A comparison of meta-analyses of trials that have reported on the effect of vitamin D and the prevention of type 2 diabetes.

Barbarawi_AveRisk includes trials in adults at average risk for type 2 diabetes; Barbarawi_PreDM includes trials in adults at high risk for type 2 diabetes (i.e., prediabetes); Shah_DPVD includes the DPVD trial, which used eldecalcitol.

The I^2 statistic was 0% for all meta-analyses except for Barbarawi_PreDM, which was 3%. The I^2 statistic is not relevant to the individual participant meta-analysis by Pittas et al.

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Table 1. Trials that were not designed for diabetes prevention but have reported on the effect of vitamin D and new-onset diabetes or regression to normal glucose regulation.

First author Year of publication [Country]	Target population (n=number of participants)	Baseline 25(OH)D concentration, ng/mL	Interventions (number of participants)	Study duration, years	Study quality (reasoning)	Designed for glycemic outcomes, (Yes/No)	Primary outcome[s]	Other glycemic outcomes?	Was the trial designed, conducted for the primary prevention of type 2 diabetes, i.e., was new-onset diabetes the primary outcome?
Populations at average risk for type 2 diabetes – Not designed for glycemic outcomes or for primary prevention of type 2 diabetes									
De Boer 2008 [US] WHI	Healthy, postmenopausal women (n=33,951)	Not available	D_3 400 IU daily plus calcium carbonate 1,000 mg daily (n=16,999) vs. placebos (n=16,952)	Median of 7 years	Fair (post-hoc analysis, self-report of new-onset diabetes, single gender)	No	-Fracture reduction	-New-onset diabetes	No
Avenell 2009 [UK]	Healthy adults ≥70 years and history of fracture (n=5,292)	Not available	D_3 800 IU daily (n=2,649) vs. placebo (n=2,643) [2x2 factorial design with calcium carbonate 1,000 mg daily]	Range of 2-5 years	Fair (post-hoc analysis, self-report of new-onset diabetes)	No	-Fracture reduction	-New-onset diabetes	No
Virtanen 2025 [Finland] VITAL	Healthy men ≥60 and women ≥65 years (n=2,271)	30	D_3 1600 IU daily (n=832) vs. D_3 3,200 IU daily (n=833) vs. placebo (n=830)	Mean 4.2 years	Moderate (post-hoc analysis, ICD-10)	No	-Cardiovascular disease and cancer	-New-onset diabetes	No

Tobias 2025 [US] VITAL	Healthy men ≥50 and women ≥55 years (n=22,220)	31	D_3 2000 IU daily (n=11,062) vs. placebo (n=11,158)	Median of 5.3 years	Moderate (post-hoc analysis, self-report of new-onset diabetes)	No	-Cardiovascular disease and cancer	-New-onset diabetes	No
Populations at risk for type 2 diabetes (prediabetes) – Not designed for primary prevention of type 2 diabetes									
Davidson 2013 [US]	Prediabetes by FG or 2hG, and 25(OH)D<30 ng/mL (n=109)	22	Treat-to-target 25(OH)D 65-90 ng/mL, mean D_3 88,865 IU weekly [~12,695 IU daily] (n = 56) vs. placebo (n=53)	Up to 1 year	Moderate (small sample size)	Yes	-OGTT-based insulin sensitivity and secretion	-New-onset diabetes -NGR	No
Dutta 2014 [Eastern India]	Prediabetes by FG or 2hG, and 25(OH)D<30 ng/mL (n=125)	17	D_3 60,000 IU weekly [~8,571 IU daily] for 8 weeks, then 60,000 IU monthly [~3,000 IU daily] (n=68) vs. no treatment (n=57); [open label]; all received calcium 500 mg daily.	Mean of 2.3 years	Poor (small sample size, open label, unclear methodology section)	Yes	-New-onset diabetes -NGR	-FG -2hG	No
Barengolts 2015 [US]	Black men with prediabetes (84%) or diabetes (16%) based on FG or HbA1c, and 25(OH)D 5-29 ng/mL, and	14	D_2 50,000 IU weekly [~7,143 IU daily] adjusted to achieve 25(OH)D 40-100 ng/mL (n=103) vs. placebo	Up to 1 year	Fair (small sample size, single race and gender; both prediabetes and diabetes populations)	Yes	-OGTT-based oral glucose insulin sensitivity	-New-onset diabetes -NGR -OGTT-based insulin secretion,	No

