

A Systematic Review Supporting the Endocrine Society Clinical Practice Guidelines on Vitamin D

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Abstract

Context: Low vitamin D status is common and is associated with various common medical conditions.

Objective: To support the development of the Endocrine Society's Clinical Practice Guideline on Vitamin D for the Prevention of Disease.

Methods: We searched multiple databases for studies that addressed 14 clinical questions prioritized by the guideline panel. Of the 14 questions, 10 clinical questions assessed the effect of vitamin D vs no vitamin D in the general population throughout the lifespan, during pregnancy, and in adults with prediabetes; 1 question assessed dosing; and 3 questions addressed screening with serum 25-hydroxyvitamin D (25[OH]D). The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess certainty of evidence.

Results: Electronic searches yielded 37 007 citations, from which we included 151 studies. In children and adolescents, low-certainty evidence suggested reduction in respiratory tract infections with empiric vitamin D. There was no significant effect on select outcomes in healthy adults aged 19 to 74 years with variable certainty of evidence. There was a very small reduction in mortality among adults older than 75 years with high certainty of evidence. In pregnant women, low-certainty evidence suggested possible benefit on various maternal, fetal, and neonatal outcomes. In adults with prediabetes, moderate certainty of evidence suggested reduction in the rate of progression to diabetes. Administration of high-dose intermittent vitamin D may increase falls, compared to lower-dose daily dosing. We did not identify trials on the benefits and harms of screening with serum 25(OH)D.

Conclusion: The evidence summarized in this systematic review addresses the benefits and harms of vitamin D for the prevention of disease. The guideline panel considered additional information about individuals' and providers' values and preferences and other important decisional and contextual factors to develop clinical recommendations.

Key Words: vitamin D, 25(OH)D, Endocrine Society, guidelines, systematic reviews

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; IRR, incidence rate ratio; RCT, randomized controlled trial; RDI, recommended daily intake; RoB, risk of bias; RR, relative risk (risk ratio); RTI, respiratory tract infection; URTI, upper respiratory tract infection.

Vitamin D is a distinctive pro-hormone in that it can be produced endogenously from exposure to UV-B rays via sunlight, or obtained through consumption of foods that naturally contain vitamin D or are fortified with vitamin D, or from supplements containing vitamin D (1, 2). Vitamin D plays a crucial role in regulating calcium and phosphorus levels in the body, which is essential for maintaining skeletal health (1). Low vitamin D status is common (3, 4), and there is strong evidence for a link between vitamin D deficiency and skeletal disease, including osteomalacia and osteoporosis in adults as well as osteomalacia and rickets in children with open growth plates (5).

The actions of vitamin D are mediated by calcitriol (1,25[OH]2D) on the vitamin D receptor, which is expressed in most tissues in the body. The widespread expression of the vitamin D receptor has led to interest in evaluating the role of vitamin D in reducing the risk of nonskeletal diseases (1, 2, 6–9). Observational studies have consistently reported inverse longitudinal associations between vitamin D status, as measured by serum 25(OH)D concentration, and the risk of numerous conditions, including cancer, infectious diseases, autoimmune conditions (eg, type 1 diabetes, multiple sclerosis), and cardiometabolic disorders (eg, type 2 diabetes, cardiovascular disease). However, randomized controlled clinical trials

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have reported conflicting results on the effect of vitamin D supplementation in lowering the risk of common chronic conditions in the general population.

Many guidelines exist on the recommended daily intake (RDI) of vitamin D (10-14) with different recommendations based on age and pregnancy status. In 2011, the Endocrine Society guideline placed emphasis on the care of patients who are at risk for having a low vitamin D status, assessed by serum 25(OH)D concentration. These recommendations relied almost exclusively on observational studies, most of which report consistent associations between low vitamin D status and risk of several common chronic diseases (15). Observational studies are limited by residual confounding, which may explain, at least in part, the observed inverse associations between vitamin D status and certain diseases. High serum 25(OH)D concentrations are associated with younger age, healthier body weight, and healthy dietary and exercise habits. Conversely, lower vitamin D status may be associated with chronic health conditions that prevent individuals from engaging in outdoor activities or having adequate sun exposure. Moreover, diet adds another layer of complexity to the study of the association between vitamin D and disease.

Since 2011, the results of several clinical trials have been published, providing new data about the effects of vitamin D on both skeletal and extraskeletal outcomes in the general population. The Endocrine Society determined that there was a need to update its guideline on vitamin D in the general population and in selected populations. The guideline panel prioritized several clinical questions relevant to practicing clinicians. This systematic review and meta-analysis were undertaken to synthesize the evidence for these questions, prioritizing data from randomized clinical trials.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (16). The study protocol and specific questions of this review were developed by a guideline panel from the Endocrine Society.

