JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Osteoporotic fractures result in significant morbidity and mortality.

OBJECTIVE To update the evidence for benefits and harms of vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults to inform the US Preventive Services Task Force.

DATA SOURCES PubMed, EMBASE, Cochrane Library, and trial registries through March 21, 2017; references; and experts. Surveillance continued through February 28, 2018.

STUDY SELECTION English-language randomized clinical trials (RCTs) or observational studies of supplementation with vitamin D, calcium, or both among adult populations; studies of populations that were institutionalized or had known vitamin D deficiency, osteoporosis, or prior fracture were excluded.

DATA EXTRACTION AND SYNTHESIS Dual, independent review of titles/abstracts and full-text articles and study quality rating using predefined criteria. Random-effects meta-analysis used when at least 3 similar studies were available.

MAIN OUTCOMES AND MEASURES Incident fracture, mortality, kidney stones, cardiovascular events, and cancer.

RESULTS Eleven RCTs (N = 51 419) in adults 50 years and older conducted over 2 to 7 years were included. Compared with placebo, supplementation with vitamin D decreased total fracture incidence (1 RCT [n = 2686]; absolute risk difference [ARD], −2.26% [95% CI, −4.53% to 0.00%]) but had no significant association with hip fracture (3 RCTs [n = 5496]; pooled ARD, −0.01% [95% CI, −0.80% to 0.78%]). Supplementation using vitamin D with calcium had no effect on total fracture incidence (1 RCT [n = 36 282]; ARD, −0.35% [95% CI, −1.02% to 0.31%]) or hip fracture incidence (2 RCTs [n = 36 727]; ARD from the larger trial, −0.14% [95% CI, −0.34% to 0.07%]). The evidence for calcium alone was limited, with only 2 studies (n = 339 total) and very imprecise results. Supplementation with vitamin D alone or with calcium had no significant effect on all-cause mortality or incident cardiovascular disease; ARDs ranged from −1.93% to 1.79%, with CIs consistent with no significant differences. Supplementation using vitamin D with calcium was associated with an increased incidence of kidney stones (3 RCTs [n = 39 213]; pooled ARD, 0.33% [95% CI, 0.06% to 0.60%]), but supplementation with calcium alone was not associated with an increased risk (3 RCTs [n = 1259]; pooled ARD, 0.00% [95% CI, −0.87% to 0.87%]). Supplementation with vitamin D and calcium was not associated with an increase in cancer incidence (3 RCTs [n = 39 213]; pooled ARD, −1.48% [95% CI, −3.32% to 0.35%]).

CONCLUSIONS AND RELEVANCE Vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence among community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture. Vitamin D with calcium was associated with an increase in the incidence of kidney stones.

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Osteoporotic fractures occur as a result of bone fragility resulting from bone loss or structural changes.[1] Although not all osteoporotic fractures may be directly attributable to deficiencies in vitamin D or calcium, these nutrients are important modifiable factors associated with optimal bone health.[2] If effective, supplementation among unselected, community-dwelling populations, which does not rely on knowledge of a person's underlying fracture risk, bone mass, vitamin D status, or diet, could be a more efficient approach for fracture prevention than a preventive approach that requires laboratory testing, imaging, or dietary assessment to determine whether treatment with vitamin D or calcium should be used. At the same time, it is important to understand potential harms of supplementation with these agents.

In 2013, the US Preventive Services Task Force (USPSTF) recommended against daily supplementation of 400 IU or less of vitamin D_3 and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women (D recommendation).[3] The USPSTF also concluded that there was insufficient evidence to recommend vitamin D with or without calcium supplementation in premenopausal women and in men and at doses greater than 400 IU with or without calcium (at doses greater than 1000 mg) for noninstitutionalized, postmenopausal women. To inform an updated recommendation, the evidence about the benefits and harms of supplemental vitamin D and calcium, alone or in combination, for the primary prevention of fractures in unselected, community-dwelling adult populations relevant to US primary care was reviewed.

Methods

Scope of the Review

Detailed methods are available in the full evidence report at : https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/vitamin-d-calcium-or-combined-supplementation-for-the-primary-prevention-of-fractures-in-adults-preventive-medication. In addition, the full evidence report includes results from sensitivity analyses not reported here. The analytic framework and key questions (KQs) that guided the review are shown in **Figure 1**.

