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Clinical Practice Guideline Systematic Review

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

Vishal Paresh Shah,[1] Tarek Nayfeh,[1] Yahya Alsawaf,[1] Samer Saadi,[1] Magdoleen Farah,[1] Ye Zhu,[1] Mohammed Firwana,[1] Mohamed Seisa,[1] Zhen Wang,[1] Robert Scragg,[2] Mairead E. Kiely,[3] Paul Lips,[4] Deborah M. Mitchell,[5] Marie B. Demay,[6] Anastassios G. Pittas,[7] and Mohammad Hassan Murad[1]

[1]Mayo Clinic Evidence-Based Practice Center, Rochester, MN 55905, USA
[2]School of Population Health, University of Auckland, Auckland 1023, New Zealand
[3]Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences and INFANT Research Centre, University College Cork, Cork T12 Y337, Ireland
[4]Internal Medicine, Endocrine Section, Amsterdam University Medical Center, Amsterdam 1007 MB, The Netherlands
[5]Pediatric Endocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[6]Endocrine Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[7]Divisions of Endocrinology, Diabetes and Metabolism, Tufts-New England Medical Center, Boston, MA 02116, USA

Correspondence: Vishal Shah, MD, MPH, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. Email: shah.vishal1@mayo.edu.

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 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 lumber 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 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 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 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 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	12	12 951	RR 0.94, 95% CI [0.87–1.02]	Very low certainty
				Incidence of respiratory infections	3	428	IRR 0.64, 95% CI [0.51–0.82]	—
				Lower respiratory tract infections	6	10 356	RR 0.93, 95% CI [0.83–1.04]	Moderate certainty
				Tuberculosis	2	10 533	RR 0.67, 95% CI [0.14–3.11]	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
				Risk of a respiratory infection	2	17 074	RR 1.02, 95% CI [0.96–1.08]	Moderate certainty
				Incidence of respiratory infections	4	1120	IRR 0.95, 95% CI [0.83–1.07]	Very low certainty
3	Nonpregnant adults < 50 years old with 25(OH)D below a threshold	Vitamin D	No vitamin D	Fatigue amelioration	1	120	RR 1.49, 95% CI [1.08–1.94]	Very low certainty
4	Adults 50-74 years old	Vitamin D	No vitamin D	Risk of a fracture	13	87 161	RR 0.97, 95% CI [0.91–1.03]	High certainty
				All-cause mortality	13	81 695	RR 1.07, 95% CI [0.95–1.20]	High certainty
				Cancer	15	91 223	RR 1.00, 95% CI [0.97–1.03]	High certainty
				CVD events	14	80 547	RR 1.00, 95% CI [0.93–1.08]	High certainty
				Stroke	7	68 273	RR 0.95, 95% CI [0.83–1.09]	High certainty
				MI	7	38 558	RR 1.00, 95% CI [0.83–1.20]	High certainty
				Adverse events (nephrolithiasis)	10	87 524	RR 1.10, 95% CI [1.00–1.19]	High certainty
				Adverse events (kidney disease)	4	28 610	RR 1.04, 95% CI [0.76–1.42]	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	1	4932	RR 1.01, 95% CI [0.81–1.24]	High certainty
				All-cause mortality	2	7005	RR 1.11, 95% CI [0.85–1.46]	High certainty
				Cancer	2	3339	RR 0.91, 95% CI [0.70–1.19]	High certainty
				CVD events	3	8274	RR 1.02, 95% CI [0.87–1.19]	High certainty
				Stroke	1	1805	RR 1.04, 95% CI [0.39–2.75]	Moderate certainty
				MI	1	1805	RR 0.93, 95% CI [0.38–2.29]	Moderate certainty
				Adverse events	1	1805	RR 1.26, 95% CI [0.77–2.12]	Low certainty
6	Adults ≥ 75 years old	Vitamin D	No vitamin D	Risk of a fracture	15	43 719	RR 1.01, 95% CI [0.94–1.08]	High certainty
				Incidence of fractures	15	25 945	IRR 0.94, 95% CI [0.81–1.09]	—
				Risk of a fall	16	12 342	RR 0.97, 95% CI [0.91–1.03]	Moderate certainty
				Incidence of falls	14	33 759	IRR 0.90, 95% CI [0.79–0.99]	—
				All-cause mortality	25	49 879	RR 0.96, 95% CI [0.93–1.00]	High certainty
				Respiratory infections	1	821	HR 1.11, 95% CI [0.94–1.30]	Low certainty
				Nephrolithiasis	3	5634	RR 0.94, 95% CI [0.54–1.65]	Moderate certainty
				Kidney disease	3	5634	RR 0.76, 95% CI [0.44–1.32]	Moderate certainty
7	Adults ≥ 75 years old with a 25(OH)D below a threshold	Vitamin D	No vitamin D	Falls	2	276	RR 0.65, 95% CI [0.40–1.05]	Very low certainty
				All-cause mortality	3	589	RR 0.88, 95% CI [0.46–1.67]	Very low certainty
				Adverse events	1	196	RR 1.26, 95% CI [0.26–6.18]	Very low certainty
8	Pregnant women	Vitamin D	No vitamin D	Preeclampsia and gestational hypertension	8	2674	RR 0.73, 95% CI [0.46–1.15]	Low certainty
				Intra-uterine mortality	4	1738	RR 0.70, 95% CI [0.34–1.46]	Moderate certainty
				Neonatal mortality	3	1576	RR 0.57, 95% CI [0.22–1.49]	Moderate certainty
				Preterm birth	6	2085	RR 0.73, 95% CI [0.39–1.36]	Low certainty
				Small for gestational age	5	2355	RR 0.78, 95% CI [0.50–1.20]	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
				Adverse events	2	3071	RR 1.20, 95% CI [0.71–2.03]	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	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 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 preeclampsia 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 eldecalcitol (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: 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).