Eligibility Criteria

The panel members prioritized 14 questions addressing use of enteral or parenteral vitamin D among various groups, including children, pregnant adults, nonpregnant adults in different age groups, and adults with prediabetes. Other questions addressed dosing of vitamin D and screening for serum 25(OH)D levels. The 14 questions are presented using the PICO (population, intervention, comparator, and outcome) format in the supplement (Supplementary Table S1 (17)).

Data Sources, and Search Strategies

A comprehensive search of several databases from the year 1946 to December 28, 2023, in any language, was conducted. The databases included MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by a medical reference librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used to search for vitamin D supplementation (cholecalciferol [vitamin D3] or ergocalciferol [vitamin D2]) and

outcomes in adults. Additional references identified by the guideline committee were also considered. The strategy listing all search terms used and how they were combined is available in the supplement (Supplementary Table S2 (17)).

Study Selection

Two independent reviewers screened abstracts and titles for eligibility. If a study was deemed eligible, the full text was screened by 2 independent reviewers. A third reviewer resolved any disagreements.

Data Extraction

Two independent reviewers abstracted data from each eligible study. When multiple reports from the same study were published, the one with the largest dataset was included. If a study reported multiple treatment arms for vitamin D dosing, outcomes were combined into a single vitamin D group. Elements of data extraction are described in the supplement (Supplementary Table S1.1 (17)). Two studies provided outcome data stratified by age for questions 4 to 7 (ViDA (18) and VITAL (19) studies).

Data Synthesis and Analysis

For binary outcomes, relative risks (RR, when the outcome was reported per participant) and incidence rate ratios (IRR, when the outcome was reported per event) were estimated with 95% CI. For continuous outcomes, the weighted mean difference (WMD) was estimated. Due to heterogeneity across study settings and populations, the random-effects model as described by DerSimonian-Laird was used. Heterogeneity was assessed using the I^2 , and low heterogeneity was considered to be $\leq 50\%$. Predefined subgroup analyses were performed based on the study's risk of bias (RoB), baseline 25(OH)D level, sex, calcium co-administration, vitamin D dose, and population setting when applicable. Vitamin D dosing was categorized into standard dose ($\leq 50\,000$ IU in single doses) or high dose ($>50\,000$ IU in single doses) regardless of the frequency of administration. The analysis was conducted using STATA software package (StataCorp (2019) Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX).

Methodologic Quality and Certainty of the Evidence

RoB was assessed by 2 independent reviewers. The Newcastle-Ottawa scale (20) was used for nonrandomized studies, and the Cochrane Risk of Bias Tool version 2 (21) was used for randomized controlled trials (RCTs). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to rate the certainty of evidence (very low, low, moderate, or high) (22). If data for both RR and IRR were available, RR was used to assess certainty. RCTs start at a high certainty, and then certainty of evidence is then downrated according to the RoB, inconsistency, indirectness, imprecision, and publication bias.

Results

Study Selection

Electronic searches yielded 37 007 citations (Supplementary Table S2 (17)). From these, 803 citations underwent full-text review, and ultimately 151 studies met inclusion criteria. The study selection process is illustrated in Supplementary Fig. S1

(17). For each PICO, study characteristics, demographics and intervention details are provided in Supplementary Table S3 and RoB is provided in Supplementary Table S4 in the supplement (17). The results of meta-analysis outcomes are presented in Table 1.

Question 1. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used for Children and Adolescents (Ages 1-18 Years)?

Fourteen RCTs (23-36) with 14 710 participants were included. Study characteristics and RoB are provided in Supplementary Tables S3.1 and S4.1, respectively (17).

There was no statistically significant difference in the risk of a child having a respiratory tract infection (RTI) with vitamin D (12 studies (23-29, 31-34, 36), very low certainty). There was evidence of subgroup difference by RoB ($P = .022$). Additionally, vitamin D was not associated with lower RTI (5 studies (24, 26, 29, 31, 33, 36), moderate certainty) or tuberculosis (2 studies (35, 36), moderate certainty). While there was no reduction in the relative risk of RTI, vitamin D was associated with a lower incidence rate of RTI (3 studies (24, 28, 30), IRR 0.64, 95% CI [0.51, 0.82]).

Three RCTs reported on asthma. Di Mauro et al (2018) (30) reported a mean 1.7 ± 0.9 and 2.6 ± 2.6 asthma attacks in the vitamin D (400 IU/d) and control groups, respectively during the 12-month study period. Urashima et al (2010) (29) reported that asthma attacks occurred in 2 children receiving 1200 IU vitamin D3 compared with 12 children receiving placebo (RR 0.17, 95% CI [0.04, 0.73]; $P = .006$) over a 4-month study period. Ganmaa et al (36) reported 2 hospitalizations for asthma exacerbations, 1 each in the intervention and control group during the 3-year study period.

Ganmaa (36) reported 1 case of symptomatic hypercalcemia in the group receiving 14 000 IU of vitamin D weekly with no cases in the placebo group, and 1 case of kidney failure in the placebo group. Gupta et al (2016) (33) reported no cases of symptomatic hypercalcemia in the treatment or control groups.