	prevalent medical problems (n=205)		(n=102). All received D_3 400 IU daily.					-HbA1c	
Kuchay 2015 [North India]	Prediabetes by FG, 2hG or HbA1c (n=137)	19	D_3 60,000 IU weekly [~2,000 IU daily] for 4 weeks, then monthly (n=69) vs. no treatment (n=68) [open label]	Up to 1 year	Poor (small sample size, open label)	Yes	-FG -2hG -HbA1c	-New-onset diabetes	No
Niroomand 2019 [Iran]	Prediabetes based on FG or 2hG, and 25(OH)D<30 ng/mL (n=162)	13	D_3 50,000 IU weekly [~7,143 IU daily] for 3 months, then monthly (n=81) vs. placebo (n=81)	Up to 6 months	Poor (small sample size, completers only analysis [50% of randomized])	Yes	-Insulin sensitivity	-New-onset diabetes -NGR -FG -2hG	No
Bhatt 2020 [India]	Prediabetes based on FG or 2hG, and 25(OH)D < 20 ng/mL (n-121)	12	D_3 60,000 IU weekly [~3,571 IU daily] for 8 weeks and repeated as needed to “avoid deficiency,” then 200 IU daily (n=61) vs. placebo (n=60) [open label]; all received calcium carbonate daily.	18 months	Poor (small sample size, open label)	Yes	-FG -2hG -HbA1c -New-onset diabetes -NGR		No
Misra 2021 [Northern India]	Prediabetes based on FG or 2hPG and 25(OH)D < 30 ng/mL	23	D_3 60,000 IU weekly [~8,571 IU daily] for 8 weeks, repeated if	Up to 2 years	Poor (small sample size, open label)	Yes	-New-onset diabetes	-NGR -FG -2hG -HbA1c	No

			needed to reach 25(OH)D > 30 ng/mL (n=67) vs. placebo (n=65) [open label]						
Zaromytidou 2022 [Greece]	Prediabetes based on FG or 2hG or HbA1c, (n=90)	20	D_3 25,000 IU weekly [~3,571 IU daily] (n=45) vs. no treatment (n=45) [open label]	Up to 1 year	Poor (small sample size, open label)	Yes	-FG -2hG -HbA1c	-New-onset diabetes -NGR	No

Three trials designed for the prevention of diabetes among adults with prediabetes are described in Table 2.
2hG, glucose 2 hours after a 75 g oral glucose load; 25(OH)D, plasma or serum 25-hydroxyvitamin D; D_3, cholecalciferol; D_2, ergocalciferol; FG, fasting glucose; HBA1c, glycated hemoglobin A1c; IU, international units; NGR, normal glucose regulation; OGTT, 75-gram oral glucose tolerance test;

FIND, Finnish Vitamin D; VITAL, Vitamin D and Omege-3; WHI, Women's Health Initiative;
To convert 25(OH)D concentration from ng/mL to nmol/L, multiply by 2.459; to convert FPG from mg/dL to mmol/L, multiply by 0.0555.

Table 2. Key characteristics of the randomized, double-blind, placebo-controlled clinical trials with vitamin D for the prevention of diabetes among adults at risk for type 2 diabetes (prediabetes).

Study name	**Tromsø study**	**D2d study**	**DPVD study**
First author, year of publication	Jorde et al, 2016	Pittas et al, 2019	Kawahara et al, 2022
Country (number of sites) [1]	Norway (1 site)	United States (22 sites)	Japan (3 sites)
Year of trial completion	2015	2018	2019
Randomized participants (vitamin D:placebo), No.	511 (256:255)	2,423 (1,211:1,212)	1,256 (630:626)
Prediabetes glycemic criteria for eligibility	IFG (FG 108-125 mg/dL) and/or IGT (2hG 140-199 mg/dL) and no criterion in the diabetes category	Two or three glycemic criteria (IFG [FG 100-125 mg/dL], IGT [2hG 140-199 mg/dL], iA1c [HbA1c 5.7-6.4%]) and no criterion in the diabetes category	IGT (2hG 140-199 mg/dL) and no criterion in the diabetes category
Mean age, years	62	60	61
Body mass index, kg/m^2	30	32	24
Mean baseline blood 25(OH)D, ng/mL	24	28	21
Percent of participants with blood 25(OH)D above 20 ng/mL,	62	80	54
Intervention	Cholecalciferol (native, vitamin D_3), 20,000 IU weekly (equivalent to 2,857 IU daily)	Cholecalciferol (native, vitamin D_3), 4,000 IU daily	Eldecalcitol (active vitamin D) 0.75 micrograms daily
Comparator	Placebo weekly	Placebo daily	Placebo daily
Lifestyle recommendations (active and control)	At baseline, all participants received information that a healthy diet and physical activity can prevent	At baseline and every visit, all participants received and were encouraged to follow the	At baseline and every visit, all participants received information that a healthy diet and physical activity can