References

1. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266-281.
2. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol*. 2014;21(3):319-329.
3. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81(3):353-373.
4. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):1080S-1086S.
5. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The health effects of vitamin D supplementation: evidence from human studies. *Nat Rev Endocrinol*. 2022;18(2):96-110.
6. Prietl B, Treiber G, Pieber T, Amrein K. Vitamin D and immune function. *Nutrients*. 2013;5(7):2502-2521.
7. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14(5):342-357.
8. Wang TJ, Pencina MJ, Booth SL, *et al*. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117(4):503-511.
9. Rosen CJ, Adams JS, Bikle DD, *et al*. The nonskeletal effects of vitamin D: an endocrine society scientific statement. *Endocr Rev*. 2012;33(3):456-492.
10. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol*. 2017;13(8):466-479.
11. Health Council of the Netherlands. Evaluation of the dietary reference values for vitamin D. 2012. https://www.healthcouncil.nl/documents/advisory-reports/2012/09/26/evaluation-of-the-dietary-reference-values-for-vitamin-d
12. *WHO Antenatal Care Recommendations for a Positive Pregnancy Experience: Nutritional Interventions Update: Vitamin D Supplements During Pregnancy*. Human Reproduction Programme, World Health Organization; 2020.
13. Ross AC, Manson JE, Abrams SA, *et al*. The 2011 report on dietary reference intakes for calcium and vitamin D from the institute of medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53-58.
14. Paxton GA, Teale GR, Nowson CA, *et al*. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. *Med J Aust*. 2013;198(3):142-143.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
16. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10(1):89.
17. Shah V., Nayfeh T, Alsawaf Y, *et al*. Supplemental file for a systematic review supporting the Endocrine Society clinical practice guidelines on vitamin D. *figshare*. Posted April 30, 2024. doi:10.6084/m9.figshare.25723914
18. Scragg R, Stewart AW, Waayer D, *et al*. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. *JAMA Cardiol*. 2017;2(6):608.
19. Manson JE, Cook NR, Lee IM, *et al*. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33-44.
20. Wells G, Shea B, O'Connell D, *et al*. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis*. The Ottawa Health Research Institute; 2011
21. Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;28:l4898.
22. Guyatt G, Oxman AD, Sultan S, *et al*. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013;66(2):151-157.
23. Huang YN, Chi H, Chiu NC, *et al*. A randomized trial of vitamin D supplementation to prevent seasonal influenza and enterovirus infection in children. *J Microbiol Immunol Infect*. 2022;55(5):803-811.
24. Singh N, Kamble D, Mahantshetti NS. Effect of vitamin D supplementation in the prevention of recurrent pneumonia in under-five children. *Indian J Pediatr*. 2019;86(12):1105-1111.
25. Loeb M, Dang AD, Thiem VD, *et al*. Effect of vitamin D supplementation to reduce respiratory infections in children and adolescents in Vietnam: a randomized controlled trial. *Influenza Other Respir Viruses*. 2019;13(2):176-183.
26. Manaseki-Holland S, Qader G, Isaq Masher M, *et al*. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial: vitamin D supplement during childhood pneumonia. *Trop Med Int Health*. 2010;15(10):1148-1155.
