JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Vitamin D Deficiency in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Low serum vitamin D levels have been associated with adverse clinical outcomes; identifying and treating deficiency may improve outcomes.

OBJECTIVE To review the evidence about screening for vitamin D deficiency in adults.

DATA SOURCES PubMed, EMBASE, the Cochrane Library, and trial registries through March 12, 2020; bibliographies from retrieved articles, outside experts, and surveillance of the literature through November 30, 2020.

STUDY SELECTION Fair- or good-quality, English-language randomized clinical trials (RCTs) of screening with serum 25-hydroxyvitamin D (25[OH]D) compared with no screening, or treatment with vitamin D (with or without calcium) compared with placebo or no treatment conducted in nonpregnant adults; nonrandomized controlled intervention studies for harms only. Treatment was limited to studies enrolling or analyzing participants with low serum vitamin D levels.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed titles/abstracts and full-text articles, extracted data, and assessed study quality; when at least 3 similar studies were available, meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Mortality, incident fractures, falls, diabetes, cardiovascular events, cancer, depression, physical functioning, and infection.

RESULTS Forty-six studies (N = 16 205) (77 publications) were included. No studies directly evaluated the health benefits or harms of screening. Among community-dwelling populations, treatment was not significantly associated with mortality (pooled absolute risk difference [ARD], 0.3% [95% CI, −0.6% to 1.1%]; 8 RCTs, n = 2006), any fractures (pooled ARD, −0.3% [95% CI, −2.1% to 1.6%]; 6 RCTs, n = 2186), incidence of diabetes (pooled ARD, 0.1% [95% CI, −1.3% to 1.6%]; 5 RCTs, n = 3356), incidence of cardiovascular disease (2 RCTs; hazard ratio, 1.00 [95% CI, 0.74 to 1.35] and 1.09 [95% CI, 0.68 to 1.76]), incidence of cancer (2 RCTs; hazard ratio, 0.97 [95% CI, 0.68 to 1.39] and 1.01 [95% CI, 0.65 to 1.58], or depression (3 RCTs, various measures reported). The pooled ARD for incidence of participants with 1 or more falls was −4.3% (95% CI, −11.6% to 2.9%; 6 RCTs). The evidence was mixed for the effect of treatment on physical functioning (2 RCTs) and limited for the effect on infection (1 RCT). The incidence of adverse events and kidney stones was similar between treatment and control groups.

CONCLUSIONS AND RELEVANCE No studies evaluated the direct benefits or harms of screening for vitamin D deficiency. Among asymptomatic, community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D has no effect on mortality or the incidence of fractures, falls, depression, diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the effect of treatment on physical functioning and infection.

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Vitamin D has a variety of actions on calcium homeostasis, bone metabolism, and other cellular regulatory functions.[1-3] Vitamin D deficiency refers to serum levels of vitamin D (serum total hydroxyvitamin D, or 25[OH]D) that are inadequate to support bodily needs. Serum total 25(OH)D is currently considered the best marker of vitamin D status.[4,5] However, there is no consensus regarding the serum level of 25(OH)D that represents optimal health or deficiency.[1,5,6]

The rationale for screening for vitamin D deficiency among asymptomatic adults is to identify low serum vitamin D levels that place persons at risk for deficiency and offer treatment before potential adverse clinical outcomes (falls, fractures, and other outcomes) occur. In 2014, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in adults (I statement). This review was conducted for the USPSTF to inform an update of its 2014 recommendation.[7-9]

Methods

Scope of the Review

The analytic framework and key questions (KQs) that guided the review are shown in **Figure 1**. Detailed methods, evidence tables, supplemental analyses, and contextual information are available in the full evidence report.[10]

Data Sources and Searches

PubMed, the Cochrane Library, and EMBASE were searched for English-language articles published from January 1, 2013, through March 12, 2020. ClinicalTrials.gov, Cochrane Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform were also searched. To supplement systematic electronic searches (eMethods in the Supplement), reference lists of pertinent articles and studies suggested by reviewers were searched. Ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on November 30, 2020.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each KQ (eMethods in the Supplement); disagreements about inclusion were resolved by discussion or by a third reviewer. For all KQs, randomized clinical trials (RCTs) conducted in nonpregnant adults were eligible for selection. For KQ1 and KQ2, studies that were conducted among participants not known to have vitamin D deficiency were eligible for selection. For KQ3 and KQ4, studies that either enrolled participants with known deficiency (defined as serum vitamin D level less than 30 ng/mL [to convert to nmol/L, multiply by 2.496]) or reported findings for a subgroup of participants with known deficiency were eligible, as were nested case-control studies within RCTs. For KQ1 and KQ2, studies that evaluated screening using total serum 25(OH)D were eligible, and for KQ3 and KQ4, studies that evaluated treatment with oral or injectable vitamin D_2 or vitamin D_3 of any dosage with or without concomitant calcium were eligible. For KQ1 and KQ3, studies reporting health outcomes, such as mortality, falls, fractures, incident disease (eg, diabetes, cancer, cardiovascular event, and others), and validated quality of life, and self-reported physical functioning measures were eligible; studies reporting only changes in serum vitamin D levels, intermediate physiologic outcomes (eg, bone mineral density, blood pressure), or physical fitness/muscle strength measures were not eligible. For KQ2 and KQ4, studies reporting harms from screening (eg, anxiety, labeling) or harms from treatment (eg, toxicity, nephrolithiasis, adverse events) were eligible; nonrandomized controlled intervention studies, cohort studies, and case-control studies were also eligible for selection.

English-language studies that met all study selection criteria, were fair or good methodological quality, and were conducted in countries categorized as very highly developed by the 2016 United Nations Human Development Index were included.[11] Studies included in the prior 2014 review for the USPSTF were reassessed against the study selection and methodological quality criteria for this update.

Data Extraction and Quality Assessment

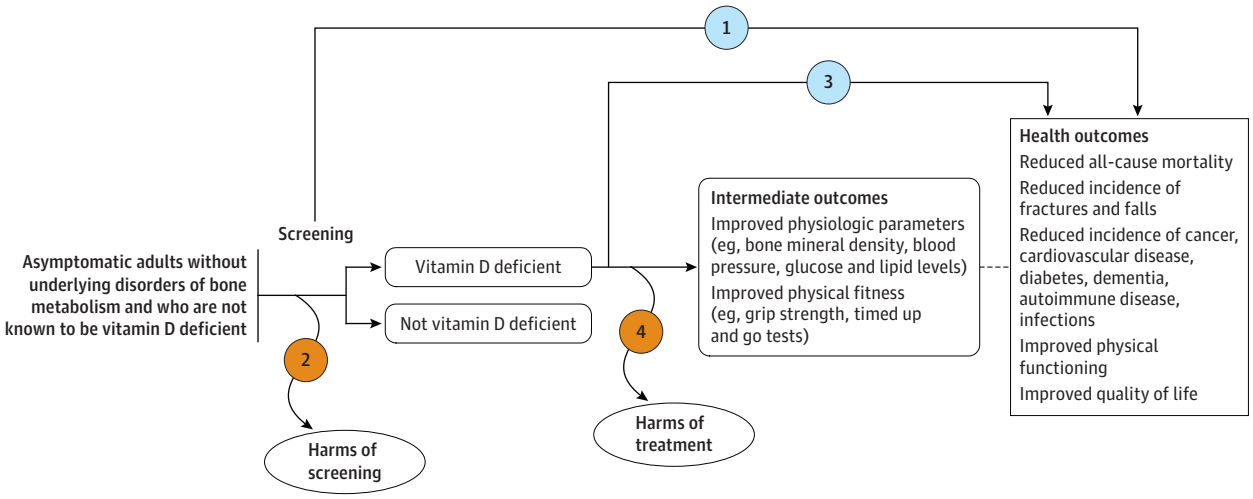
For each included study, 1 reviewer abstracted relevant study characteristics (ie, population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy. Two senior reviewers independently assessed each study's methodological quality using predefined criteria established by the USPSTF (eMethods in the Supplement) and others.[12] Disagreements in study quality ratings were resolved through discussion or with a third senior reviewer.

Data Synthesis and Analysis

Data were synthesized in tabular and narrative formats. When at least 3 similar studies were available, a quantitative synthesis was performed using random-effects models with the inverse-variance weighted method of DerSimonian and Laird in Stata version 16 (StataCorp) to generate pooled estimates of the absolute risk difference (ARD), the relative risk ratio (RR), the incidence rate difference, or the incidence rate ratio.[13] Analyses were stratified based on study population (community dwelling vs institutionalized) when possible. For rare event outcomes, such as mortality, sensitivity analyses were also conducted using other estimators and models with and without continuity corrections to assess robustness of the main findings. Significance testing was based on the exclusion of the null value by the 95% confidence interval around the pooled estimate.

The strength of evidence was assessed based on the Agency for Healthcare Quality and Research *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest.[14] Two senior reviewers independently developed initial strength-of-evidence assessments for each relevant outcome and comparison across the KQs; disagreements were resolved through discussion or input of a third senior reviewer.

Figure 1. Analytic Framework: Screening for Vitamin D Deficiency in Adults



Key questions

1 a. Does screening for vitamin D deficiency improve health outcomes?
b. Does screening efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

2 What are the harms of screening for vitamin D deficiency?

3 a. Does treatment of vitamin D deficiency with vitamin D improve health outcomes?
b. Does treatment efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

4 a. What are the harms of treatment of vitamin D deficiency with vitamin D?
b. Do harms vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

Results

Forty-six studies (N = 16 205) from 77 publications were included (**Figure 2**). Twenty-seven studies of treatment benefits (KQ3)[15-59] and 36 studies evaluating the harms of treatment (KQ4)[15-19,21-29,35,36,39-43,58-88] were identified. Study characteristics of included RCTs are described in **Table 1**. A list of full-text articles screened but excluded is provided in the Supplement.