	the development of type 2 diabetes, especially when accompanied by weight loss.	recommended lifestyle-based advice for diabetes prevention through a structured intervention. The study developed written Diabetes Prevention Program-based diabetes prevention material and held twice-a-year participant meetings focusing on traditional, lifestyle-based approaches to prevent diabetes.	prevent the development of type 2 diabetes, especially when accompanied by weight loss.
Vitamin D amount from supplements allowed outside of the study	≤400 IU/day	≤1,000 IU/day	0
Definition of primary outcome, new-onset diabetes	Any glycemic-positive criteria: FG ≥126 mg/dL, 2hG ≥200 mg/dL, HbA1c ≥6.5%. A positive HbA1c required confirmation.	Two or 3 glycemic-positive criteria: FG ≥126 mg/dL, 2hG ≥200 mg/dL, HbA1c ≥6.5%, or 1 criterion positive with confirmation	HbA1c ≥6.5% and either: FG ≥126 mg/dL, 2hG ≥200 mg/dL or casual glucose ≥200 mg/dL
Median (interquartile range) [range] follow-up, years [2]	4.0 (1.5 to 5.0) [0.2-5.2]	2.5 (1.9 to 3.5) [0-4.7] (event-driven)	2.9 (2.8 to 3.0) [0.1-3.0]
Incidence of diabetes in the placebo group, per 100 person-years			
Expected	10.0	10.5	8.4
Actual	8.7	10.7	4.7
Relative risk reduction in new-onset diabetes,			

vitamin D vs. placebo, %			
Expected	30	25	36
Actual	10	12	13
Hazard ratio (95%CI)	0.90 (0.69 to 1.18)	0.88 (0.75 to 1.04)	0.87 (0.67 to 1.17)

2hG, glucose 2 hours after a 75-gram oral glucose load; 25(OH)D, plasma or serum 25-hydroxyvitamin D; HbA1c, glycated hemoglobin A1c; iA1c, impaired hemoglobin A1c; IFG, impaired fasting glucose; FG, fasting glucose; IGT, impaired glucose tolerance.

[1] Tromsø had one site in Norway (University Hospital of North Norway at 70° north latitude); D2d had 22 sites (22 different locations) in the United States (12 sites were above 37° north latitude and 10 sites were below 37° north latitude); DPVD had 3 sites at two locations in Japan (Fukuoka location at 34° north latitude and Kanagawa location at 35° north latitude).

[2] The Tromsø study was designed to follow participants up to 5 years or until the diagnosis of diabetes. The D2d study was designed as an event-driven trial and follow-up, as expected, varied among participants. The DPVD study was designed to follow participants for up to 3 years or until diabetes diagnosis.

Table 3. Select interventions for Prevention of Type 2 Diabetes: Comparative Summary

Intervention	NNT	Dosing / Approach	Population in Whom Effect Strongest	Estimated Monthly Cost (U.S.)	Key Considerations
Intensive lifestyle modification (Diabetes Prevention Program)	7	Sixteen individual core sessions over 24 weeks, then monthly support; weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and moderate intensity physical activity at least 150 minutes per week	BMI ≥35 kg/m^2; older than 60 years; individuals motivated for behavioral change	$300-500 during the first year; variable in subsequent years	Highly effective in the trials; resource- and time-intensive; long-term adherence low; additional benefits.
Metformin	14	850 mg orally, twice daily (1700 mg/day)	BMI ≥35 kg/m^2; younger adults; history of gestational diabetes; elevated fasting glucose	$4-15	GI side effects (common); lactic acidosis (rare); adherence ~70%; limited effect in BMI <30; dose adjustment based on kidney function
Vitamin D	30	Vitamin D3 orally, 2000–4000 IU daily or 20,000 IU weekly	BMI <30 kg/m^2; BMI up to 40 kg/m^2 when 25(OH)D target achieved	$5	Safe and inexpensive; targeting 25(OH)D level (40-60 ng/mL) may be important (adding complexity and cost)
Semaglutide (GLP-1 receptor agonist)	19	Up to 2.4 mg subcutaneous, weekly	BMI ≥27 kg/m^2	$349 (direct-to-consumer) – $1350 (list price)	Dose-dependent GI side effects; complications (cholecystitis); greater effect at higher BMI; additional benefits.
Tirzepatide (dual GIP/GLP-1	9	Up to 15 mg subcutaneous, weekly	BMI ≥27 kg/m^2	$299-449 (direct-to-consumer) –	Dose-dependent GI effects; greater effect at higher

receptor agonist)				$1100 (list price)	BMI; additional benefits.

NNT, Number needed to treat to prevent one case of type 2 diabetes over ~3 years; 25(OH)D, 25-hydroxyvitamin D.
Data from Knowler, NEJM 2025 (lifestyle and metformin); Pittas, Annals of Internal Medicine 2023 (vitamin D); Kahn, Diabetes Care 2024 (semaglutide); Jastreboff, New England Journal of Medicine 2025 (tirzepatide)