27. Mandlik R, Mughal Z, Khadilkar A, *et al*. Occurrence of infections in schoolchildren subsequent to supplementation with vitamin D-calcium or zinc: a randomized, double-blind, placebo-controlled trial. *Nutr Res Pract*. 2020;14(2):117.
28. Camargo CA, Ganmaa D, Frazier AL, *et al*. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics*. 2012;130(3):e561-e567.
29. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr*. 2010;91(5):1255-1260.
30. Di Mauro A, Baldassarre ME, Capozza M, *et al*. THE IMPACT OF VITAMIN D SUPPLEMENTATION IN PAEDIATRIC PRIMARY CARE ON RECURRENT RESPIRATORY INFECTIONS: a RANDOMIZED CONTROLLED TRIAL. *EuroMediterranean Biomed J*. 2019;13(44):194-199.
31. Chowdhury F, Shahid ASMSB, Tabassum M, *et al*. Vitamin D supplementation among Bangladeshi children under-five years of age hospitalised for severe pneumonia: a randomised placebo controlled trial. *PLoS One*. 2021;16(2):e0246460.
32. Dubnov-Raz G, Hemilä H, Cohen AH, Rinat B, Choleva L, Constantini NW. Vitamin D supplementation and upper respiratory tract infections in adolescent swimmers: a randomized controlled trial. *Pediatr Exerc Sci*. 2015;27(1):113-119.
33. Gupta P, Dewan P, Shah D, *et al*. Vitamin D supplementation for treatment and prevention of pneumonia in under-five children: a randomized double-blind placebo controlled trial. *Indian Pediatr*. 2016;53(11):967-976.

34. Jadhav S, Khanwelkar C, Jadhav A, Seshla S. Vitamin D supplementation in the prevention of recurrent acute respiratory tract infections in children aged<5 years. *J Med Sci*. 2021;41(3):129.
35. Middelkoop K, Stewart J, Walker N, *et al*. Vitamin D supplementation to prevent tuberculosis infection in South African schoolchildren: multicenter phase 3 double-blind randomized placebo-controlled trial (ViDiKids). *Int J Infect Dis*. 2023;134:63-70.
36. Ganmaa D, Uyanga B, Zhou X, *et al*. Vitamin D supplements for prevention of tuberculosis infection and disease. *N Engl J Med*. 2020;383(4):359-368.
37. Gaffney-Stomberg E, Lutz LJ, Rood JC, *et al*. Calcium and vitamin D supplementation maintains parathyroid hormone and improves bone density during initial military training: a randomized, double-blind, placebo controlled trial. *Bone*. 2014;68:46-56.
38. Murdoch DR, Slow S, Chambers ST, *et al*. Effect of vitamin D $_3$ supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA*. 2012;308(13):1333.
39. Andersen R, Mølgaard C, Skovgaard LT, *et al*. Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. *Br J Nutr*. 2008;100(1):197-207.
40. Islam MZ, Shamim AA, Viljakainen HT, *et al*. Effect of vitamin D, calcium and multiple micronutrient supplementation on vitamin D and bone status in Bangladeshi premenopausal garment factory workers with hypovitaminosis D: a double-blinded, randomised, placebo-controlled 1-year intervention. *Br J Nutr*. 2010;104(2):241-247.
41. Nowak A, Boesch L, Andres E, *et al*. Effect of vitamin D3 on self-perceived fatigue: a double-blind randomized placebo-controlled trial. *Medicine (Baltimore)*. 2016;95(52):e5353.
42. Jorde R, Sneve M, Torjesen PA, Figenschau Y, Hansen JB, Grimnes G. No significant effect on bone mineral density by high doses of vitamin D3 given to overweight subjects for one year. *Nutr J*. 2010;9(1):1.
43. Gaffney-Stomberg E, Hughes JM, Guerriere KI, *et al*. Once daily calcium (1000 mg) and vitamin D (1000 IU) supplementation during military training prevents increases in biochemical markers of bone resorption but does not affect tibial microarchitecture in army recruits. *Bone*. 2022;155:116269.
44. Brunvoll SH, Nygaard AB, Ellingjord-Dale M, *et al*. Prevention of COVID-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement: quadruple blinded, randomised placebo controlled trial. *BMJ*. 2022;378:e071245.
45. Wamberg L, Pedersen SB, Richelsen B, Rejnmark L. The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study. *Calcif Tissue Int*. 2013;93(1):69-77.
46. Lewis RM, Redzic M, Thomas DT. The effects of season-long vitamin D supplementation on collegiate swimmers and divers. *Int J Sport Nutr Exerc Metab*. 2013;23(5):431-440.