Benefits of Screening

Key Question 1a. Does screening for vitamin D deficiency improve health outcomes?

Key Question 1b. Does screening efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

No studies were identified.

Harms of Screening

Key Question 2. What are the harms of screening for vitamin D deficiency?

No studies were identified.

Benefits of Treatment

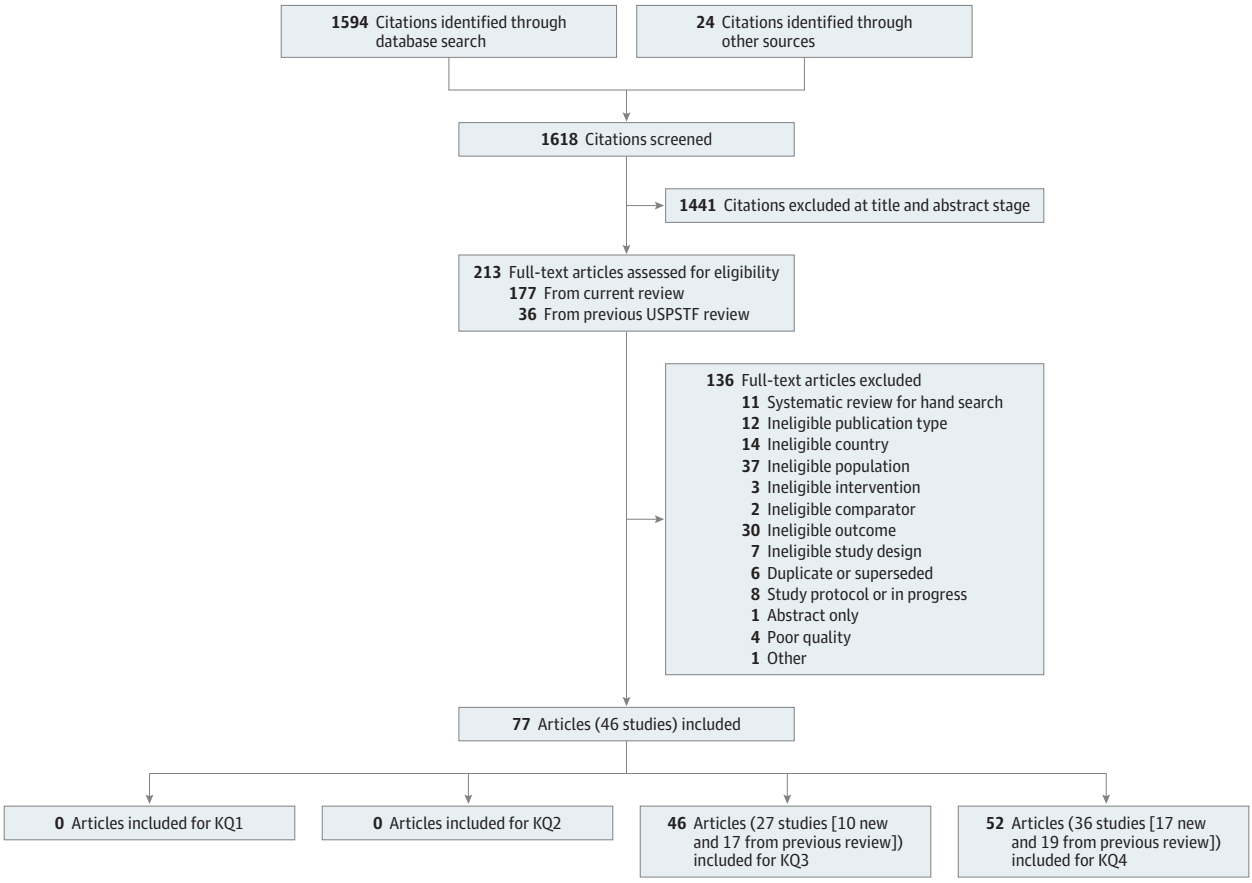
Key Question 3a. Does treatment of vitamin D deficiency with vitamin D improve health outcomes?

Key Question 3b. Does treatment efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

Twenty-six RCTs[15-29,35-59] and 1 nested case-control study from the Women's Health Initiative (WHI) Calcium and Vitamin D RCT[30-34] reported eligible outcomes. Nine RCTs were assessed as good quality,[17,20,22,26,27,41,46,54,57] and the rest were assessed as fair quality. Detailed study characteristics, outcomes, and individual study methodological quality are described in eTables 1-7 and 13-17 in the Supplement.

Five studies were conducted exclusively or predominantly among populations in nursing homes or homes for the elderly (ie, "institutionalized" settings)[16,19,35,42]; the rest were conducted exclusively or predominantly among community-dwelling populations. The mean age of included populations ranged from 36 to 85, but 54% were conducted among study populations with a mean age of 60 years or older. Twelve studies were conducted exclusively among female populations.[16-19,21,22,26,30,39,42,52,58] The race/ethnicity of the studied populations included multiple

Figure 2. Literature Search Flow Diagram: Screening for Vitamin D Deficiency in Adults



KQ indicates key question.

races and ethnicities in 9 studies,[15,21,22,26,30,46,53,54,57] was exclusively White in 1 study,[58] was mostly Latino in 1 study,[20] and was not reported in the remaining studies.

Nine studies[17,18,21,22,35,36,43,52,57] enrolled participants with serum vitamin D levels less than 20 ng/mL, and 5 studies enrolled participants using thresholds between 20 and 30 ng/mL.[15,20,26,41,51] Eight studies did not require participants to meet specific serum vitamin D–level criteria for enrollment, but the mean baseline serum vitamin D levels reported among the enrolled populations suggested that 90% or more of the enrolled participants had baseline serum levels less than 30 ng/mL.[16,19,25,27,39,42,44,58] Five studies did not require participants to be vitamin D deficient for enrollment but reported results separately for the subgroup of participants with serum levels less than 20 ng/mL.[30,37,46,53,54] Vitamin D assays used by studies varied.

All studies used vitamin D_3 as part of the active treatment intervention. Most studies used daily doses, which varied from as low as 400 IU to as high as 4000 IU. Two studies used a high initial loading dose, followed by lower monthly doses[26,54]; 1 of these studies also titrated the dose to reach a target serum level of 30 ng/mL.[26] One study titrated the weekly dose to achieve a target serum level between 65 ng/mL and 90 ng/mL, resulting in an average weekly dose of 88 865 IU.[20] The rest of the studies used weekly, twice weekly, twice monthly, or monthly doses. Two studies used a no-intervention control group[39,42]; the rest used placebo controls. Four studies included various doses of oral calcium as part of the active treatment intervention.[18,19,39,42] Six studies provided calcium to both the active vitamin D treatment group and control group.[16,21,22,43,51,52] Treatment duration ranged from 8 weeks to 7 years.

All-Cause Mortality

Twelve RCTs[18,19,21,22,25-27,35,39,42-44] reported all-cause mortality outcomes over 4 months to 3 years (eTable 4 in the Supplement); however, none evaluated mortality as a primary study aim. The pooled ARD comparing vitamin D treatment with control among studies conducted in community-dwelling populations was 0.3 percentage points (95% CI, −0.6% to 1.1%; 2006 participants; 8 RCTs; I^2 = 0%), and the pooled RR was 1.13 (95% CI, 0.39 to 3.28) (**Figure 3**). Because events were rare, sensitivity analyses were conducted using alternative pooling methods, and ARD estimates were stable (eResults and eTables 18 and 19 in the Supplement). The findings from the WHI nested case-control study were consistent with the findings from the RCTs.[30,34]