Data Sources and Searches

PubMed/MEDLINE, EMBASE, and the Cochrane Library were searched for English-language articles. For the evaluation of vitamin D alone or vitamin D combined with calcium, the search built on the prior review for the USPSTF[5] and included January 1, 2011, through March 21, 2017. For calcium-alone interventions, which were not considered in the prior review, the search was conducted from inception through March 21, 2017. The search strategies are listed in eMethods 1 in the Supplement. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were also searched.

To supplement electronic searches, studies included in relevant existing systematic reviews and reference lists of pertinent articles, and studies suggested by reviewers, were reviewed. Since March 2017, ongoing surveillance through article alerts and targeted searches of journals with high impact factor and journals relevant to the topic was conducted to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on February 28, 2018.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each KQ (eTable 1 in the Supplement), with disagreements about inclusion resolved by discussion. Studies of community-dwelling adults with no known disorders of bone metabolism or vitamin D deficiency were included. Studies were excluded if participant enrollment was based on known high risk of fracture or falls or if more than 20% of participants had a prior history of osteoporotic fractures or prevalent fractures at baseline. Studies with between 20% and 50% of participants with exclusionary medical conditions were used in sensitivity analyses.

Eligible vitamin D interventions included oral or intramuscular vitamin D_2 or vitamin D_3 at any dosage or frequency. Eligible calcium interventions included oral calcium salt preparations at any dose and frequency. Eligible comparator groups were no treatment, placebo, or lower- or higher-dose vitamin D or calcium regimens.

Studies of vitamin D plus calcium vs calcium alone were considered vitamin D–alone interventions, since the only difference between groups was the vitamin D intervention. Studies were excluded in which the intervention and comparator groups would not allow for evaluation of the independent contribution of vitamin D or calcium to the effect; for example, when these supplements were taken in a multivitamin or used as part of a multicomponent intervention that included other pharmacologic agents or environmental or behavioral interventions.

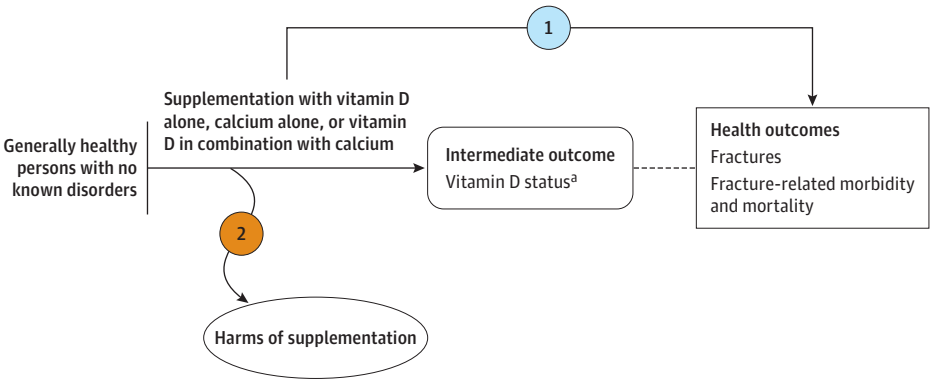
To synthesize the benefits of supplementation (KQ1), studies that reported incident fractures or fracture-related morbidity and mortality were included, regardless of whether fracture outcomes were considered the primary reported outcome. To synthesize the harms of supplementation (KQ2), studies that reported on all-cause mortality, symptomatic acute or chronic vitamin D or calcium toxicity, incident kidney stones, incident cancer, and incident cardiovascular disease (including stroke and venous thromboembolism) were included.

Randomized clinical trials (RCTs) were eligible for KQ1 and KQ2; prospective cohort and case-control study designs were also eligible for KQ2. Systematic reviews using study selection criteria similar to this review were also eligible for both KQs. Studies and articles that were not published in English, were not original research, or were conducted in countries other than those categorized as "very high" on the 2015 Human Development Index (as defined by the United Nations Human Development Programme) were excluded.[6] Studies reviewed at the full-text stage but excluded, and reasons for their exclusion, are available in the full evidence report.

Data Extraction and Quality Assessment

For each included study, 1 investigator extracted information about design, population, intervention, and outcomes, and

Figure 1. Analytic Framework: Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Adults



Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. A dashed line is used to reflect the natural progression of disease between an intermediate outcome and a health outcome. Further details are available from the USPSTF procedure manual.[4]

[a] Measures of whole-body calcium status do not exist; thus, the indirect evidence pathway for calcium cannot be evaluated.

a second investigator reviewed for completeness and accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor, using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement)[7,8] and adapted for this topic based on guidance from the Cochrane Collaboration.[9] Quality ratings for the individual studies are reported in eTables 2 through 15 in the Supplement.