47. Laaksi I, Ruohola J, Mattila V, Auvinen A, Ylikomi T, Pihlajamäki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *J Infect Dis*. 2010;202(5):809-814.
48. Jung H, Seo MW, Lee S, Kim S, Song J. Vitamin D3 supplementation reduces the symptoms of upper respiratory tract infection during winter training in vitamin D-insufficient taekwondo athletes: a randomized controlled trial. *Int J Environ Res Public Health*. 2018;15(9):2003.
49. Goodall EC, Granados AC, Luinstra K, *et al*. Vitamin D3and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. *BMC Infect Dis*. 2014;14(1):273.
50. Simpson S, Van Der Mei I, Stewart N, Blizzard L, Tettey P, Taylor B. Weekly cholecalciferol supplementation results in significant reductions in infection risk among the vitamin D deficient: results from the CIPRIS pilot RCT. *BMC Nutr*. 2015;1(1):7.
51. Wood AD, Secombes KR, Thies F, *et al*. A parallel group double-blind RCT of vitamin D3 assessing physical function: is the biochemical response to treatment affected by overweight and obesity? *Osteoporos Int*. 2014;25(1):305-315.
52. Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of vitamin D3 supplementation in African American women. *Arch Intern Med*. 2005;165(14):1618.
53. Peila R, Xue X, Cauley JA, *et al*. A randomized trial of calcium plus vitamin D supplementation and risk of ductal carcinoma in situ of the breast. *JNCI Cancer Spectrum*. 2021;5(4):pkab072.
54. Baron JA, Barry EL, Mott LA, *et al*. A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*. 2015;373(16):1519-1530.
55. Cauley JA, Chlebowski RT, Wactawski-Wende J, *et al*. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the women's health initiative. *J Womens Health*. 2013;22(11):915-929.
56. LaCroix AZ, Kotchen J, Anderson G, *et al*. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the women's health initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2009;64A(5):559-567.
57. Chlebowski RT, Johnson KC, Kooperberg C, *et al*. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst*. 2008;100(22):1581-1591.
58. Wactawski-Wende J, Assaf AR, Margolis KL, *et al*. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696.
59. Jackson RD, Robbins J, Blanchette P, *et al*. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.
60. Tang JY, Fu T, LeBlanc E, *et al*. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. *J Clin Oncol*. 2011;29(22):3078-3084.
61. Hsia J, Heiss G, Ren H, *et al*. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115(7):846-854.
62. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab*. 2001;86(8):3618-3628.
63. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337(10):670-676.
64. Khaw KT, Stewart AW, Waayer D, *et al*. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. *Lancet Diabetes Endocrinol*. 2017;5(6):438-447.
65. Lappe J, Watson P, Travers-Gustafson D, *et al*. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. *JAMA*. 2017;317(12):1234.
66. Salovaara K, Tuppurainen M, Kärkkäinen M, *et al*. Effect of vitamin D3 and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial-the OSTPRE-FPS. *J Bone Miner Res*. 2010;25(7):1487-1495.
67. Witham MD, Dove FJ, Khan F, Lang CC, Belch JJF, Struthers AD. Effects of vitamin D supplementation on markers of vascular function after myocardial infarction—a randomised controlled trial. *Int J Cardiol*. 2013;167(3):745-749.
68. Rake C, Gilham C, Bukasa L, *et al*. High-dose oral vitamin D supplementation and mortality in people aged 65–84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation. *Health Technol Assess*. 2020;24(10):1-54.
69. Macdonald HM, Wood AD, Aucott LS, *et al*. Hip bone loss is attenuated with 1000 IU but not 400 IU daily vitamin D3: a 1-year

double-blind RCT in postmenopausal women: VITAMIN D RCT ON BONE. *J Bone Miner Res*. 2013;28(10):2202-2213.
70. Komulainen MH, Heikkinen AM, Alhava E, Honkanen R, Saarikoski S. HRT and vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas*. 1998;31(1):45-54.
71. Ammann EM, Drake MT, Haraldsson B, *et al*. Incidence of hematologic malignancy and cause-specific mortality in the Women's health initiative randomized controlled trial of calcium and vitamin D supplementation: hematologic malignancy in WHI CaD trial. *Cancer*. 2017;123(21):4168-4177.
72. Ding EL, Mehta S, Fawzi WW, Giovannucci EL. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's health initiative randomized trial. *Int J Cancer*. 2007;122(8):1690-1694.