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
Aloia et al,[61] 2005 Talwar et al,[62] 2007	US; fair	Placebo once daily (n = 104) Vitamin D_3 800 IU once daily, changed to 2000 IU once daily at 2 y (n = 104)	Active and control intervention	3 y	Placebo: 61.2 (6.3) Vitamin D_3: 59.9 (6.2)	208 (100)	Community-dwelling	Serious adverse events Kidney stones
PODA Aloia et al,[60] 2018	US; fair	Placebo once daily, titrated to match vitamin D group (n = 130) Vitamin D_3 titrated to a serum level of 30 ng/mL; dosage adjusted every 3 mo; doses provided as a single daily dose (n = 130)	Active and control intervention	3 y	Median, 68.2 (IQR, 65.4-72.5)	258 (100)	Community-dwelling	Total adverse events Serious adverse events
Arvold et al,[15] 2009	US; fair	Placebo weekly (n = 50) Vitamin D_3 50 000 IU weekly (n = 50)	None	8 wk	Placebo: 57.8 (15.8) Vitamin D_3: 59.7 (14.0)	Placebo: 15 (36) Vitamin D_3: 21 (44)	Community-dwelling	Physical functioning Total adverse events
Bischoff et al,[16] 2003	Switzerland; fair	Placebo twice daily (n = 60) Vitamin D_3 400 IU twice daily (total daily dose, 800 IU) (n = 62)	Active and control intervention	12 wk	Placebo: 85.4 (5.9) Vitamin D_3: 84.9 (7.7)	122 (100)	Institutionalized	Falls Total adverse events Other harms
Bislev et al,[17] 2018	Denmark; good	Placebo once daily (n = 41) Vitamin D_3 2800 IU once daily (n = 40)	None	12 wk	NR, all women participating were aged between 60 and 79 y	81 (100)	Community-dwelling	Fractures Total adverse events Serious adverse events
Borgi et al,[63] 2016 McMullan et al,[64] 2017	US; good	Placebo weekly (n = 47) Vitamin D_2 50 000 IU tablets weekly (n = 46)	None	8 wk	37 (12.3)	Placebo: 31 (66[a]) Vitamin D_2: 31 (67[a])	Community-dwelling	Total adverse events Serious adverse events
Brazier et al,[18] 2005	France; fair	Placebo twice daily (n = 97) 500 mg calcium carbonate + vitamin D_3 400 IU twice daily (1000 mg/800 IU total daily dose) (n = 95)	Active treatment intervention	52 wk	74.6 (6.9)	192 (100)	Community-dwelling	Mortality Total adverse events Serious adverse events Discontinuation
Decalyos II Chapuy et al,[19] 2002	France; fair	Placebo once daily (N NR) Vitamin D_3 800 IU and 1200 mg tricalcium phosphate as fixed combination (N NR) Vitamin D_3 800 IU and 1200 mg tricalcium phosphate as separate combination (N NR)	Active treatment intervention	2 y	Placebo: 85.7 (7.6) Vitamin D_3 + calcium (fixed): 84.9 (6.6) Vitamin D_3 + calcium (separate): 84.9 (7.0)	583 (100)	Institutionalized	Mortality Falls Fractures Other harms Kidney stones
Davidson et al,[20] 2013	US; good	Placebo weekly (n = 53) Vitamin D_3 weekly, dosing based on body weight and baseline serum vitamin D level to achieve a target serum level of 65 ng/mL to 90 ng/mL; average weekly dose, 88 865 IU (SD, 16 154) (n = 56)	None	52 wk	Placebo: 52.5 (7.0) Vitamin D_3: 52.3 (8.0)	Placebo: 38[a] (71) Vitamin D_3: 36[a] (64)	Community-dwelling	Diabetes mellitus
Gagnon et al,[65] 2014	Australia; fair	Placebo once daily (n = 49) 2000-IU vitamin D_3, dose increased by 2000 IU every 2 mo if serum levels not at target (30 ng/mL) (n = 46)	Active and control intervention	26 wk	Placebo: 55.3 (11.1) Vitamin D_3: 53.8 (11.9)	Placebo: 30[a] (67) Vitamin D_3: 25[a] (71)	Community-dwelling	Total adverse events Discontinuation Kidney stones

(continued)

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults (continued)

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
VIDOS Gallagher et al,[23] 2013 Smith et al,[24] 2017 Gallagher et al,[22] 2012	US; good	Placebo, once daily (n = 38) Vitamin D_3 400 IU once daily (n = 22) Vitamin D_3 800 IU once daily (n = 45) Vitamin D_3 1600 IU once daily (n = 43) Vitamin D_3 2400 IU once daily (n = 44) Vitamin D_3 3200 IU once daily (n = 23) Vitamin D_3 4000 IU once daily (n = 24) Vitamin D_3 4800 IU once daily (n = 34)	Active and control intervention	52 wk	White: 67 (7.3) Black: 66.6 (7.5)	273 (100)	Community-dwelling	Mortality Serious adverse events Kidney stones Other harms
VITADAS Gallagher et al,[21] 2014	US; fair	Placebo once daily (n = 38) Vitamin D_3 400 IU once daily (n = 37) Vitamin D_3 800 IU once daily (n = 42) Vitamin D_3 1600 IU once daily (n = 41) Vitamin D_3 2400 mg IU once daily (n = 40)	Active and control intervention	52 wk	36.7 (5.9)	198 (100)	Community-dwelling	Mortality Serious adverse events Kidney stones
Grimnes et al,[25] 2011	Norway; fair	Placebo twice weekly (n = 53) Vitamin D_3 20 000 IU twice weekly (weekly dose, 40 000 IU) (n = 51)	None	26 wk	52.1 (9.3)	53 (49.1)	Community-dwelling	Mortality Total adverse events Kidney stones
Hansen et al,[26] 2015	US; good	Placebo once daily (n = 76) Vitamin D_3 800 IU once daily (n = 75) Vitamin D_3 5000 IU twice monthly after an initial loading dose of 50 000 IU once daily for 15 d; women with serum levels <30 ng/mL at follow-up study visits had doses increased and titrated to target (n = 79)	None	52 wk	61 (6)	230 (100)	Community-dwelling	Mortality Falls Fractures Physical functioning Kidney stones
Best-D Hin et al,[27] 2016	UK; good	Placebo once daily (n = 101) Vitamin D_3 2000 IU once daily (n = 102) Vitamin D_3 4000 IU once daily (n = 102)	None	52 wk	Placebo: 72 (6) Vitamin D_3 2000 IU: 72 (6) Vitamin D_3 4000 IU: 71 (6)	Placebo: 49 (49) Vitamin D_3 2000 IU: 51 (50) Vitamin D_3 4000 IU: 50 (49)	Community-dwelling	Mortality Falls Fractures Serious adverse events
Honkanen et al,[66] 1990	Finland; fair	No intervention (n = 63) Vitamin D_3 1800 IU with calcium 1558 mg once daily (n = 63)	Active treatment intervention	11 wk	Mean, community dwelling: Control: 69.6 (SE, 0.49) Vitamin D_3: 69.4 (SE, 0.54) Hospital: Control:82.8 (1.3) Vitamin D_3: 82.2 (1.0)	126 (100)	Mixed	Kidney stones Other harms
Janssen et al,[35] 2010	The Netherlands; fair	Placebo once daily (n = 34) Vitamin D_3 400 IU once daily (n = 36)	None	24 wk	Placebo: 79.2 (6.7) Vitamin D_3: 82.4 (6.4)	70 (100)	Institutionalized	Mortality Fractures Total adverse events Discontinuation

(continued)

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults (continued)

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
Jorde et al,[37,38] 2016	Norway; fair	Unplanned subgroup analysis of 173 participants Placebo once weekly Vitamin D_3 20 000 IU weekly	None	5 y	Placebo[b]: 61.9 (9.2) Vitamin D_3[b]: 62.3 (8.1)	Placebo[b]: 102 (40.0) Vitamin D_3[b]: 95 (37.1)	Community-dwelling	Diabetes mellitus Infection
Jorde et al,[36] 2018	Norway; fair	Post hoc outcome analysis Placebo, 5-capsule loading dose followed by 1 capsule each wk (n = 202) Loading dose of 100 000 IU vitamin D_3 capsules followed by 20 000 IU each wk (n = 206)	None	16 wk	52.0 (8.8)	191 (46.8)	Community-dwelling	Depression Serious adverse events
OSTPRE-FPS Kärkkäinen et al,[39,40] 2010	Finland; fair	No intervention (n = 313) Vitamin D_3 400 IU twice daily (total daily dose, 800 IU) with calcium 500 mg twice daily (total daily dose, 1000 mg) (n = 290)	Active treatment intervention	3 y	Control: 67.4 (1.9) Vitamin D_3: 67.4 (2.0)	593 (100)	Community-dwelling	Mortality Falls Discontinuation
Kearns et al,[67] 2015	US; fair	5 placebo pills by mouth at once (n = 14) 5 vitamin D_3 50 000 IU tablets by mouth once, for a total single dose of 250 000 IU (n = 14)	None	1-time dose, 1 y of follow-up	Placebo: 26.5 (5.2) Vitamin D_3: 28.2 (6.7)	Placebo: 10 (71) Vitamin D_3: 12 (86)	Community-dwelling	Total adverse events
Tromo Study Kjaergaard et al,[41] 2012	Norway; good	Placebo weekly (n = 121) Vitamin D_3 40 000 IU weekly (n = 122)	None	12 wk	Placebo: 53.3 (10.1) Vitamin D_3: 53.4 (10.3)	129 (56)	Community-dwelling	Depression Total adverse events Discontinuation
Knutsen et al,[68] 2014	Norway; fair	Placebo once daily (n = 82) Vitamin D_3 400 IU once daily (n = 85) Vitamin D_3 1000 IU once daily (n = 84)	None	16 wk	Placebo: 39 (7.6) Vitamin D_3 400 IU: 37 (7.6) Vitamin D_3 1000 IU: 36 (8.2)	Placebo: 63 (77) Vitamin D_3 400 IU: 61 (72) Vitamin D_3 1000 IU: 58 (69)	Community-dwelling	Total adverse events Serious adverse events
Krieg et al,[42] 1999	Switzerland; fair	No intervention (n = 124) Vitamin D_3 880 IU + 1000 mg calcium once daily (n = 124)	Active treatment intervention	2 y	Control[c]: 85 (7) Vitamin D_3[c]: 84 (8)	248 (100)	Institutionalized	Mortality Discontinuation
Lehmann et al,[69] 2013	Germany; fair	Placebo once daily (n = 20) Vitamin D_2 2000 IU once daily (n = 50) Vitamin D_3 2000 IU once daily (n = 49)	None	8 wk	Placebo: 31.6 (9.3) Vitamin D_2: 33.2 (12.4) Vitamin D_3: 35.6 (13.5)	68 (63.6)	Community-dwelling	Total adverse events
Vitamin D &TT Lerchbaum et al[70] 2017	Austria; fair	50 placebo drops weekly (n = 50) Vitamin D_3 20 000 IU as 50 drops weekly (n = 50)	None	12 wk	Median, 37 (IQR, 27-50)	0	Community-dwelling	Total adverse events
Lips et al,[44] 1996 Ooms et al,[45] 1995	The Netherlands; fair	Placebo once daily (n = 1287) Vitamin D_3 400 IU once daily (n = 1291)	None	3 to 3.5 y	80 (6)	1916 (74)	Mixed[d]	Mortality Fractures
Lips et al,[43] 2010	Multicountry (Canada, Germany, The Nether-lands, Mexico, US); fair	Placebo weekly (n = 112) Vitamin D_3 8400 IU weekly (n = 114)	Active and control intervention	16 wk	Placebo: 77.6 (6.6) Vitamin D_3: 78.5 (6.2)	NR	Mixed[d]	Mortality Total adverse events Serious adverse events Discontinuation Kidney stones