No RCTs were found that evaluated symptomatic rickets, fractures in adulthood, development of autoimmune disease, prediabetes, or type 2 diabetes.

Forest plots are shown in Supplementary Fig. S2.1 and summary of findings are described in Supplementary Table S5.1 (17).

Question 2. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used for Nonpregnant Adults < 50 Years of Age?

Fourteen RCTs (37-50) studies with 19 113 participants were included. Study characteristics and RoB are provided in Supplementary Tables S3.2 and S4.2, respectively (17).

Vitamin D was not associated with a significant effect on bone mineral density (BMD) in the lumbar spine (4 studies (39, 40, 42, 45)), femoral neck (2 studies (40, 45)), or tibia (2 studies (37, 43)) with low certainty. Vitamin D was associated with a statistically significant but likely trivial decrease in total hip BMD (2 studies (42, 45), mean difference -0.049 g/cm^2 , 95% CI $[-0.060, -0.038]$), low certainty. There was no statistically significant association with the risk of developing RTI (2 studies (38, 44), moderate certainty) or RTI events (4 studies (38, 47, 49, 50), very low certainty). There were no reported

cases of symptomatic hypercalcemia, nephrolithiasis, or kidney disease/renal failure in the included studies.

Forest plots are shown in Supplementary Fig. S2.2, and summary of findings are described in Supplementary Table S5.2, and a summary of the studies without sufficient data for meta-analysis is shown in Supplementary Table S6 (17).

Question 3. Should Vitamin D Supplementation vs No Vitamin D Supplementation Be Used for Nonpregnant Adults < 50 Years of Age Only When 25(OH)D Levels Are Below a Threshold?

Four RCTs (38, 41, 48, 50) were identified that reported findings in subgroups below a threshold 25(OH)D level but were not amenable to meta-analysis.

Three RCTs reported findings related to RTIs by baseline 25(OH)D level. Murdoch 2012 (38) did not report a statistically significant difference in upper RTI (URTI) when data was analyzed by baseline 25(OH)D levels $< 20 \text{ ng/mL}$ (50 nmol/L). Simpson et al (2015) (50) did not find a decrease in respiratory infections in participants receiving 20 000 IU/week of vitamin D compared with placebo, but there was a trend for a protective effect with vitamin D, most notably below 16 ng/mL (40 nmol/L), attenuated at 20 ng/mL (50 nmol/L), and absent at 24 ng/mL (60 nmol/L). Jung et al (2018) (48) reported changes in URTI symptom score in collegiate male Taekwondo athletes with 25(OH)D level $< 20 \text{ ng/mL}$ (50 nmol/L), comparing 5000 IU of vitamin D3 daily to placebo over 4 weeks. There was a significant difference in Wisconsin Upper Respiratory Symptom Survey-11 between the vitamin D group (7.7 ± 1.06) and the placebo group (13.0 ± 1.60) ($P = .011$). The study reported a negative correlation between change in 25(OH)D level during the trial and total URTI symptoms ($r = -0.435$, $P = .015$).

While no studies reported on new-onset fatigue, Nowak et al (2016) (41) evaluated 120 adults presenting with fatigue and 25(OH)D levels $< 20 \text{ ng/mL}$ (50 nmol/L). Participants were randomized to a single dose of 100 000 IU vitamin D3 or placebo. At 4 weeks, the fatigue assessment scale decreased more in the vitamin D group (-3.3 ± 5.3) compared with placebo (-0.8 ± 5.3) ($P = .01$). Improvement in fatigue score correlated with the rise in 25(OH)D level ($R = -0.22$, $P = .02$). Amelioration of fatigue was reported in a higher proportion of participants in the vitamin D group, relative to the placebo group (72% vs 50%; RR 1.49, 95% CI [1.08, 1.94]).

Question 4. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used for Adults Aged 50 to 74 Years?

Forty-six manuscripts (18, 19, 51-94) from 22 RCTs with 111 331 participants were included. Five observational studies (95-99) were also identified. Study characteristics and RoB are provided in Supplementary Tables S3.3 and S4.3, respectively (17).

Vitamin D supplementation was associated with increased risk of kidney stones (10 studies (19, 54, 59, 62, 65, 74, 83, 85, 88, 93), RR 1.10 95% CI [1.01, 1.19], high certainty). There was no statistically significant difference in the risk of a cardiovascular event (14 studies (18, 19, 54, 61, 62, 67, 75, 76, 85, 86, 91-94), high certainty); stroke (7 studies (18, 19, 54, 61, 62, 91, 93), high certainty); myocardial infarction (7 studies (18, 19, 54, 62, 76, 91, 93), high certainty); total