73. Scragg R, Khaw KT, Toop L, *et al*. Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the vitamin D assessment randomized clinical trial. *JAMA Oncol*. 2018;4(11):e182178.
74. Malihi Z, Lawes CMM, Wu Z, *et al*. Monthly high-dose vitamin D supplementation does not increase kidney stone risk or serum calcium: results from a randomized controlled trial. *Am J Clin Nutr*. 2019;109(6):1578-1587.
75. Hin H, Tomson J, Newman C, *et al*. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. *Osteoporos Int*. 2017;28(3):841-851.
76. Komulainen M, Kröger H, Tuppurainen MT, *et al*. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab*. 1999;84(2):546-552.
77. Donneyong MM, Hornung CA, Taylor KC, *et al*. Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the Women's health initiative. *Circ: Heart Failure*. 2015;8(1):49-56.
78. Passarelli MN, Karagas MR, Mott LA, Rees JR, Barry EL, Baron JA. Risk of keratinocyte carcinomas with vitamin D and calcium supplementation: a secondary analysis of a randomized clinical trial. *Am J Clin Nutr*. 2020;112(6):1532-1539.
79. LeBoff MS, Chou SH, Ratliff KA, *et al*. Supplemental vitamin D and incident fractures in midlife and older adults. *N Engl J Med*. 2022;387(4):299-309.
80. Neale RE, Baxter C, Romero BD, *et al*. The D-health trial: a randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol*. 2022;10(2):120-128.
81. Blondon M, Rodabough RJ, Budrys N, *et al*. The effect of calcium plus vitamin D supplementation on the risk of venous thromboembolism: from the Women's health initiative randomized controlled trial. *Thromb Haemost*. 2015;113(05):999-1009.
82. Waterhouse M, Ebeling PR, McLeod DSA, *et al*. The effect of monthly vitamin D supplementation on fractures: a tertiary outcome from the population-based, double-blind, randomised, placebo-controlled D-health trial. *Lancet Diabetes Endocrinol*. 2023;11(5):324-332.
83. Pham H, Waterhouse M, Baxter C, *et al*. The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: an analysis of data from the D-health trial. *Lancet Diabetes Endocrinol*. 2021;9(2):69-81.
84. Ali S, Pham H, Waterhouse M, *et al*. The effect of vitamin D supplementation on risk of keratinocyte cancer: an exploratory analysis of the D-health randomized controlled trial. *Br J Dermatol*. 2022;187(5):667-675.
85. Hansen KE, Johnson RE, Chambers KR, *et al*. Treatment of vitamin D insufficiency in postmenopausal women: a randomized clinical trial. *JAMA Intern Med*. 2015;175(10):1612.
86. Wood AD, Secombes KR, Thies F, *et al*. Vitamin D $_3$ supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab*. 2012;97(10):3557-3568.
87. Aloia JF, Islam S, Mikhail M. Vitamin D and acute respiratory infections—the PODA trial. *Open Forum Infect Dis*. 2019;6(9):ofz228.
88. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85(6):1586-1591.
89. Aloia JF, Rubinova R, Fazzari M, Islam S, Mikhail M, Ragolia L. Vitamin D and falls in older African American women: the PODA randomized clinical trial. *J Am Geriatr Soc*. 2019;67(5):1043-1049.
90. LeBoff MS, Murata EM, Cook NR, *et al*. VITamin D and OmegA-3 TriaL (VITAL): effects of vitamin D supplements on risk of falls in the US population. *J Clin Endocrinol Metab*. 2020;105(9):2929-2938.
91. Joseph P, Pais P, Gao P, *et al*. Vitamin D supplementation and adverse skeletal and non-skeletal outcomes in individuals at increased cardiovascular risk: results from the international polycap study (TIPS)-3 randomized controlled trial. *Nutr Metab Cardiovasc Dis*. 2023;33(2):434-440.
92. Thompson B, Waterhouse M, English DR, *et al*. Vitamin D supplementation and major cardiovascular events: D-health randomised controlled trial. *BMJ*. 2023;381:e075230.
93. Virtanen JK, Nurmi T, Aro A, *et al*. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish vitamin D trial: a randomized controlled trial. *Am J Clin Nutr*. 2022;115(5):1300-1310.
94. Aloia J, Fazzari M, Islam S, *et al*. Vitamin D supplementation in elderly black women does not prevent bone loss: a randomized controlled trial. *J Bone Miner Res*. 2018;33(11):1916-1922.
95. Harvey NC, D'Angelo S, Paccou J, *et al*. Calcium and vitamin D supplementation are not associated with risk of incident ischemic cardiac events or death: findings from the UK biobank cohort. *J Bone Miner Res*. 2018;33(5):803-811.