(continued)

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults (continued)

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
VITAL Manson et al,[46] 2019 LeBoff et al,[89]2020 Manson et al,[47] 2019 Manson et al,[48] 2012l Donlon et al,[49] 2018 Bassuk et al,[50] 2016	US; good	Planned subgroup analysis of 2001 participants Placebo once daily Vitamin D_3 2000 IU once daily	None	NR, but median length of follow-up was 5.3 y (IQR, 3.8 to 6.1)	67 (7.1)	13 085 (50.6)	Community-dwelling	Cancer Cardiovascular Falls Depression
Martineau et al,[71] 2007	UK; fair	Placebo (1-time dose) (n = 96) Vitamin D_2 100 000 IU (1-time dose) (n = 96)	None	NA	Placebo: median, 37.5 (IQR, 29.8-45.2) Vitamin D_2: median, 30.1 (IQR, 25.1-44.1)	67 (51.2)	Community-dwelling	Total adverse events
ViDA (US) Mason et al,[72] 2014	US; fair	Placebo once daily (n = 109) Vitamin D_3 2000 IU once daily (n = 109)	None	52 wk	59.6 (5.1)	218 (100)	Community-dwelling	Total adverse events Serious adverse events
Moreira-Lucas et al,[73] 2017	Canada; fair	Placebo cheese weekly (n = 36) Vitamin D_3 28 000 IU in cheese weekly (n = 35)	None	24 wk	Placebo: 45.6 (14.3) Vitamin D_3: 49.1 (13.9)	Placebo: 20 (56) Vitamin D_3: 18 (51)	Community-dwelling	Total adverse events
Ng et al,[74] 2014 Chandler et al,[75] 2014 Chandler et al,[76] 2013	US; good	Placebo once daily (n = 81) Vitamin D_3 1000 IU once daily (n = 81) Vitamin D_3 2000 IU once daily (n = 83) Vitamin D_3 4000 IU once daily (n = 83)	Active and control intervention	12 wk	Median, 51.0 (IQR, 43.6-59.4)	222 (67.7)	Community-dwelling	Other harms
Nowak et al,[77] 2016	Switzerland; good	Placebo (1-time dose) (n = 63) Vitamin D_3 100 000 IU (1-time dose) (n = 59)	None	1-time dose (4-wk follow-up)	Placebo: 28 (6) Vitamin D_3: 29 (7)	Placebo: 33 (52) Vitamin D_3: 31 (53)	Community-dwelling	Total adverse events
Pfeifer et al,[52] 2000	Germany; fair	Calcium twice daily (n = 74) Vitamin D_3 400 IU twice daily (total daily dose, 800 IU) (n = 74)	Active and control intervention	8 wk	Calcium: 74.7 (0.5) Vitamin D_3: 74.8 (0.5)	148 (100)	Community-dwelling	Falls Fractures
Pfeifer et al,[51] 2009	Multicountry (Austria, Germany); fair	Calcium twice daily (n = 121) Vitamin D_3 400 IU twice daily (total daily dose, 800 IU) (n = 121)	Active and control intervention	1 y	Calcium: 77 (4) Vitamin D_3: 76 (4)	Calcium: 91[a] (75) Vitamin D_3: 90[a] (74)	Community-dwelling	Falls Fractures
Styrian Vitamin D Hypertension Trial Pilz et al,[78] 2015 Grubler et al,[79] 2016 Grubler et al,[80] 2016 Grubler et al,[81] 2018	Austria; fair	Placebo once daily (n = 100) Vitamin D_3 2800 IU once daily (n = 100)	None	8 wk	60.0 (11.1)	94[a] (47)	Community-dwelling	Serious adverse events
D2d Pittas et al,[53] 2019	US; fair	Planned subgroup analysis of 525 participants Placebo once daily; Vitamin D_3 4000 IU once daily	None	2.5 y	60.0 (9.9)[†]	1086 (44.8)[b]	Community-dwelling	Diabetes mellitus

(continued)

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults (continued)

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
Raed et al,[82] 2017 Bhagatwala et al,[83] 2015	US; fair	Placebo monthly (n = 17) Vitamin D_3 18 000 IU monthly (equivalent to 600 IU daily) (n = 17) Vitamin D_3 60 000 IU monthly (equivalent to 2000 IU daily) (n = 18) Vitamin D_3 120 000 IU monthly (equivalent to 4000 IU daily) (n = 18)	None	16 wk	Placebo: 27.8 (9.9) Vitamin D_3 18 000 IU: 26.2 (9.8) Vitamin D_3 60 000 IU: 24.4 (8.7) Vitamin D_3 120 000 IU: 25.5 (9.0)	Placebo: 13 (76) Vitamin D_3 18 000 IU: 15 (88) Vitamin D_3 60 000 IU: 15 (83) Vitamin D_3 120 000 IU: 16 (89)	Community-dwelling	Total adverse events
ViDA New Zealand Scragg et al,[55] 2017 Khaw et al,[54] 2017 Scragg et al,[90] 2018	New Zealand; good	Planned subgroup analysis of 1270 participants Placebo monthly Vitamin D_3 200 000 IU initial dose followed by monthly doses of 100 000 IU	None	3.3 y	65.9 (8.3)[b]	2139 (41.9)[b]	Community-dwelling	Falls Fractures Cardiovascular Cancer
Shea et al,[57] 2019	US; good	Placebo bid (n = 51) Vitamin D_3 858 IU daily (n = 49)	None	52 wk	Mean, 69.6 (SD, 6.9)	36 (36[a])	Community-dwelling	Falls
2012 D-Health Tran et al,[84] 2014 Tran et al,[85] 2012	Australia; good	Placebo monthly (n = 214) Vitamin D_3 30 000 IU monthly (n = 215) Vitamin D_3 60 000 IU monthly (n = 215)	Active and control intervention	48 wk	72 (NR)	288[a] (47)	Community-dwelling	Total adverse events Serious adverse events
Wamberg et al,[86,87] 2013	Denmark; fair	Placebo once daily (n = 26) Vitamin D_3 7000 IU once daily (n = 26)	None	26 wk	Placebo: 41.2 (6.8) Vitamin D_3: 39.5 (8.0)	39 (71)	Community-dwelling	Total adverse events
Witham et al,[88] 2013	UK; fair	Placebo once (n = 25) Vitamin D_3 100 000 IU once (n = 25)	None	1-time dose (8-wk follow-up)	Placebo: 39.4 (11.8) Vitamin D_3: 41.7 (13.4)	50 (100)	Community-dwelling	Total adverse events Serious adverse events Kidney stones
Wood et al,[58] 2012 Macdonald et al,[59] 2017	UK; fair	Placebo once daily (n = 102) Vitamin D_3 400 IU once daily (n = 102) Vitamin D_3 1000 IU once daily (n = 101)	None	52 wk	Placebo: 63.9 (2.3) Vitamin D_3 400 IU: 63.5 (1.9) Vitamin D_3 1000 IU: 64.1 (2.3)	305 (100)	Community-dwelling	Falls Diabetes mellitus Total adverse events Serious adverse events

Abbreviations: BEST-D, Biochemical Efficacy and Safety Trial of vitamin D; D2d, Vitamin D and Type 2 Diabetes; IQR, interquartile range; NR, not reported; OSTPRE-FPS, Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; PODA, Physical Performance, Osteoporosis Prevention, and Vitamin D in Older African Americans; RCT, randomized clinical trial; ViDA New Zealand, Vitamin D Assessment Study; ViDA (US), Vitamin D, Diet, and Activity Study; VIDOS, Vitamin D Supplementation in Older Subjects; VITAL, VITamin D and OmegA-3 TriaL; Vitamin D &TT, Vitamin D and Testosterone Trial.

SI conversion factor: To convert vitamin D levels to nmol/L, multiply by 2.496.

[a] Calculated value.

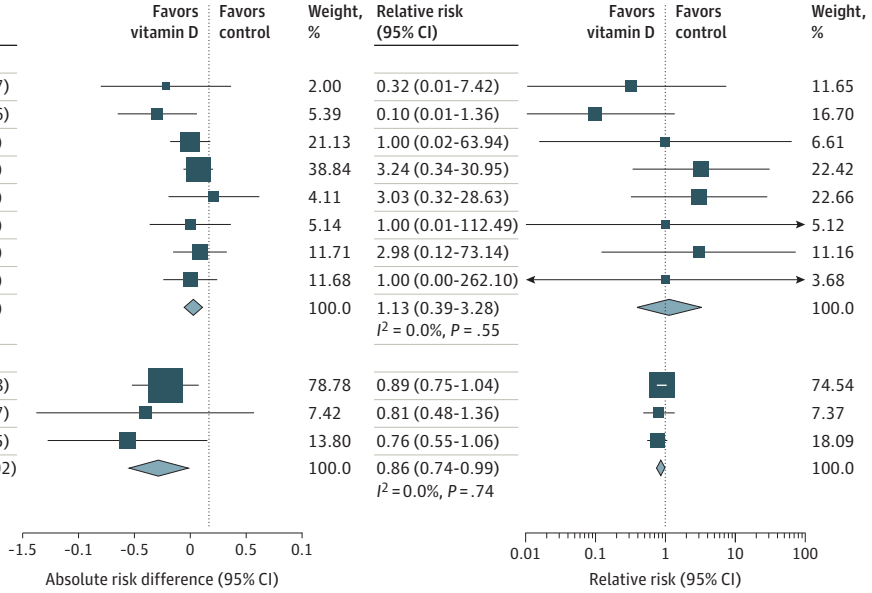
[b] Characteristic for the entire study population, not the subgroup that was vitamin D deficient.