Table 1. Summary of meta-analysis

Question	Population	Intervention	Comparator	Outcome	Studies (n)	Population (n)	Effect [95% CI]	GRADE
1	Children and adolescents (age 1-18)	Vitamin D	No vitamin D	Risk of a respiratory infection Incidence of respiratory infections Lower respiratory tract infections Tuberculosis	12 3 6 2	12 951 428 10 356 10 533	RR 0.94, 95% CI [0.87-1.02] IRR 0.64, 95% CI [0.51-0.82] RR 0.93, 95% CI [0.83-1.04] RR 0.67, 95% CI [0.14-3.11]	Very low certainty — Moderate certainty Moderate certainty
2	Nonpregnant adults < 50 years old	Vitamin D	No vitamin D	Bone mineral density (> 6 months of intervention)	7	737	Lumbar spine MD -0.003 g/cm ² , 95% CI [-0.042-0.036] Total hip MD -0.049 g/cm ² , 95% CI [-0.060-0.038] Femoral neck MD 0.033 g/cm ² , 95% CI [-0.023-0.090] Tibia MD 6.862mg/cm ³ , 95% CI [-8.082-21.805]	Low certainty
3	Nonpregnant adults < 50 years old with 25(OH)D below a threshold	Vitamin D	No vitamin D	Risk of a respiratory infection Incidence of respiratory infections Fatigue amelioration	2 4 1	17 074 1120 120	RR 1.02, 95% CI [0.96-1.08] IRR 0.95, 95% CI [0.83-1.07] RR 1.49, 95% CI [1.08-1.94]	Moderate certainty Very low certainty Very low certainty
4	Adults 50-74 years old	Vitamin D	No vitamin D	Risk of a fracture All-cause mortality Cancer CVD events Stroke MI Adverse events (nephrolithiasis) Adverse events (kidney disease)	13 13 15 14 7 7 10 4	87 161 81 695 91 223 80 547 68 273 38 558 87 524 28 610	RR 0.97, 95% CI [0.91-1.03] RR 1.07, 95% CI [0.95-1.20] RR 1.00, 95% CI [0.97-1.03] RR 1.00, 95% CI [0.93-1.08] RR 0.95, 95% CI [0.83-1.09] RR 1.00, 95% CI [0.83-1.20] RR 1.10, 95% CI [1.00-1.19] RR 1.04, 95% CI [0.76-1.42]	High certainty High certainty High certainty High certainty High certainty High certainty High certainty High certainty
5	Adults 50-74 years old with a 25(OH)D below a threshold	Vitamin D	No vitamin D	Risk of a fracture All-cause mortality Cancer CVD events Stroke MI Adverse events	1 2 2 3 1 1 1	4932 7005 3339 8274 1805 1805 1805	RR 1.01, 95% CI [0.81-1.24] RR 1.11, 95% CI [0.85-1.46] RR 0.91, 95% CI [0.70-1.19] RR 1.02, 95% CI [0.87-1.19] RR 1.04, 95% CI [0.39-2.75] RR 0.93, 95% CI [0.38-2.29] RR 1.26, 95% CI [0.77-2.12]	High certainty High certainty High certainty High certainty Moderate certainty Moderate certainty Low certainty
6	Adults ≥ 75 years old	Vitamin D	No vitamin D	Risk of a fracture Incidence of fractures Risk of a fall Incidence of falls All-cause mortality Respiratory infections Nephrolithiasis Kidney disease	15 15 16 14 25 3 3 3	43 719 25 945 12 342 33 759 49 879 821 5634 5634	RR 1.01, 95% CI [0.94-1.08] IRR 0.94, 95% CI [0.81-1.09] RR 0.97, 95% CI [0.91-1.03] IRR 0.90, 95% CI [0.79-0.99] RR 0.96, 95% CI [0.93-1.00] HR 1.11, 95% CI [0.94-1.30] RR 0.94, 95% CI [0.54-1.65] RR 0.76, 95% CI [0.44-1.32]	High certainty — Moderate certainty — High certainty Low certainty Moderate certainty Moderate certainty
7	Adults ≥ 75 years old with a 25(OH)D below a threshold	Vitamin D	No vitamin D	Falls All-cause mortality Adverse events	2 3 1	276 589 196	RR 0.65, 95% CI [0.40-1.05] RR 0.88, 95% CI [0.46-1.67] RR 1.26, 95% CI [0.26-6.18]	Very low certainty Very low certainty Very low certainty
8	Pregnant women	Vitamin D	No vitamin D	Preeclampsia and gestational hypertension Intra-uterine mortality Neonatal mortality Preterm birth Small for gestational age	8 4 3 6 5	2674 1738 1576 2085 2355	RR 0.73, 95% CI [0.46-1.15] RR 0.70, 95% CI [0.34-1.46] RR 0.57, 95% CI [0.22-1.49] RR 0.73, 95% CI [0.39-1.36] RR 0.78, 95% CI [0.50-1.20]	Low certainty Moderate certainty Moderate certainty Low certainty Low certainty

(continued)