Data Synthesis and Analysis

Findings were qualitatively synthesized for each KQ in tabular and narrative formats by intervention: vitamin D alone, calcium alone, or vitamin D with calcium. Studies were included in the main analysis if they met all study selection criteria and were fair or good quality; this included studies from the prior review that informed the 2013 USPSTF recommendation that met the study selection criteria for this update. Sensitivity analyses were conducted using RCTs excluded for poor quality and RCTs excluded because of mixed study populations (ie, those with between 20% and 50% of the population having a history of prior fracture).

To determine whether a quantitative synthesis was appropriate, the number of studies and the clinical and methodological heterogeneity present were assessed based on established guidance.[10] When at least 3 independent and similar RCTs were available, random-effects models using the inverse-variance weighted method of DerSimonian and Laird was used to estimate pooled effects using Stata version 14 (StataCorp).[11] Statistical heterogeneity was assessed using the I^2 statistic.[12] Because fracture and harm events were rare in many studies, both absolute risk differences (ARDs) and relative risk ratios (RRs) or hazard ratios (HRs) were used for assessing effects.

The strength of evidence for each outcome was assessed based on the Agency for Healthcare Research and Quality *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[13] which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest.

Results

Study selection included reviewing 3131 unique titles and abstracts and assessing 291 full-text articles for eligibility (**Figure 2**); 11 RCTs (N = 51 419) were eligible. Characteristics of included studies are reported in **Table 1**. Detailed individual study characteristics and findings of studies are reported in eTables 16 through 18 in the Supplement.

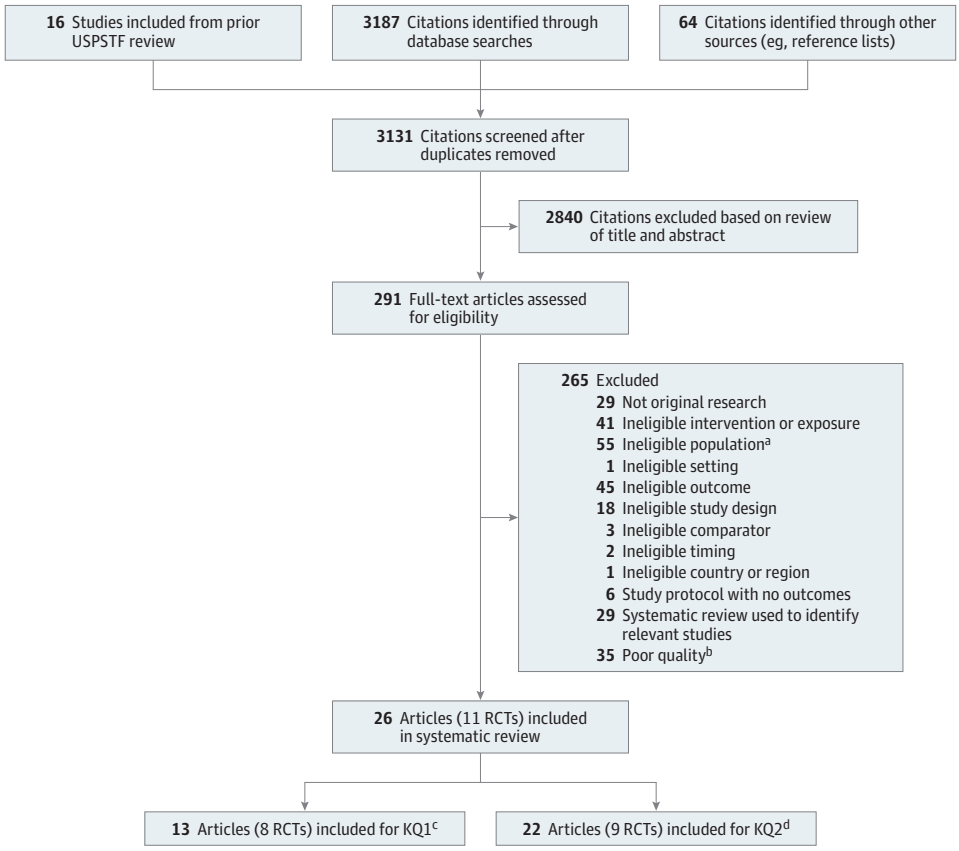
Benefits of Supplementation

Key Question 1. Is there direct evidence for supplementation with vitamin D or calcium alone or vitamin D combined with calcium for the prevention of fractures or reduction in fracture-related morbidity and mortality?