[c] Of those who completed the study.

[d] Lips et al (1996)[44] included a majority of participants from institutionalized settings; thus, this study was considered an institutionalized setting in all stratified analyses. Lips et al (2010)[43] included a majority of participants who were community-dwelling participants; thus, this study was considered community-dwelling in all stratified analyses.

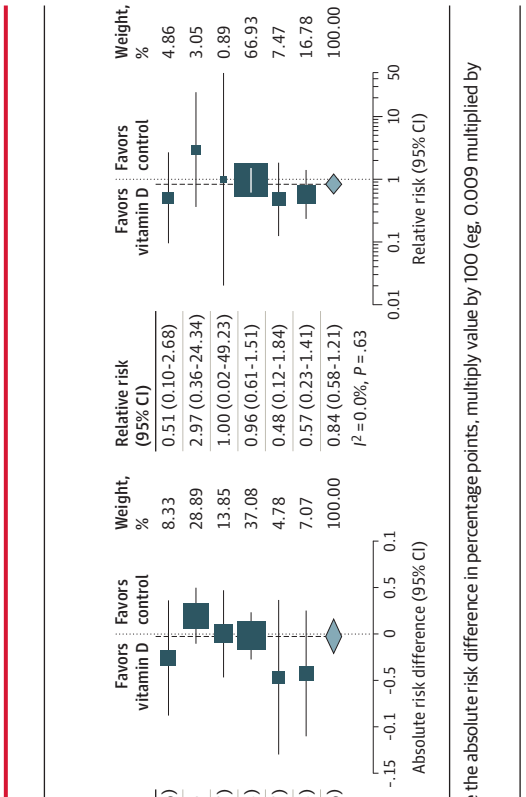
Figure 3. Effect of Vitamin D Treatment on Mortality Stratified by Setting

Source	Treatment duration	Calcium received	Vitamin D: No. with event	Vitamin D: No. without event	Control: No. with event	Control: No. without event	Absolute risk difference (95% CI)	Weight, %	Relative risk (95% CI)	Weight, %
Community										
Grimnes et al,[25] 2011	26 wk	None	0	49	1	44	-0.022 (-0.080 to 0.037)	2.00	0.32 (0.01-7.42)	11.65
Hin et al,[27] 2017	52 wk	None	0	204	3	98	-0.030 (-0.065 to 0.006)	5.39	0.10 (0.01-1.36)	16.70
Hansen et al,[26] 2015	52 wk	None	0	154	0	76	0.000 (-0.018 to 0.018)	21.13	1.00 (0.02-63.94)	6.61
Kärkkäinen et al,[39] 2010	3 y	Active intervention	3	287	1	312	0.007 (-0.006 to 0.020)	38.84	3.24 (0.34-30.95)	22.42
Brazier et al,[18] 2005	52 wk	Active intervention	3	92	1	95	0.021 (-0.019 to 0.062)	4.11	3.03 (0.32-28.63)	22.66
Gallagher et al,[21] 2014	52 wk	Both groups	0	100	0	28	0.000 (-0.036 to 0.036)	5.14	1.00 (0.01-112.49)	5.12
Lips et al,[43] 2010	16 wk	Both groups	1	113	0	112	0.009 (-0.015 to 0.033)	11.71	2.98 (0.12-73.14)	11.16
Gallagher et al,[22] 2012	52 wk	Both groups	0	196	0	33	0.000 (-0.024 to 0.024)	11.68	1.00 (0.00-262.10)	3.68
Subtotal							0.003 (-0.006 to 0.011) I^2 = 0.0%, P = .56	100.0	1.13 (0.39-3.28) I^2 = 0.0%, P = .55	100.0
Institutionalized										
Lips et al,[44] 1996	3-3.5 y	None	223	1068	251	1036	-0.022 (-0.052 to 0.008)	78.78	0.89 (0.75-1.04)	74.54
Krieg et al,[42] 1999	2 y	Active intervention	21	103	26	98	-0.040 (-0.138 to 0.057)	7.42	0.81 (0.48-1.36)	7.37
Chapuy et al,[19] 2002	2 y	Active intervention	71	322	45	145	-0.056 (-0.128 to 0.015)	13.80	0.76 (0.55-1.06)	18.09
Subtotal							-0.028 (-0.055 to -0.002) I^2 = 0.0%, P = .67	100.0	0.86 (0.74-0.99) I^2 = 0.0%, P = .74	100.0



Size of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

Figure 4. Effect of Vitamin D Treatment on Incidence of Any Fracture in Community-Dwelling Participants



Size of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

Fractures

Nine RCTs[17,19,26,27,35,44,51,52,54] reported fracture outcomes over 12 weeks to 3.3 years (eTable 5 in the Supplement); studies varied by type of fracture reported and ascertainment methods. The pooled ARD comparing vitamin D treatment with control among studies conducted in community-dwelling participants for incidence of fractures was −0.3 percentage points (95% CI, −2.1% to 1.6%; 2186 participants; 6 RCTs; I^2 = 13.0%), and the pooled RR was 0.84 (95% CI, 0.58 to 1.21) (**Figure 4**). Findings from the WHI nested case-control study were consistent with findings from the RCTs.[30] Four RCTs[19,35,44,52] reported the incidence of hip fracture, but only 1 was conducted among community-dwelling populations[52]; only 1 hip fracture occurred, leading to an imprecise effect estimate (eFigure 1 in the Supplement).

Falls

Eleven RCTs reported fall outcomes over 1 to 3 years among either community-dwelling or institutionalized populations (eTable 6 in the Supplement).[16,19,26,27,39,46,51,52,54,57,58,89] Four RCTs reported the number of participants who experienced 1 or more falls,[19,27,54,57] 1 RCT reported the number of participants who experienced 2 or more falls,[89] 2 RCTs reported the total number of falls experienced in each treatment group,[26,58] and 4 RCTs reported both outcomes.[16,39,51,52] The pooled ARD comparing vitamin D treatment with control for the incidence of participants with 1 or more falls among community-dwelling populations was −4.3 percentage points (95% CI, −11.6% to 2.9%; 2633 participants; 6 RCTs; I^2 = 70.1%), and the RR was 0.90 (95% CI, 0.75 to 1.08) (**Figure 5**). Heterogeneity was high, as indicated by the I^2 statistic.

The 2 studies observing a more than 10-percentage-point absolute decrease in incidence were conducted by the same research team using similar methods and calcium controls[51,52]; findings were statistically significant in only 1 of the studies.[51] The other 4 studies observed smaller effects ranging from a decrease of 4.6 percentage points to an increase of 3.1 percentage points; these findings were not statistically significant.[27,39,54,57] In the RCT reporting on the incidence of 2 or more falls, no significant difference was observed between vitamin D and placebo groups among participants with baseline vitamin D levels less than 12 ng/mL (adjusted odds ratio, 1.03 [95% CI, 0.59 to 1.79]) or for participants with baseline levels between 12 and 20 ng/mL (adjusted odds ratio, 1.13 [95% CI, 0.87 to 1.48]).[46,89]

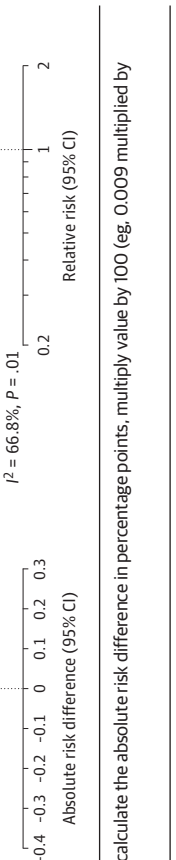
Vitamin D treatment was associated with fewer total falls compared with control in studies conducted among community-dwelling populations (incidence rate difference, 0.10 fewer falls per person-year [95% CI, −0.19 to −0.002]; 2838 person-years; 6 RCTs; I^2 = 76.9%; incidence rate ratio, 0.76 [95% CI, 0.57 to 0.94]) (**Figure 6**).