Table 1. Continued

Question	Population	Intervention	Comparator	Outcome	Studies (n)	Population (n)	Effect [95% CI]	GRADE
9	Adults with prediabetes	Vitamin D	No vitamin D	Diabetes	10	4060	RR 0.90, 95% CI [0.81–1.00]	Moderate certainty
				Change in HbA1c (%)	15	2150	MD –0.05, 95% CI [–0.10–0.01]	—
				Change in FBS (mg/dL)	12	1630	MD –5.29, 95% CI [–7.90––2.68]	—
				Change in OGTT (2-hour, mg/dL)	13	1802	MD –7.61, 95% CI [–12.55––2.66]	—
				Fractures	1	92	RR, 95% CI 3.00 [0.13–71.78]	Very low certainty
				All-cause mortality	2	2979	RR 0.75, 95% CI [0.26–2.18]	Low certainty
				CVD events	2	2979	RR 1.08, 95% CI [0.33–3.57]	Low certainty
10	Nonpregnant people for whom vitamin D treatment is indicated	Intermittent high-dose vitamin D	Low dose daily vitamin D or no vitamin D	Adverse events	2	3071	RR 1.20, 95% CI [0.71–2.03]	Low certainty
				Risk of a fracture	5	25 914	RR 1.08, 95% CI [0.98–1.19]	High certainty
				Incidence of fractures	7	9835	IRR 0.96, 95% CI [0.75–1.21]	—
				Risk of fall	6	14 018	RR 1.01, 95% CI [0.93–1.10]	Low certainty
				Incidence of falls	6	30 268	IRR 1.05, 95% CI [0.96–1.13]	—
				Risk of a respiratory infection	5	12 893	RR 1.00, 95% CI [0.98–1.03]	Moderate certainty
				Incidence of respiratory infections	4	17 550	IRR 0.98, 95% CI [0.88–1.03]	—
				Nephrolithiasis	3	26 596	RR 1.00, 95% CI [0.84–1.19]	High certainty
				Kidney Disease	2	5829	RR 0.64, 95% CI [0.28–1.47]	Low certainty

Abbreviations: CVD, cardiovascular disease; FBS, fasting blood sugar; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HbA1c, glycated hemoglobin (A1c); IRR, incidence rate ratio; MD, mean difference; MI, myocardial infarction; OGTT, oral glucose tolerance test; RR, relative risk.

cancer (15 studies (19, 54, 55, 62, 65, 68, 73, 76, 78, 84, 86, 88, 91, 93, 94), high certainty); any fracture (13 studies (54, 59, 62-64, 66, 69, 70, 75, 82, 85, 90, 91), high certainty); or kidney disease (4 studies (19, 86, 91, 100), high certainty) with vitamin D supplementation. Vitamin D supplementation was not associated with all-cause mortality (13 studies (18, 19, 52, 54, 56, 62, 68, 75, 80, 91, 93, 94, 100), high certainty); however, there was a significant subgroup effect by dose ($P = .003$) and by calcium co-administration ($P = .021$), with vitamin D alone and higher-dose vitamin D associated with increased risk of death.

Forest plots are shown in Supplementary Fig. S2.3, funnel plots are shown in Supplementary Figs. S3.1 and S3.2, summary of findings are described in Supplementary Table S5.3, and summary of studies without sufficient data for meta-analysis are shown in Supplementary Table S6 (17).

Question 5. Should Vitamin D Supplementation vs No Vitamin D Supplementation Be Used for Adults Aged 50 to 74 Years Only When 25(OH)D Levels Are Below a Threshold?

Three studies with 8274 participants with reported outcomes below a threshold 25(OH)D of 20 ng/mL (50 nmol/L) were identified.

Vitamin D supplementation was not associated with a significant effect on cardiovascular events (3 studies (18, 19, 92), high certainty), total cancer (2 studies (18, 19), high certainty), mortality (2 studies (19, 80), high certainty), fracture (1 study (82), high certainty), stroke (1 study (19), moderate certainty), MI (1 study (19), moderate certainty), or nephrolithiasis/kidney disease (1 study (19), low certainty). Forest plots are shown in Supplementary Fig. S2.4, and summary of findings are described in Supplementary Table S5.4 (17).

Question 6. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used by Adults Ages ≥ 75 Years?

Forty-three studies (19, 56, 64, 74, 80, 82, 90, 100-134) from 36 RCTs with 71 473 participants were identified. Study characteristics and RoB are provided in Supplementary Tables S3.4 and S4.4, respectively (17).

There was a trend with vitamin D to reduce the risk of mortality (25 studies (19, 56, 64, 80, 100, 101, 104, 105, 107, 109, 110, 112, 113, 115-117, 120-124, 128, 130, 132, 133), RR 0.96 [0.93, 1.00], high certainty). In absolute terms, the reduction was 6 fewer deaths per 1000 (from 11 fewer to 0 fewer). Vitamin D was associated with a decreased incidence of falls (15 studies (100, 103, 106, 111, 112, 114, 115, 119, 126, 127, 130-132, 134), IRR 0.91, 95% CI [0.81, 0.99]). Subgroup analysis suggested that the reduction in falls was noted in studies at high RoB, with calcium co-administration, standard vitamin D dose, and in institutionalized participants. There were no significant differences in the risk of a person falling (16 studies (64, 100, 102, 103, 106, 107, 109, 111-113, 116, 119, 126, 127, 129, 130), moderate certainty). Subgroup analyses suggested a potential for increased risk of a participant having a fall in studies using high vitamin D doses and for lower risk in studies using calcium co-administration.