Eight good- or fair-quality RCTs that randomized 47 672 participants examined the effect of supplementation with vitamin D alone,[14-18] calcium alone,[19,20] or vitamin D with calcium[23,24] on fracture prevention over 3 to 7 years. No studies reporting outcomes related to fracture-related morbidity or mortality were identified. The rest of this section describes characteristics of included studies, followed by results organized by intervention and then by fracture type.

One RCT (Women's Health Initiative Calcium and Vitamin D [WHI CaD] trial[24]) enrolled 36 282 women; the other trials enrolled only women (3 RCTs,[14,19,20] 571 total participants) or both women and men (4 RCTs,[15-18,23] 10 819 total participants). The vitamin D_3 doses used included 300 IU, 400 IU, or 700 IU daily or 100 000 IU every month (after an initial dose of 200 000 IU) or every 4 months. The calcium doses used included daily doses of 1000 mg, 1200 mg, or 1600 mg alone, or 500 mg or 1000 mg daily in

Figure 2. Literature Search Flow Diagram



KQ indicates key question; RCT, randomized clinical trial; USPSTF, US Preventive Services Task Force.

[a] Five RCTs (in 7 articles) that were excluded for ineligible study population were used in sensitivity analyses (the study populations in these studies included between 20% and 50% of participants with prior or prevalent fracture).

[b] Eight RCTs (in 9 articles) and 22 cohort or case-control studies (in 26 articles) were excluded for poor quality. Seven of the poor-quality RCTs were used in the sensitivity analyses.

[c] Ten RCTs (in 13 articles) were used in sensitivity analyses for KQ1; 4 were excluded from the main analyses because of ineligible population, 5 were excluded because of poor quality, and 1 was excluded for both ineligible population and poor quality.

[d] Eleven RCTs (in 15 articles) were used in sensitivity analyses for KQ2; 4 were excluded from the main analyses because of ineligible population, 6 were excluded because of poor quality, and 1 was excluded for both ineligible population and poor quality.

combination with vitamin D. The comparator group was a placebo control in all but 1 study.[14] Three studies stated that the effect on incident fracture was the study aim[15,16,24]; however, only 1 study (WHI CaD trial) used fractures as the primary end point to determine required sample size.[24] Incident fracture outcomes ascertained across studies included total fractures at any site, hip fractures, clinical or morphometric vertebral fractures, nonvertebral fractures, and peripheral fractures (distal radius, humerus, ankle, foot, leg). Three studies reported confirmation of fractures through practitioner verification, medical or hospital record review, radiographic review, or claims.[14,17,18,26]

Figure 3 summarizes findings from these RCTs. All but 1 study reported statistically nonsignificant differences in fracture incidence between supplementation and placebo groups over 3 to 7 years, with ARDs ranging from −6.99% to 7.26% and RRs ranging from 0.36 to 1.34. Most estimates were imprecise, with confidence intervals spanning a range that would include a clinical benefit or harm.

Four RCTs reported the effect of vitamin D alone compared with placebo[15-18] or control group with no placebo[14] on fracture incidence. Only 1 reported on total fracture incidence; in this trial, fractures were reported in 119 participants (8.8%) in the vitamin D group and 149 participants (11.1%) in the placebo group over 5 years (unadjusted ARD, −2.26% [95% CI, −4.53% to 0.00%]; unadjusted RR, 0.80 [95% CI, 0.63 to 1.00]; age-adjusted RR, 0.78 [95% CI, 0.61 to 0.99]).[16] Three RCTs reported incident hip fracture over 3 to 5 years, and pooled estimates suggest no association (pooled ARD, −0.01% [95% CI, −0.80% to 0.78%]; I^2 = 0.0%; pooled RR, 1.08 [95% CI, 0.79 to 1.48]; I^2 = 0.0%; 3 RCTs [5496 participants]) (eFigures 1 and 2 in the Supplement).