96. Prentice RL, Pettinger MB, Jackson RD, *et al*. Health risks and benefits from calcium and vitamin D supplementation: women's health initiative clinical trial and cohort study. *Osteoporos Int*. 2013;24(2):567-580.
97. Sha S, Nguyen TMN, Kuznia S, *et al*. Real-world evidence for the effectiveness of vitamin D supplementation in reduction of total and cause-specific mortality. *J Intern Med*. 2023;293(3):384-397.
98. Park SM, Li T, Wu S, Li WQ, Qureshi AA, Cho E. Vitamin D intake and risk of skin cancer in US women and men. *PLoS One*. 2016;11(8):e0160308.
99. O'Brien KM, Keil AP, Harmon QE, *et al*. Vitamin D supplement use and risk of breast cancer by race-ethnicity. *Epidemiology*. 2022;33(1):37-47.
100. Witham MD, Price RJG, Struthers AD, *et al*. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA Intern Med*. 2013;173(18):1672-1679.
101. Avenell A, MacLennan GS, Jenkinson DJ, *et al*. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D $_3$ and/or calcium (RECORD trial). *J Clin Endocrinol Metab*. 2012;97(2):614-622.
102. Bischoff HA, Stähelin HB, Dick W, *et al*. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res*. 2003;18(2):343-351.
103. Bischoff-Ferrari HA, Freystätter G, Vellas B, *et al*. Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. *Am J Clin Nutr*. 2022;115(5):1311-1321.
104. Bischoff-Ferrari HA, Vellas B, Rizzoli R, *et al*. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA*. 2020;324(18):1855.
105. Brazier M, Grados F, Kamel S, *et al*. Clinical and laboratory safety of one year's use of acombination calcium + vitamin D tablet in

ambulatory elderly women with vitamin D insufficiency: results of a mlticenter, rndomized, double-blind, placebo-controlled study. *Clin Ther*. 2005;27(12):1885-1893.
106. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc*. 2007;55(2):234-239.
107. Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age Ageing*. 2007;36(5):507-513.
108. Camargo CA, Sluyter J, Stewart AW, *et al*. Effect of monthly high-dose vitamin D supplementation on acute respiratory infections in older adults: a randomized controlled trial. *Clin Infect Dis*. 2020;71(2):311-317.
109. Chapuy MC, Pamphile R, Paris E, *et al*. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the decalyos II study. *Osteoporos Int*. 2002;13(3):257-264.
110. Chapuy MC, Arlot ME, Duboeuf F, *et al*. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*. 1992;327(23):1637-1642.
111. Dhesi JK, Jackson S, Bearne L, *et al*. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing*. 2004;33(6):589-595.
112. Flicker L, MacInnis RJ, Stein MS, *et al*. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc*. 2005;53(11):1881-1888.
113. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *J Bone Miner Res*. 2012;27(1):170-176.
114. Grant AM, Avenell A, Campbell MK, *et al*. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (randomised evaluation of calcium or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365(9471):1621-1628.
115. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham neck of femur (NONOF) study. *Age Ageing*. 2004;33(1):45-51.
116. Houston DK, Tooze JA, Demons JL, *et al*. Delivery of a vitamin D intervention in homebound older adults using a meals-on-wheels program: a pilot study. *J Am Geriatr Soc*. 2015;63(9):1861-1867.
117. Inkovaara J, Gothoni G, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroid in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age Ageing*. 1983;12(2):124-130.
118. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res*. 2003;19(3):370-378.
119. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing*. 2006;35(5):482-486.
120. Lips P. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 1996;124(4):400.
121. Lips P, Binkley N, Pfeifer M, *et al*. Once-weekly dose of 8400 IU vitamin D3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. *Am J Clin Nutr*. 2010;91(4):985-991.
122. Lyons RA, Johansen A, Brophy S, *et al*. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporos Int*. 2007;18(6):811-818.
123. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *J Bone Miner Res*. 2002;17(4):709-715.
124. Ooms ME, Roose JC, Bezemer D, Van Der Vijgh WJF, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. *J Clin Endocrinol Metab*. 1995;80(4):1052-1058.
125. Peacock M, Liu G, Carey M, *et al*. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab*. 2000;85(9):3011-3019.
126. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int*. 2009;20(2):315-322.
127. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res*. 2000;15(6):1113-1118.
128. Porthouse J, Cockayne S, King C, *et al*. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *BMJ*. 2005;330(7498):1003.