Vitamin D was not associated with incidence of fractures (14 studies (104, 110, 113, 115, 118, 119, 122, 125-127,

129, 130, 132, 135)), but there was a significant interaction with subgroup analysis by calcium co-administration, suggesting a decreased incidence of falls with calcium co-administration ($P = .005$).

There were no significant differences with vitamin D in the risk of fracture (15 studies (64, 82, 107, 109, 112, 114, 117, 119, 120, 122, 123, 126, 128, 130, 131, 136), high certainty), kidney stones (3 studies, moderate certainty), or kidney disease (3 studies, moderate certainty).

Two studies reported on RTI. In a subgroup of 248 participants aged ≥ 75 years from the DO-HEALTH trial receiving 2000 IU vitamin D3 vs placebo daily, the crude IRR for respiratory infections was 1.02 (99% CI [0.89, 1.16]) (104). Adjustment for age, sex, prior fall, body mass index, study site, and offset of log person-years revealed an IRR of 1.15 (99% CI [0.94, 1.41]).

Camargo et al (2020) (108) reported findings from the ViDA study, an RCT comparing 200 000 IU vitamin D3 followed by 100 000 IU vitamin D3 monthly to placebo. In a subgroup of 568 participants ≥ 75 years old, the adjusted hazard ratio for a participant developing a RTI in the vitamin D group compared to placebo was 1.11 (95% CI [0.94-1.30]) (adjusted for age, sex, and ethnicity).

Forest plots are shown in Supplementary Fig. S2.5, funnel plot for mortality is shown in Supplementary Fig. S3.3, and summary of findings are described in Supplementary Table S5.5 (17).

Question 7. Should Vitamin D Supplementation vs No Vitamin D Supplementation Be Used by Adults Aged ≥ 75 Years Only When 25(OH)D Levels Are Below a Threshold?

Three studies contributing 589 participants with reported outcomes below a threshold 25(OH)D of 20 ng/mL (50 nmol/L) were identified.

In this subgroup, vitamin D supplementation was not associated with significant differences in risk of mortality (3 studies (19, 105, 121), very low certainty) or falls (2 studies (111, 127), very low certainty), kidney stone or kidney disease (1 study (19), very low certainty).

Forest plots are shown in Supplementary Fig. S2.6, and summary of findings are described in Supplementary Table S5.6 (17).

Question 8. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used During Pregnancy?

Ten RCTs (137-146) with 2928 participants were included. Study characteristics and RoB are provided in Supplementary Tables S3.5 and S4.5, respectively (17).

There was no statistically significant difference for pre-eclampsia and gestational hypertension (8 studies (137-143, 145, 147), low certainty), intra-uterine mortality (4 studies (139, 140, 144, 145), moderate certainty), neonatal mortality (3 studies (140, 144, 145), moderate certainty), preterm birth (6 studies (138-142, 145), low certainty), or small-for-gestational-age (SGA) births (5 studies (139, 141, 142, 145, 146), low certainty). However, absolute risk differences suggested potential important benefit for all outcomes.

Roth et al 2018 (29) reported 1/259 maternal death in the placebo arm and 1/1007 death in the other 4 arms receiving different doses of supplemental vitamin D during pregnancy ($P = .37$). For

adverse events, Roth et al (2018) reported that there were no cases of symptomatic hypercalcemia in placebo or treatment groups. Among participants with asymptomatic hypercalcemia, there were no cases of nephrolithiasis. Yu et al 2009 (144) reported that one participant on vitamin D developed significant proteinuria and was diagnosed with nephritic syndrome. There was no kidney disease reported in the placebo group.

Forest plots are shown in Supplementary Fig. S2.7, and summary of findings are described in Supplementary Table S5.7 (17).

Question 9. Should Vitamin D Supplementation vs No Vitamin D Supplementation Be Used During Pregnancy Only When 25(OH)D Levels Are Below a Threshold?

There were no studies that reported outcomes of interest by 25(OH)D level below a threshold in this population.

Question 10. Should Empiric Vitamin D Supplementation vs No Empiric Vitamin D Supplementation Be Used for Adults With Prediabetes (by Glycemic Criteria)?

Twenty-four studies (148-171) with 5549 participants were identified. A trial by Kawahara (2022) that used eldelcalcitol (172) was excluded from the primary analyses but was included in sensitivity analyses (Supplementary Fig. S2.8h (17)). Study characteristics and RoB are provided in Supplementary Tables S3.6 and S4.6, respectively (17).