For calcium alone compared with placebo, neither of the 2 eligible studies comparing calcium with placebo reported incident total or hip fracture.[19,20] One reported nonvertebral fractures in 11 participants (9.2%) assigned to receive calcium and 12 participants (10.3%) assigned to receive placebo (ARD, −1.01% [95% CI,

Table 1. Study Characteristics of Randomized Clinical Trials Evaluating the Effect of Vitamin D, Calcium, or Combined Supplementation

Source	No. of Participants Analyzed	Population	No. (%)		Age, Mean (SD), y	Intervention	Control	Follow-up, y	Study Quality
			Women	Nonwhite					
Vitamin D vs Placebo or Control									
Komulainen et al,[14] 1998 (Finland)	232	Community-dwelling women (52-61 y) between 6 and 24 mo postmenopause recruited from enrollees in the OSTPRE study	232 (100)	NR	52.7 (NR)	D_3 (300 IU) with calcium (93 mg) daily	Calcium (93 mg) daily	Mean, 4.3 (range, 0-5.9)	Fair
Lips et al,[15] 1996 (The Netherlands)	2578	Adults (≥70 y) recruited from general practitioners or from apartment houses or homes for elderly persons[a]	1916 (74.3)	NR	80.0 (6.0)	D_3 (400 IU) daily	Placebo	Median, 3.5	Fair
Trivedi et al,[16] 2003 (United Kingdom)	2686	Community-dwelling adults (65-85 y) recruited from the British Doctor's Study and general practice registers	649 (24.2)	NR	74.7 (4.6)	D_3 (100 000 IU) every 4 mo	Placebo	5 (planned)	Fair
ViDA Scragg et al,[17] 2017 Khaw et al,[18] 2017 (New Zealand)	5108	Community-dwelling adults (50-84 y) recruited from general practices	2141 (41.9)	857 (16.8)	65.9 (8.3)	D_3 (200 000 IU) initial dose followed by 100 000 IU every mo	Placebo	Median, 3.3 (range, 2.5-4.2)	Good
Calcium vs Placebo									
Recker et al,[19] 1996 (United States)	103[b]	Community-dwelling women (≥60 y) who were ambulatory and living independently, recruited from government-sponsored meal sites	103 (100)	NR	72.5 (6.7)	Calcium (1200 mg) daily	Placebo	Mean, 4.3 (SD, 1.1)	Fair for benefits; poor for harms
Riggs et al,[20] 1998 (United States)	236	Community-dwelling women (61-70 y) who were postmenopausal for ≥10 y and identified through medical record review	236 (100)	0	66.3 (NR)	Calcium (1600 mg) daily	Placebo	4 (planned)	Fair
Lappe et al,[21] 2007 (United States)	1179[c]	Community-dwelling postmenopausal women (≥55 y) in rural areas, recruited through random-digit dialing	1179 (100)	0	66.7 (7.3)	Calcium (1400 mg) daily	Placebo	4 (planned)	Fair to good[d]
Reid et al,[22] 2008 (New Zealand)	290	Healthy men (≥40 y) recruited through newspaper advertisement	0	NR	56.0 (10)	Calcium (600 mg and 1200 mg) daily	Placebo	2 (planned)	Fair for harms; poor for benefits
Vitamin D With Calcium vs Placebo									
Dawson-Hughes et al,[23] 1997 (United States)	389	Healthy, community-dwelling adults (≥65 y) recruited through direct mailings and community presentations	213 (54.8)	15 (3.9)	Women: 71.5 (4.5) Men: 70.5 (4.5)	D_3 (700 IU) + calcium (500 mg) daily	Placebo	3 (planned)	Fair
WHI Calcium and Vitamin D Trial Jackson et al,[24] 2006 (United States)	36 282	Community-dwelling postmenopausal women (50-79 y) recruited from enrollees in either the WHI Dietary Modification or WHI Hormone Therapy trials	36 282 (100)	6129 (16.9)	62.4 (7.0)	D_3 (400 IU) + calcium (1000 mg) daily	Placebo	Mean, 7.0 (SD, 1.4)	Fair
Lappe et al,[21] 2007 (United States)	1179[c]	Community-dwelling postmenopausal women (≥55 y) in rural areas, recruited through random-digit dialing	1179 (100)	0	66.7 (7.3)	D_3 (1000 IU) + calcium (1400 mg) daily	Placebo	4 (planned)	Fair to good[d]
Lappe et al,[25] 2017 (United States)	2197	Community-dwelling postmenopausal women (≥55 y) recruited through population-based mailings	2197 (100)	NR (0.5)	65.0 (NR)	D_3 (2000 IU) + calcium (1500 mg) daily	Placebo	4 (planned)	Fair

Abbreviations: D_3, vitamin D_3 (cholecalciferol); NR, not reported; OSTPRE, Osteoporosis Risk Factor and Prevention Study; ViDA, Vitamin D Assessment; WHI, Women's Health Initiative.