129. Prince RL. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med*. 2008;168(1):103.
130. Sanders KM, Stuart AL, Williamson EJ, *et al*. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815.
131. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology*. 2007;46(12):1852-1857.
132. Trivedi DP. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469-469.
133. Uusi-Rasi K, Patil R, Karinkanta S, *et al*. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med*. 2015;175(5):703.
134. Waterhouse M, Sanguineti E, Baxter C, *et al*. Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-health trial. *J Cachexia Sarcopenia Muscle*. 2021;12(6):1428-1439.
135. Patil R, Kolu P, Raitanen J, *et al*. Cost-effectiveness of vitamin D supplementation and exercise in preventing injurious falls among older home-dwelling women: findings from an RCT. *Osteoporos Int*. 2016;27(1):193-201.
136. Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee M. The effects of an open design on trial participant recruitment, compliance and retention—a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clin Trials*. 2004;1(6):490-498.
137. Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. *Gynecol Obstet Invest*. 1987;24(1):38-42.
138. Naghshineh E, Sheikhaliyan S. Effect of vitamin D supplementation in the reduce risk of preeclampsia in nulliparous women. *Adv Biomed Res*. 2016;5(1):7.
139. Hossain N, Kanani FH, Ramzan S, *et al*. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. *J Clin Endocrinol Metab*. 2014;99(7):2448-2455.
140. Roth DE, Al Mahmud A, Raqib R, *et al*. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3

supplementation in Bangladesh: the AViDD trial. *Nutr J*. 2013;12(1):47.
141. Sablok A, Batra A, Thariani K, *et al*. Supplementation of vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clin Endocrinol*. 2015;83(4):536-541.
142. Corcoy R, Mendoza LC, Simmons D, *et al*. The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: no major benefit shown besides vitamin D sufficiency. *Clin Nutr*. 2020;39(3):976-984.
143. Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The effects of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. *Obstet Gynecol Int*. 2017;2017:1-5.
144. Yu CKH, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clin Endocrinol (Oxf)*. 2009;70(5):685-690.
145. Roth DE, Morris SK, Zlotkin S, *et al*. Vitamin D supplementation in pregnancy and lactation and infant growth. *N Engl J Med*. 2018;379(6):535-546.
146. Brooke OG, Brown IR, Bone CD, *et al*. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *BMJ*. 1980;280(6216):751-754.
147. Cagiran FT, Kali Z. Role of vitamin D on gestational hypertension, diabetes mellitus, timing and mode of delivery. *Diabetes Mellit*. 2023;27:511-526.
148. Barengolts E, Manickam B, Eisenberg Y, Akbar A, Kukreja S, Ciubotaru I. Effect of high-dose vitamin D repletion on glycemic control in African-American males with prediabetes and hypovitaminosis D. *Endocr Pract*. 2015;21(6):604-612.
149. Bhatt SP, Misra A, Pandey RM, Upadhyay AD, Gulati S, Singh N. Vitamin D supplementation in overweight/obese Asian Indian women with prediabetes reduces glycemic measures and truncal subcutaneous fat: a 78 weeks randomized placebo-controlled trial (PREVENT-WIN trial). *Sci Rep*. 2020;10(1):220.
150. Davidson MB, Duran P, Lee ML, Friedman TC. High-dose vitamin D supplementation in people with prediabetes and hypovitaminosis D. *Diabetes Care*. 2013;36(2):260-266.
151. Desouza C, Chatterjee R, Vickery EM, *et al*. The effect of vitamin D supplementation on cardiovascular risk in patients with prediabetes: a secondary analysis of the D2d study. *J Diabetes Complications*. 2022;36(8):108230.
152. Dutta D, Mondal SA, Choudhuri S, *et al*. Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: an open label randomized prospective study from eastern India. *Diabetes Res Clin Pract*. 2014;103(3):e18-e23.
153. Forouhi NG, Menon RK, Sharp SJ, *et al*. Effects of vitamin D_2 or D_3 supplementation on glycaemic control and cardiometabolic risk among people at risk of type 2 diabetes: results of a randomized double-blind placebo-controlled trial. *Diabetes Obes Metab*. 2016;18(4):392-400.
154. Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. *Diabetes Obes Metab*. 2012;14(9):789-794.
155. Iraj B, Aminorroaya A, Amini M. Does the intramuscular injection of vitamin D increase insulin resistance? *J Res Pharm Pract*. 2012;1(2):60.