Vitamin D supplementation was associated with reduced risk of incident diabetes (10 studies (148-150, 152, 157, 159, 161, 164, 167, 170), RR 0.90, 95% CI [0.81, 1.00], moderate certainty). There was no association with all-cause mortality (2 studies (156, 157), low certainty), cardiovascular disease events (2 studies (151, 157), low certainty), fractures (1 study (160), very low certainty), or adverse events (nephrolithiasis) (2 studies (156, 157), low certainty).

Vitamin D supplementation was associated with a decrease in fasting blood glucose (12 studies (149, 150, 152, 157, 159, 162-164, 167, 169-171), mean difference -5.29 mg/dL, 95% CI $[-7.90, -2.68]$) and 2-hour blood glucose after a 75-gram oral glucose load (13 studies (149, 150, 152, 157, 159, 162-165, 167, 169-171), mean difference -7.61 mg/dL, 95% CI $[-12.55, -2.66]$). Studies at increased RoB showed more reduction in 2-hour blood glucose. There was no statistically significant effect of vitamin D supplementation in glycated hemoglobin (HbA1c) (15 studies (148-150, 152-155, 157, 159, 161-163, 169-171), mean difference -0.05% , 95% CI $[-0.10, 0.01]$). Sollid et al (2014) (168) reported outcomes below the threshold of 20 ng/mL (50 nmol/L) and did not show statistically significant changes in HbA1c, fasting blood sugar, or 2-hour glucose.

Forest plots are shown in Supplementary Fig. S2.8, and summary of findings are described in Supplementary Table S5.8 (17).

Question 11. Should a Daily, Lower-Dose Vitamin D vs Nondaily (Ie, Intermittent), Higher-Dose Vitamin D Be Used for Nonpregnant People for Whom Vitamin D Treatment Is Indicated?

Two studies (173, 174) with 537 participants were initially identified. The eligibility criteria were expanded to include

trials comparing intermittent high-dose vitamin D to no vitamin D. Nineteen studies (38, 64, 68, 74, 80, 83, 85, 91, 100, 108, 113, 116, 122, 130-132, 134, 173, 174) from 15 RCTs and 53 527 participants were included in the analysis. Study characteristics and RoB are provided in Supplementary Tables S3.7 and S4.7, respectively (17).

Vitamin D was not associated with significant differences in RTI (5 studies (38, 68, 91, 108, 173), moderate certainty), fracture (5 studies (64, 91, 122, 130, 131), high certainty), renal stones (3 studies (74, 80, 85), high certainty), or kidney disease (2 studies (91, 100), low certainty). Vitamin D was not associated with differences in risk for falls (6 studies (64, 85, 91, 113, 116, 130), low certainty); however, there was a subgroup effect by intermittency ($P = .010$), with intermittent administration of high-dose vitamin D (at > 12 -week intervals) showing increased risk of falls compared to less frequent administration of lower doses of vitamin D.

Forest plots are shown in Supplementary Fig. S2.9, and summary of findings are described in Supplementary Table S5.9 (17).

Question 12. Should Screening With a 25(OH)D Test (With Vitamin D Supplementation/Treatment Only if Below a Threshold) vs No Screening With a 25(OH)D Test Be Used for Healthy Adults?

We did not identify studies that evaluated the effect of a screening strategy with serum 25(OH)D on outcomes of interest. Indirect evidence from studies that evaluated the effectiveness of vitamin D in this population can be derived from Questions 2 to 7.

Question 13. Should Screening With a 25(OH)D Test (With Vitamin D Supplementation/Treatment Only if Below a Threshold) vs No Screening With a 25(OH)D Test Be Used for Adults With Dark Complexion?

We did not identify studies that evaluated the effect of a screening strategy with serum 25(OH)D on outcomes of interest. Indirect evidence from studies that evaluated the effectiveness of vitamin D in groups that may belong to this population is summarized in Supplementary Table S7 (17).

Question 14. Should Screening With a 25(OH)D Test (With Vitamin D Supplementation/Treatment Only if Below a Threshold) vs No Screening With a 25(OH)D Test Be Used for Adults With Obesity?

We did not identify studies that evaluated the effect of a screening strategy with serum 25(OH)D on outcomes of interest. Indirect evidence from studies that evaluated the effectiveness of vitamin D in this population is summarized in Supplementary Table S7 (17).

Discussion

Main Findings

This systematic review summarized evidence to support the development of a clinical practice guideline by the Endocrine Society on vitamin D for the prevention of disease.

In children and adolescents (ages 1-18), evidence suggested reduction in incidence rate of RTIs. We did not find trial evidence supporting the prevention of rickets, although extensive indirect evidence exists about this important outcome and trials are unlikely to be conducted in this context (175).