Other Morbidities

Studies also reported on the incidence of other morbidities, including diabetes, cardiovascular disease, cancer, depression, and infection, and on physical functioning (eTable 7 in the Supplement). Five RCTs, all conducted among community-dwelling populations, reported on incident diabetes over 1 to 7 years, although ascertainment methods varied.[20,31,37,53,58]

Figure 5. Effects of Vitamin D Treatment on Incidence of Falls in Community-Dwelling Participants

Source	Treatment duration	Calcium received	Vitamin D		Control		Absolute risk difference (95% CI)	Weight, %	Relative risk (95% CI)	Weight, %
			No. with event	No. without event	No. with event	No. without event				
Hin et al,[27] 2017	1 y	None	34	170	14	87	0.028 (-0.057 to 0.113)	19.09	1.20 (0.68-2.14)	7.61
Khaw et al,[54] 2017	3.3 y	None	307	295	316	338	0.027 (-0.029 to 0.082)	22.45	1.06 (0.94-1.18)	30.19
Shea et al,[57] 2019	1 y	None	14	35	13	38	0.031 (-0.143 to 0.205)	10.34	1.12 (0.59-2.14)	6.34
Kärkkäinen et al,[39] 2010	3 y	Active intervention	179	108	205	101	-0.046 (-0.123 to 0.031)	20.00	0.93 (0.83-1.05)	29.68
Pfeifer et al,[51] 2009	1.75 y	Both groups	49	72	75	46	-0.215 (-0.338 to -0.092)	14.78	0.65 (0.51-0.84)	20.12
Pfeifer et al,[52] 2000	1 y	Both groups	11	59	19	48	-0.126 (-0.264 to 0.011)	13.35	0.55 (0.29-1.08)	6.06
Subtotal							-0.043 (-0.116 to 0.029) I^2 = 70.1%, P = .005	100.0	0.90 (0.75-1.08) I^2 = 66.8%, P = .01	100.0



Size of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

The pooled ARD for incident diabetes was 0.1 percentage points (95% CI, −1.3% to 1.6%; 3356 participants; 5 RCTs; I^2 = 0%), and the pooled RR was 0.96 (0.80 to 1.15) (eFigure 2 in the Supplement).

Two RCTs conducted among community-dwelling populations reported the effect of vitamin D treatment on the incidence of cardiovascular disease and cancer among subgroups of participants with serum levels less than 20 ng/mL at baseline.[46,53] No statistically significant differences in cardiovascular events (subgroup n = 2000; hazard ratio [HR], 1.09 [95% CI, 0.68 to 1.76] over 5.3 years[46] and subgroup n = 1270; HR, 1.00 [95% CI, 0.74 to 1.53] over 3.3 years[54,55]) or incident invasive cancer (HR, 1.01 [95% CI, 0.65 to 1.58][90] and HR, 0.97 [95% CI, 0.68 to 1.39][46]) were observed in either trial. No statistically significant associations were observed between vitamin D treatment and incident breast or colorectal cancer over 7 years in the WHI nested case-control study among participants with low serum vitamin D levels at baseline.[32,33]

Three RCTs[36,41] (subgroup n = 1328,[46,91] n = 243,[39] and n = 408[34]) reported on depression outcomes over 5.3 years, 16 weeks, and 26 weeks, respectively, and found no statistically significant differences between treatment and control as measured by various validated depression symptom rating scales. Two RCTs (n = 230[24] and n = 100[13]) reported measures of physical functioning (eg, fibromyalgia impact questionnaire at 8 weeks,[13] modified Stanford Health Assessment Questionnaire[24] at 1 year); findings were mixed. One RCT[37] (subgroup n = 173) reported on incident urinary tract infection over 5 years of follow-up (HR, 0.53 [95% CI, 0.17 to 1.64]).

Variation in Benefits by Subgroup

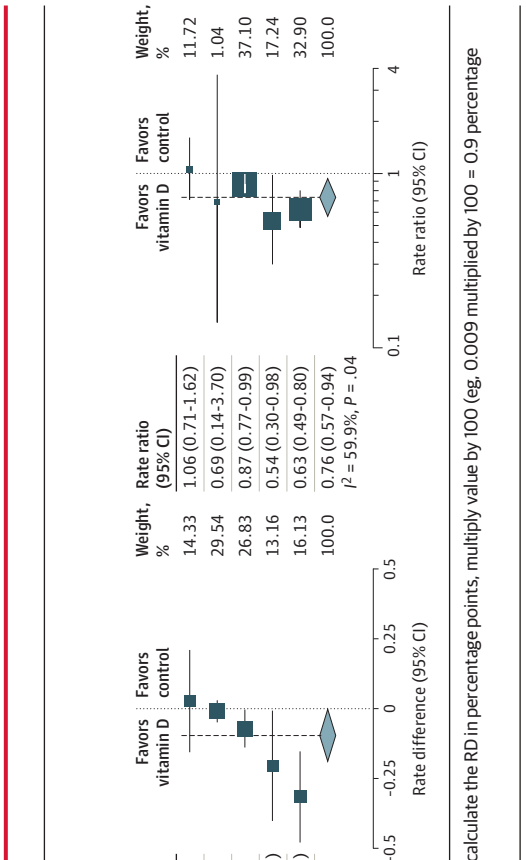
One of the RCTs conducted in institutional settings reported mortality (1 participant), but this was not reported by group, so it could not be included in the quantitative synthesis.[35] Among the 3 RCTs conducted among institutionalized populations, an absolute risk decrease ranging from 2.2 to 5.6 percentage points was observed; however, no individual study estimates were precise enough to exclude the null effect (Figure 3). When pooled, the ARD was −2.8 percentage points (95% CI, −5.5% to −0.2%; 3409 participants; I^2 = 0%). The RR was 0.86 (95% CI, 0.74 to 0.99). Data were limited for evaluating effects among other subgroups, but for mortality, fractures, and falls, no differences between men and women or among studies using lower thresholds to define deficiency (eg, <20 ng/mL) for enrollment or calcium cointerventions were observed (eFigures 3-8 in the Supplement).

Only 1 study reported benefits of vitamin D treatment stratified by race or ethnicity.[22,23] In this study, no mortality events occurred among either the White or African American populations enrolled. With the exception of 1 study conducted primarily among a Latino population,[20] the studies reporting the race or ethnicity of the enrolled population were conducted among exclusively or majority White populations. Thus, the ability to determine the influence of race/ethnicity on benefit outcomes was limited.

Harms of Treatment

Key Question 4a. What are the harms of treatment of vitamin D deficiency with vitamin D?

Figure 6. Effect of Vitamin D Treatment on Total Number of Falls in Community-Dwelling Participants



Source	Treatment duration	Vitamin D: No. of falls	Vitamin D: Person-years	Vitamin D: No. of falls per person-year	Control: No. of falls	Control: Person-years	Control: No. of falls per person-year	Rate difference (95% CI)	Weight, %	Rate ratio (95% CI)	Weight, %
Hansen et al,[26] 2015	52 wk	71	154	.46	33	76	.43	0.03 (-0.16 to 0.21)	14.33	1.06 (0.71-1.62)	11.72
Wood et al,[58] 2012	52 wk	4	193	.02	3	100	.03	-0.01 (-0.05 to 0.03)	29.54	0.69 (0.14-3.70)	1.04
Kärkkäinen et al,[39] 2010	3 y	430	861	.50	524	918	.57	-0.07 (-0.14 to 0.00)	26.83	0.87 (0.77-0.99)	37.10
Pfeifer et al,[52] 2000	1 y	17	70	.24	30	67	.45	-0.20 (-0.40 to -0.01)	13.16	0.54 (0.30-0.98)	17.24
Pfeifer et al,[51] 2009	1.75 y	106	199.5	.53	169	199.5	.85	-0.32 (-0.48 to -0.15)	16.13	0.63 (0.49-0.80)	32.90
Subtotal								-0.10 (-0.19 to 0.00) I^2 = 76.9%, P = .002	100.0	0.76 (0.57-0.94) I^2 = 59.9%, P = .04	100.0

Size of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the RD in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

Key Question 4b. Do harms varyamong patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

Thirty-six RCTs[15-19,21-29,35,36,39-43,58-88] reported on harms of treatment; 16 of these were also included for KQ3. Nine of the studies were assessed as good quality[17,22,26,27,41,63,74,77,84]; the rest were assessed as fair quality. See the Supplement for additional study characteristics (eTables 1-3) and individual study quality ratings (eTables 15 and 16).

Four studies were conducted among institutionalized populations,[16,19,35,42] 2 were conducted among mixed community-dwelling and institutionalized populations,[43,66] and the rest were conducted exclusively in community-dwelling populations. Four studies exclusively enrolled Black participants.[60,61,74,82] Three studies evaluated vitamin D_2 as a 2000 IU daily dose,[69] a 50 000 IU weekly dose,[63] or a single 100 000 IU dose.[71] The rest of the studies evaluated various daily, weekly, monthly, or single doses of vitamin D_3. In the studies using daily doses, the doses ranged from as low as 400 IU to as high as 4000 IU, and the studies using weekly doses ranged from 20 000 IU to 50 000 IU. Nine studies provided calcium to both the active vitamin D treatment group and the control group.[16,21,22,43,60,61,65,74,84] The rest of the included studies did not include any calcium as part of the active or control intervention. The duration of the intervention ranged from a single, 1-time dose to 3 years; however, the duration of intervention was less than 6 months in 22 of the 36 studies.

No studies specified adverse events as primary outcomes. With 1 exception,[39] primary outcomes included laboratory (eg, serum vitamin D level), imaging (eg, bone mineral density), or physical strength (eg, grip strength) measures. Seven studies collected data on adverse events at study visits,[16,43,65,67,72,77,86] 2 used follow-up telephone calls,[25,63] 1 used a toll-free call-in line available to participants to report adverse events,[84] and 1 used multiple methods.[41] Fourteen studies did not report how adverse events were ascertained.[15,17,18,35,36,58,60,68-71,73,82,88] Consistent definitions for total and serious adverse events were not used across studies.