[a] Participants recruited from practitioners lived independently; participants recruited from apartments or homes for elderly persons received some care (but less than they would receive in a nursing home, per study report).

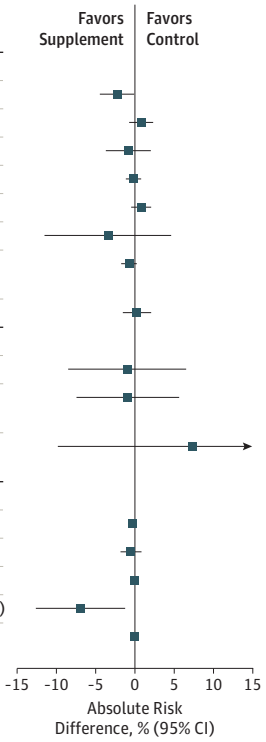
[b] Only data for the subgroup (n = 103) of participants without prevalent vertebral fracture at baseline were included in this review.

[c] Includes 3 study groups: placebo (n = 288), calcium alone (n = 445), and vitamin D with calcium (n = 446).

[d] Study quality rated as good for cancer outcomes and fair for kidney stone outcomes.

Figure 3. Comparison of Incident Fracture in Randomized Trials Comparing Vitamin D, Calcium, or Both With Placebo or Control

Source	Fracture Type	No. of Patients With Fractures/ Total No. (%)		Risk Ratio (95% CI)	Absolute Risk Difference, % (95% CI)
		Supplement	Control		
Vitamin D					
Trivedi et al,[16] 2003	Total	119/1345 (8.8)	149/1341 (11.1)	0.80 (0.63-1.00)[a]	-2.26 (-4.53 to 0.00)
Lips et al,[15] 1996	Hip	58/1291 (4.5)	48/1287 (3.7)	1.20 (0.83-1.75)	0.76 (-0.77 to 2.30)
Komulainen et al,[14] 1998	Hip	1/116 (0.9)	2/116 (1.7)	0.50 (0.05-5.44)	-0.86 (-3.77 to 2.04)
Trivedi et al,[16] 2003	Hip	21/1345 (1.6)	24/1341 (1.8)	0.87 (0.49-1.56)	-0.23 (-1.20 to 0.74)
ViDA,[17,18] 2017	Nonvertebral	156/2558 (6.1)	136/2550 (5.3)	1.14 (0.91-1.43)	0.77 (-0.51 to 2.04)
Komulainen et al,[14] 1998	Nonvertebral	11/116 (9.5)	15/116 (12.9)	0.73 (0.35-1.53)	-3.45 (-11.55 to 4.66)
Trivedi et al,[16] 2003	Vertebral (clinical)	18/1345 (1.3)	28/1341 (2.1)	0.64 (0.36-1.15)	-0.75 (-1.73 to 0.23)
Lips et al,[15] 1996	Peripheral	77/1291 (6.0)	74/1287 (5.8)	1.04 (0.76-1.41)	0.21 (-1.60 to 2.03)
Calcium					
Riggs et al,[20] 1998	Nonvertebral	11/119 (9.2)	12/117 (10.3)	0.90 (0.41-1.96)	-1.01 (-8.58 to 6.56)
Riggs et al,[20] 1998	Vertebral (morphometric)	8/119 (6.7)	9/117 (77)	0.87 (0.35-2.19)	-0.97 (-7.57 to 5.63)
Recker et al,[19] 1996	Vertebral (morphometric)	12/42 (28.6)	13/61 (21.3)	1.34 (0.68-2.64)	7.26 (-9.84 to 24.36)
Vitamin D with calcium					
WHI,[24] 2006	Total	2102/18 176 (11.6)	2158/18 106 (11.9)	0.97 (0.92-1.03)	-0.35 (-1.02 to 0.31)
Dawson-Hughes et al,[23] 1997	Hip	0/187 (0)	1/202 (0.5)	0.36 (0.01-8.78)	-0.50 (-1.88 to 0.89)
WHI,[24] 2006	Hip	175/18 176 (1.0)	199/18 106 (1.1)	0.88 (0.72-1.07)	-0.14 (-0.34 to 0.07)
Dawson-Hughes et al,[23] 1997	Nonvertebral	11/187 (5.9)	26/202 (12.9)	0.46 (0.23-0.90)	-6.99 (-12.71 to -1.27)
WHI,[24] 2006	Vertebral (clinical)	181/18 176 (1.0)	197/18 106 (1.1)	0.92 (0.75-1.12)	-0.09 (-0.30 to 0.12)



Placebo alone was the comparator for all studies except Komulainen et al,[14] for which calcium was the comparator (See Table 1). ViDA indicates Vitamin D Assessment; WHI, Women's Health Initiative.