156. Johnson KC, Pittas AG, Margolis KL, *et al*. Safety and tolerability of high-dose daily vitamin D3 supplementation in the vitamin D and type 2 diabetes (D2d) study—a randomized trial in persons with prediabetes. *Eur J Clin Nutr*. 2022;76(8):1117-1124.
157. Jorde R, Sollid ST, Svartberg J, *et al*. Vitamin D 20 000 IU per week for five years does not prevent progression from prediabetes to diabetes. *J Clin Endocrinol Metab*. 2016;101(4):1647-1655.
158. Jorde R, Sollid ST, Svartberg J, Joakimsen RM, Grimnes G, Hutchinson MYS. Prevention of urinary tract infections with vitamin D supplementation 20,000 IU per week for five years. Results from an RCT including 511 subjects. *Infect Dis*. 2016;48(11-12):823-828.
159. Kuchay M, Laway B, Bashir M, Wani A, Misgar R, Shah Z. Effect of vitamin D supplementation on glycemic parameters and progression of prediabetes to diabetes: a 1-year, open-label randomized study. *Indian J Endocr Metab*. 2015;19(3):387.
160. Larsen AU, Grimnes G, Jorde R. The effect of high-dose vitamin D3 supplementation on bone mineral density in subjects with prediabetes. *Osteoporos Int*. 2018;29(1):171-180.
161. Misra P, Kant S, Misra A, *et al*. A community based randomized controlled trial to see the effect of vitamin d supplementation on development of diabetes among women with prediabetes residing in a rural community of northern India. *J Family Med Prim Care*. 2021;10(8):3122.
162. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the calcium and vitamin D for diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr*. 2011;94(2):486-494.
163. Moreira-Lucas TS, Duncan AM, Rabasa-Lhoret R, *et al*. Effect of vitamin D supplementation on oral glucose tolerance in individuals with low vitamin D status and increased risk for developing type 2 diabetes (EVIDENCE): a double-blind, randomized, placebo-controlled clinical trial. *Diabetes Obes Metab*. 2017;19(1):133-141.
164. Niroomand M, Fotouhi A, Irannejad N, Hosseinpanah F. Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. *Diabetes Res Clin Pract*. 2019;148:1-9.
165. Oosterwerff MM, Eekhoff EM, Van Schoor NM, *et al*. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-western immigrants in The Netherlands: a randomized placebo-controlled trial. *Am J Clin Nutr*. 2014;100(1):152-160.
166. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care*. 2007;30(4):980-986.
167. Pittas AG, Dawson-Hughes B, Sheehan P, *et al*. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med*. 2019;381(6):520-530.
168. Sollid ST, Hutchinson MYS, Fuskevåg OM, *et al*. No effect of high-dose vitamin D supplementation on glycemic status or cardiovascular risk factors in subjects with prediabetes. *Diabetes Care*. 2014;37(8):2123-2131.
169. Tuomainen TP, Virtanen JK, Voutilainen S, *et al*. Glucose metabolism effects of vitamin D in prediabetes: the VitDmet randomized placebo-controlled supplementation study. *J Diabetes Res*. 2015;2015:1-8.
170. Zaromytidou E, Koufakis T, Dimakopoulos G, *et al*. The effect of vitamin D supplementation on glycemic status of elderly people with prediabetes: a 12-month open-label, randomized-controlled study. *Exp Rev Clin Pharmacol*. 2022;15(1):89-97.
171. Zarrin R, Ayremlou P, Ghassemi F. The effect of vitamin D supplementation on the glycemic status and the percentage of body fat mass in adults with prediabetes: a randomized clinical trial. *Iran Red Crescent Med J*. 2016;19(3):1-8.
172. Kawahara T, Suzuki G, Mizuno S, *et al*. Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population. *BMJ*. 2022;377:e066222.
173. Martineau AR, Hanifa Y, Witt KD, *et al*. Double-blind randomised controlled trial of vitamin D_3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu). *Thorax*. 2015;70(10):953-960.
174. Grimnes G, Joakimsen R, Figenschau Y, Torjesen PA, Almås B, Jorde R. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with

low bone mass—a randomized controlled 1-year trial. *Osteoporos Int*. 2012;23(1):201-211.
175. Munns CF, Shaw N, Kiely M, *et al*. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab*. 2016;101(2):394-415.
176. Centers for Disease Control and Prevention. National Diabetes Statistics Report Website. Accessed November 29, 2023. https://www.cdc.gov/diabetes/php/data-research/index.html
177. Pittas AG, Kawahara T, Jorde R, *et al*. Vitamin D and risk for type 2 diabetes in people with prediabetes: a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann Intern Med*. 2023;176(3):355-363.