Total Adverse Events

Twenty-four studies (n = 3938) reported overall adverse events (eTable 8 in the Supplement).[15-18,25,35,41,43,58,60,63,65,67-73,77,82,84,86,88] The incidence of adverse events varied by study, ranging from 0% to 92% across the treatment and control groups. However, within any given study, the incidence of adverse events was generally similar between treatment and control groups. Seven studies reported no adverse events.[15,35,60,70,71,73,82] However, 1 of the studies that reported no adverse events did in fact note adverse effects (eg, nausea) and discontinuations from the study.[35] Of the 14 studies reporting total adverse events by group, only 3 conducted statistical significance testing, and all reported no significant differences between groups.[18,77,86] Although many studies did not list the specific adverse events experienced by participants, those that did reported the following types of adverse events: abdominal discomfort, gastrointestinal issues, fatigue, musculoskeletal symptoms, nontoxic goiter, light-headedness, severe headaches, nausea, rash/hives, weakness, numbness, constipation, and itching.[16,35,60,63,65,72,86]

Serious Adverse Events

Sixteen RCTs (n = 3912) reported serious adverse events (eTable 9 in the Supplement).[17,18,21,22,27,36,43,58,60,61,63,68,72,78,84,88] The incidence of serious adverse events ranged from 0% to 29.4% across the groups within the studies; the incidence appeared similar between treatment and control groups, although formal statistical significance testing was not conducted in any study. Seven studies (n = 1702) reported 0 serious adverse events overall.[17,36,60,63,72,84,88] Five studies (n = 1341) reported serious adverse events, but authors indicated that these were most likely unrelated to the study medication.[21,22,27,58,61]

Kidney Stones

Ten RCTs (n = 2120) reported on kidney stones (eTable 11 in the Supplement).[19,21,22,25,26,43,61,65,66,88] In all but 1 of those studies, the incidence of kidney stones was reported in 0% of both the active treatment and control groups. In the study reporting more than 0 events, 1 participant in the lower-dose vitamin D group (800 IU daily) reported a kidney stone; no kidney stones were reported in the placebo group or in the higher-dose vitamin D group (50 000 IU twice monthly).[26] This study did not use calcium as part of the active treatment or control intervention.

Other Harms

Discontinuations due to adverse events and various other specific harms are detailed in the eResults and eTables 10 and 12 in the Supplement.

Variation in Harms by Subgroup

Data were too limited to evaluate differences in harms by subgroups of participants.

Discussion

This review is an updated report regarding screening for vitamin D deficiency in adults. However, no studies were identified that evaluated screening for vitamin D deficiency; thus, this evidence report was limited to an evaluation of the benefits and harms of vitamin D treatment among participants at risk for deficiency based on low serum vitamin D levels. Compared with the 2014 review for the USPSTF on this topic,[8,9] 23 new RCTs were added, and 4 RCTs were excluded. **Table 2** summarizes the evidence by KQ and provides an assessment of the strength of evidence.

For benefits of treatment (KQ3) among community-dwelling populations, the strength of evidence was assessed as moderate for no benefit for mortality, any fractures, incident diabetes, cardiovascular disease, and incident cancer. For these outcomes, the strength of evidence was downgraded for study limitations or imprecision. The strength of evidence was assessed as low for no benefit for hip fractures and depression because of study limitations and imprecision. The strength of evidence for incidence of falls was assessed as low for no benefit; it was downgraded because of inconsistency between the various fall measures (incidence vs total falls) and for imprecision in effect estimates. The strength of evidence for physical functioning and infection was assessed as insufficient because of inconsistency, imprecision, and study limitations. For harms of treatment (KQ4), the strength of evidence was assessed as low for no harm for total adverse events, serious adverse events, discontinuations due to adverse events, kidney stones, and other harms. The strength of evidence was downgraded for these outcomes because of imprecision and study limitations. Although studies were consistent in demonstrating no difference in harms between active treatment and control groups, the absolute incidence of reported adverse events varied vastly across studies, likely because of different approaches to defining and ascertaining these outcomes across the studies.

Despite a reasonable number of studies reporting falls outcomes, the body of evidence demonstrated mixed findings. Among the studies reporting the incidence of 1 or more falls, a numerical but not statistically significant decrease (pooled ARD, −4.3%) was observed among community-dwelling populations. The most recent good-quality trial reported the incidence of 2 or more falls among subgroups of participants with low vitamin D levels and also found no significant association, although effect estimates were imprecise. Among the studies reporting total number of falls, a small but statistically significant decrease (−0.1 falls per person-year) in the total number of falls was observed. Estimates for both types of outcomes were inconsistent and imprecise. Some studies reported both outcomes, but others reported only 1 of these outcomes, raising the possibility of selective outcome reporting. One hypothesis to explain the difference between these 2 outcomes is that although vitamin D may not prevent a first fall, it may have some benefit in preventing repeat falls.

A related systematic review on behalf of the USPSTF recommendation for fall prevention in community-dwelling populations at increased risk of falls found mixed findings for vitamin D interventions.[92] There was also evidence of possible harms from high-dose vitamin D in such populations, resulting in a recommendation against vitamin D supplementation in community-dwelling adults 65 years or older.[92,93] The falls prevention review excluded studies conducted among vitamin D–deficient populations; thus, additional evidence specifically in vitamin D–deficient populations is needed to be able to draw definitive conclusions about the effect of screening for vitamin D deficiency on falls among community-dwelling adults.

Findings regarding benefits of treatment in this review are not directly comparable with those from other reviews of vitamin D supplementation because this review was focused specifically on persons with low vitamin D levels (ie, less than 20 or 30 ng/mL) and other differences in study selection criteria. Despite these differences, the findings from this review are largely consistent with those from other reviews conducted in broader populations with respect to most outcomes.

Limitations

This evidence review had several limitations. First, no available evidence that directly evaluated the health benefits and harms of screening (KQ1 and KQ2) was identified. Second, studies selected for this review included some conducted in institutionalized settings. However, the synthesis and strength of evidence assessment focused mainly on community-dwelling populations because USPSTF recommendations are for clinical preventive services in or referred from primary care settings. Studies focused

Table 2. Summary of Evidence for Screening for Vitamin D Deficiency in Adults

Outcome	No. of studies, study designs (No. of participants)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ3: Benefits of treatment of vitamin D deficiency with vitamin D						
Mortality	8 RCTs[18,21,22,25-27,39,43] (n = 2006) 1 nested case-control[30] (n = 2285)	Among community-dwelling populations: Pooled ARD from RCTs, 0.3% (95% CI, −0.6% to 1.1%; I^2 = 0%) Nested case-control consistent with findings from RCTs	Consistent, precise[a]	Five of the RCTs were fair quality; mortality was not a primary outcome in any study; ascertainment of mortality was heterogenous across studies; follow-up was of short duration in some studies (particularly considering populations were relatively healthy at the start of study); and mortality events were rare in most studies	Moderate for no benefit	Studies included community-dwelling men and women Applicable to various doses of vitamin D with or without calcium
Any fractures	6 RCTs,[17,26,27,51,52,54,55] (n = 2186) 1 nested case-control[30] (n = 2982)	Among community-dwelling populations: Pooled ARD from RCTs, −0.3% (95% CI, −2.1% to 1.6%; I^2 = 13.0%) Nested CC consistent with findings from the RCTs	Consistent, precise[b]	Five of the RCTs were fair quality; type of fracture and methods of ascertainment heterogenous across studies and, in some cases, based on self-report without verification	Moderate for no benefit	Community-dwelling populations, all but 2 studies conducted among female and male populations Applicable to various doses of vitamin D with or without calcium
Hip fractures	4 RCTs[19,35,44,52] (n =3349) 1 nested case-control[30] (n = 714)	Pooled ARD from 3 RCTs, −0.86% (95% CI, −3.5% to 1.8%); I^2 = 47.4% Nested case-control consistent with findings from the RCTs	Consistent, imprecise[c]	All studies were fair quality, outcome ascertainment methods variable across studies	Low for no benefit	Two studies conducted in institutionalized populations; 2 studies conducted exclusively in women; mean age, 75-85 y in the studies Applicable to various doses of vitamin D with or without calcium
Falls	Incidence of ≥1 falls: 6 RCTs[27,39,51,52,54,57] (n = 2633) Incidence of ≥2 falls: 1 RCT[46,89] (subgroup N NR) Total number of falls: 5 RCTs[26,39,51,52,58] (2838 person-years)	Among community-dwelling populations: Incidence of ≥1 falls: pooled ARD, −4.3% (95% CI, −11.6% to 2.9%); 6 RCTs, I^2 = 70.1% Incidence of ≥2 falls (1 RCT): adjusted OR, 1.03 (95% CI, 0.59 to 1.79) for participants with vitamin D level <12 ng/mL; adjusted OR, 1.13 (95% CI, 0.87 to 1.48) for participants with vitamin D level between >12 ng/mL and ≤20 ng/mL Total number of falls: pooled IRD, −0.10 falls per person-year (95% CI, −0.19 to −0.002); 5 RCTs, I^2 = 76.9%	Inconsistent,[d] imprecise[e]	Most studies were fair quality, outcome ascertainment methods were variable across studies, potential for selective outcome reporting (total falls vs incidence of falls)	Low for no benefit	Community-dwelling populations; studies predominantly in women but some included men Applicable to various doses of vitamin D with or without calcium
Diabetes	5 RCTs[20,30,31,37,53,58] (n = 3356)	Pooled ARD, 0.1% (95% CI, −1.3% to 1.6%); I^2 = 0%	Consistent, precise[f]	One good quality and 4 fair quality (2 were planned subgroup analyses and 1 was unplanned); diabetes captured as an adverse event in 1 study (criteria and methods of ascertainment NR)	Moderate for no benefit	Four studies included men and women, and all were community-dwelling; 3 studies included participants with prediabetes, impaired fasting glucose, or glucose intolerance Applicable to various doses of vitamin D with or without calcium