While there was no evidence to support empiric vitamin D supplementation (ie, above the Institute of Medicine RDI and without measuring 25(OH)D levels) in healthy adults aged 19 to 75, baseline levels of 25(OH)D in many of the included trials can be considered adequate, likely reflecting adherence to the RDI recommendations in a healthy study population without risk factors for low vitamin D status. This systematic review identified a very small, but likely clinically important reduction in mortality in the subgroup of adults 75 years or older. Dosing in the available trials varied considerably; hence, identifying an optimal dose was not feasible. However, our analyses suggest that higher intermittent dosing may be associated with increased falls, implying that daily dosing is preferable. In pregnant women, low certainty evidence suggests possible benefits on various maternal, fetal, and neonatal outcomes.

In the United States, 1 in 3 adults has prediabetes (176) and the evidence from longitudinal observational studies consistently shows that higher levels of serum 25(OH)D are inversely associated with risk of developing diabetes. This systematic review suggests a reduction in the incidence of diabetes associated with vitamin D. Three trials were specifically designed for diabetes prevention. An individual participant data meta-analysis of these 3 trials showed that vitamin D reduced the risk for diabetes by 15% with a 3-year absolute risk reduction of 3.3%. In this population, vitamin D increased the likelihood of regression to normal glucose regulation by 30% (rate ratio, 1.30, 95% CI [1.16, 1.46]) (177).

We did not identify screening trials that can provide evidence on the benefits and harms of screening with blood 25(OH)D in the general population and other selected populations.

Strength and Limitations

A limitation of this systematic review is the frequent absence of baseline and postsupplementation 25(OH)D levels in many included studies. In those trials that did report baseline 25(OH)D levels, most were in ranges considered sufficient for many outcomes. While it is assumed that those with low 25(OH)D levels will benefit more from supplementation than those with higher levels, this has not been rigorously demonstrated. Additionally, it is possible that different target levels of 25(OH)D are required for optimal outcomes in different tissues. For example, whereas skeletal effects are dependent upon promoting intestinal calcium absorption, the effects on the immune system are thought to be direct. Another factor that may affect outcomes is latency; for example, effects on infections may require short-term vitamin D, whereas other outcomes, such as malignancies and cardiac disease, may require a more prolonged exposure to “optimal” levels of 25(OH)D. Additional limitations reflect the study design in that the analysis was based on individuals with an event in some trials (eg, number of patients who fell), while in other trials the analysis was based on events (eg, number of falls). These types of analyses could not be combined.

This review focused on the general population without comorbidities (eg, skeletal disease, lung disease, acute illness, etc), or disorders that effect vitamin D absorption, activation, or metabolism. Thus, the review is relevant to the general (healthy) population rather than patients with specific disease states. A limitation of the review was that the included trials compared vitamin D supplementation to control groups not receiving vitamin D and could not fully account for exposure

to vitamin D via sun exposure or dietary intake. Furthermore, given the availability of vitamin D supplements and other guideline recommendations, many trial participants may have taken supplemental vitamin D on their own, and in several trials, participants were allowed to remain on outside of the study vitamin D supplements at doses not higher than the RDI.

Conclusion

The current evidence suggests potential benefits of empiric vitamin D in children, individuals 75 years or older, pregnant women, and adults with prediabetes.

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Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Disclosures

V.P.S., T.N., Y.A., S.S., Ma.Fa., Y.Z., Mo.Fi., M.S., Z.W.: nothing to declare.

R.S.: Disclosures (2020-2024):

- Health Research Council of New Zealand: Investigator on arterial function and cardiovascular disease

M.E.K.: Disclosures (2020-2024):

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- Member: UK Scientific Advisory Committee for Nutrition (SACN)
- Member: Vitamin D Workshop Executive Committee; Co-chair 2024 Workshop

P.L.: Disclosures (2020-2024):

- Abiogen: Speaking Engagement on controversies in vitamin D
- Vitamin D Workshop: Scientific Programme Advisory Board

D.M.M.: Disclosures (2020-2024):

- Amolyt: Consultant for hypoparathyroidism
- American Society for Bone and Mineral Research: Education Committee Member, Chair of the Pediatric Working Group

M.B.D.: Disclosures (2020-2024):

- National Institutes of Health: Investigator on vitamin D action, growth plate
- Endocrine Society: Annual Meeting Steering Committee Member

A.G.P.: Disclosures (2020-2024):

- National Institutes of Health: Investigator on vitamin D
- National Institutes of Health: Data Safety Monitoring Board for melatonin, lifestyle intervention

- National Institutes of Health: Data Safety Monitoring Board for the DISCOVERY study, diabetes risk in children
- Expert testimony for various hospitals on cases that involved diabetes

M.H.M.: *Disclosures (2020-2024)*:

- Society for Vascular Surgery: Methodology Consultant
- American Society of Hematology: Methodology Consultant
- CHEST: Methodology Consultant
- World Health Organization: Methodology Consultant
- Evidence Foundation: Board Member

Data Availability

Original data generated and analyzed during this study are included in the repository listed in references. The data that support the findings of this study are openly available in *figshare* (17).

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