(continued)

Table 2. Summary of Evidence for Screening for Vitamin D Deficiency in Adults (continued)

Outcome	No. of studies, study designs (No. of participants)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Cardiovascular	2 RCTs[46,54,55] (n = 3271 subgroup participants)	No difference in cardiovascular events between treatment and control groups were observed in either trial over a 3- to 5-y follow-up (VITAL RR, 1.09 [95% CI, 0.68 to 1.76]; ViDA (NZ) RR, 1.00 [95% CI, 0.74 to 1.35])	Consistent, imprecise[g]	Findings from both good-quality RCTs were from planned subgroup analyses; a broad definition of CVD events was used by 1 of the trials	Moderate for no benefit	Both RCTs included men and women; all were community-dwelling populations Uncertain applicability to participants with preexisting cardiovascular disease, applicable to use of vitamin D without calcium
Cancer	2 RCTs[46,90] (n = 3271 subgroup participants) 1 nested case-control[30,32,33] (n = 1201)	No difference in incident cancer (HR, 0.97 and 1.01 in the 2 RCTs); no significant association between active treatment exposure and incident breast or colorectal cancer in case-control study	Consistent, imprecise[h]	Findings from both good-quality RCTs were from planned subgroup analysis; nested case-control study was fair quality	Moderate for no benefit	The RCTs included both men and women, the nested case-control only included women Applicable to participants without a prior history of cancer, applicable to use of vitamin D with or without calcium
Depression	3 RCTs[36,41,46,91] (n = 1993)	No difference between active treatment and control groups on validated measures of depression in any study	Consistent, imprecise[i]	Two good-quality RCTs (1 with subgroup findings) and 1 fair-quality RCT; duration of intervention was 12 wk, with measurement at 26 wk in 1 study, 16 wk in 1 study, and median of 5.3 y of follow-up in 1 study; unclear whether study enrolled participants with prevalent depression in 2 of the 3 studies	Low for no benefit	Both RCTs included men and women Findings not applicable to patients with serious depression; applicable to use of vitamin D without calcium
Physical functioning	2 RCTs[15,26] (n = 320)	One trial showed small but statistically significant improvement on the fibromyalgia impact questionnaire at 8 wk for active treatment group compared with control; the other trial showed no difference in change on the modified Stanford Health Assessment Questionnaire after 1 y	Inconsistent, Imprecise[i]	One good-quality RCT; the fair-quality RCT had differential attrition and unclear randomization and allocation concealment methods and was only conducted over 8 wk; different measures used by the 2 trials	Insufficient	One trial included both men and women, the other trial only included women; both studies conducted at single centers Applicable to use of vitamin D without calcium
Infection	1 RCT[37,38] (n = 173 subgroup participants)	Lower incidence of urinary tract infection over 5 y for active treatment compared with control group (HR, 0.53 [95% CI, 0.17 to 1.64])	Consistency cannot be evaluated (single study body of evidence), Imprecise[i]	Unplanned subgroup analysis from a fair-quality RCT with possible selective outcome reporting	Insufficient	Study included both men and women, all had prediabetes
KQ4: Harms of treatment of vitamin D deficiency with vitamin D						
Total adverse events	24 RCTs[15-18,25,35,41,43,58,60,63,65,67-73,77,82,84,86,88] (n = 3938)	Incidence was similar between active treatment and control groups	Consistent, imprecise[i]	Five good-quality studies; the rest were fair quality Methods of ascertainment varied greatly among studies, likely leading to widely differing estimates of incidence	Low for no harm	Studies included men and women; most of the evidence was from community-dwelling populations Applicable to various doses of vitamin D with or without calcium

(continued)

Table 2. Summary of Evidence for Screening for Vitamin D Deficiency in Adults (continued)

Outcome	No. of studies, study designs (No. of participants)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Serious adverse events	16 RCTs[17,18,21,22,27,36,43,58,60,61,63,68,72,78,84,88] (n = 3912)	Incidence was similar between active treatment and control groups	Consistent, imprecise[i]	Five good-quality studies; the rest were fair quality Definitions of serious adverse events and methods of ascertainment varied greatly among studies, likely leading to widely differing estimates of incidence	Low for no harm	Studies included men and women; most of the evidence was from community-dwelling populations Applicable to various doses of vitamin D with or without calcium
Discontinuations due to adverse events	7 RCTs[18,35,39-43,65] (n = 1677)	Incidence reported and was similar between active treatment and control groups	Consistent, imprecise[i]	One good-quality study; the rest were fair quality Methods of ascertaining adverse events varied greatly among studies likely leading to widely differing estimates of discontinuations	Low for no harm	All but 3 studies conducted exclusively in women; most of the evidence was from community-dwelling populations Applicable to vitamin D with or without calcium
Kidney stones	10 RCTs[19,21,22,25,26,43,61,65,66,88] (n =2120)	Only 1 event reported in the low-dose vitamin D group in 1 study	Consistent, imprecise[i]	Two good-quality studies; the rest were fair quality Most studies did not report how this outcome was ascertained	Low for no harm	Most of the evidence was from female community-dwelling populations Applicable to various doses of vitamin D with or without calcium
Other harms	5 RCTs[16,19,22-24,66,74-76] (n = 1459)	No difference between active treatment and control groups for various other specific harms reported (eg, specific GI adverse effects)	Consistent, imprecise[i]	Two good-quality studies, the rest were fair quality Most studies did not report how these outcomes were ascertained; potential for selective outcome reporting (nonstandardized selection of outcomes and various approaches to reporting used)	Low for no harm	All but 1 study was conducted exclusively in women Applicable to both community-dwelling and institutionalized populations; applies to various doses of vitamin D with or without calcium

Abbreviations: ARD, absolute risk difference; CVD, cardiovascular disease; GI, gastrointestinal; HR, hazard ratio; IRD, incidence rate difference; KQ, key question; NR, not reported; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; ViDA (NZ), Vitamin D Assessment Study (New Zealand); VITAL, Vitamin D and Omega-3 Trial.

SI conversion factor: To convert vitamin D levels to nmol/L, multiply by 2.496.

[a] Although this estimate could be considered imprecise based on strict interpretation of optimal information size criteria, the event rates were very low, resulting in excessively wide CIs around the relative effect measure, which was 1.13 (95% CI, 0.39-3.28). Because of this, evaluation of the ARD was prioritized, and the CI was determined precise enough to exclude a clinically meaningful benefit or harm. This approach is consistent with current Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) recommendations for assessing precision.[96]

[b] The pooled RR was 0.84 (9% CI, 0.58-1.21); although this estimate could be considered imprecise based on strict interpretation of optimal information size criteria, evaluation of the ARD was prioritized, and the CI was determined precise enough to exclude a clinically meaningful absolute benefit or harm. This approach is consistent with current GRADE recommendations for assessing precision.[96]

[c] The pooled RR was 0.86 (95% CI, 0.50-1.47). Required sample size would be 13 658, assuming 5% control group risk, 80% power, α = .05 for detecting effect size of RR 0.8.

[d] Findings are inconsistent between outcomes (incidence of ≥1 falls vs total falls). For incidence of falls, 2 studies among community-dwelling populations both conducted by the same author showed a larger beneficial effect compared with the other 3 studies that had findings close to and on both sides of the null effect. The RCT using a more stringent definition of falls (≥2) also showed no association even among participants with the lowest of vitamin D levels (<12 ng/mL); however, these estimates were imprecise. For total falls, a small, statistically significant benefit of treatment was observed among community-dwelling populations.

[e] Required sample size of 834 for RR 0.8, control risk 50%, so optimal information size criteria are met, but CI does not exclude the null, and the 95% CI cannot rule out a clinically meaningful effect.

[f] Required sample size of 2944 for RR 0.8, control risk 20%, so optimal information size criteria met. Pooled RR, 0.96 (95% CI, 0.80-1.15); however, CIs around ARD exclude a clinically meaningful effect.

[g] Required sample size of 9920, 7% control risk, RR 0.8, α = .05. Data to calculate ARD not provided; cannot exclude a clinically meaningful treatment effect based on the RR alone.

[h] Required sample size of 11 476, 6% control risk, RR 0.8, α = .05 to meet optimal information size criteria. Data not provided to calculate ARDs.

[i] Optimal information size criteria will vary depending on outcome used but sample size combined with rare events means that optimal information size criteria are unlikely to be met.

on populations with a specific clinical condition to evaluate the treatment of vitamin D deficiency for the alleviation of specific symptoms or issues associated with that condition were not included. Third, the comparative benefits or harms of various vitamin D doses, formulations, or durations of treatment were not assessed. Fourth, this review included studies that enrolled participants based on 25(OH)D levels that used various assays and that may not have been standardized according to current criteria from the Vitamin D Standardization Program.[94] Fifth, for the trials enrolling participants unselected with respect to vitamin D status, only findings from the vitamin D–deficient subgroups were reported. Findings from the overall population were not included, but these may be eligible to be included in the next update of a related review of vitamin D supplementation conducted on behalf of the USPSTF.[95]

Conclusions

No studies evaluated the direct benefit or harms of screening for vitamin D deficiency. Among asymptomatic, community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D (with or without calcium) has no effect on mortality or incidence of fractures, falls, depression, diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the effect of treatment on physical functioning and infection.

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Concept and design: Kahwati, LeBlanc, Palmieri Weber, Clark, Viswanathan.
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Drafting of the manuscript: Kahwati, LeBlanc, Giger, Clark, Suvada, Guisinger.
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