[a] Calculated based on raw data provided in study; the authors reported an age-adjusted RR of 0.78 (95% CI, 0.61-0.99).

−8.58% to 6.56%]; RR, 0.90 [95% CI, 0.41 to 1.96]).[20] Both reported nonsignificant effects on morphometric vertebral fractures, but estimates were imprecise.

For vitamin D combined with calcium compared with placebo, the WHI CaD trial reported 2102 fractures (11.6%) in the vitamin D with calcium group and 2158 (11.9%) in the placebo group (ARD, −0.35% [95% CI, −1.02% to 0.31%]; HR, 0.96 [95% CI, 0.91 to 1.02]).[24] In that trial, 175 participants (1.0%) in the vitamin D with calcium group had a hip fracture at 7 years, compared with 199 participants (1.1%) in the placebo group (ARD, −0.14% [95% CI, −0.34% to 0.07%]; HR, 0.88 [95% CI, 0.72 to 1.08]).[24] The only other eligible trial reporting hip fracture incidence reported 1 hip fracture (in the placebo group) over the duration of study follow-up.[23]

No studies reported subgroup findings by dose or dosing interval; some studies reported subgroup findings by age, sex, or other participant characteristic, such as menopausal hormone therapy use or baseline use of supplemental vitamin D or calcium. Details of subgroup results are provided in the full evidence report.

Harms of Supplementation

Key Question 2. Is there direct evidence for the harms of supplementation with vitamin D or calcium alone or vitamin D combined with calcium?

Nine RCTs that randomized 51 375 participants reported on the effect of supplementation with vitamin D alone, calcium alone, or vitamin D with calcium on all-cause mortality,[14-18,22,24,25] incident kidney stones,[20-22,24,25,27,28] cardiovascular disease,[14,16-18,22,24,29-32] or cancer.[14,16,21,24,28,29,33-37] The rest of this section describes study characteristics, followed by results organized by outcome and then by intervention.

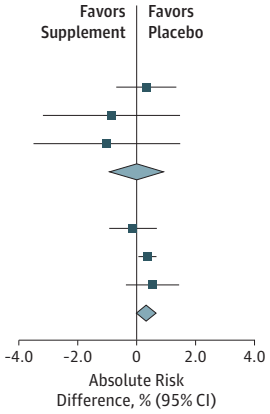
Six of the 8 RCTS contributing evidence to KQ1 were also eligible for KQ2.[14-18,20,24] Three additional RCTs were also identified as eligible for KQ2.[21,22,25] The evidence is dominated by the WHI CaD trial,[24] which enrolled 36 282 women; the others enrolled only women (4 RCTs),[14,20,21,25] only men (1 RCT),[22] or both women and men (3 RCTs).[15-18] The doses and comparators used are similar to what has been described for KQ1. Although all included studies reported on KQ2-specified outcomes, these outcomes were primary end points in only 2 studies.

All-Cause Mortality

Seven RCTs examined the effect of supplementation with vitamin D alone,[14-18] calcium alone,[22] or vitamin D with calcium[24,25] on all-cause mortality. For vitamin D alone compared with placebo, the pooled ARD was −0.74% (95% CI, −1.80% to 0.32%; I^2 = 19.6%; 4 RCTs [10 599 participants]), and the pooled RR was 0.91 (95% CI, 0.82 to 1.01; I^2 = 0.0%) (eFigures 3 and 4 in the Supplement), suggesting no association. For calcium alone compared with placebo, only 1 study was eligible, and it compared 600-mg or 1200-mg doses with placebo and reported 1 death in each of the placebo and 2 treatment groups.[22] For vitamin D

Figure 4. Comparison of Incident Kidney Stones in Randomized Trials Comparing Calcium or Both Vitamin D and Calcium With Placebo

Source	No. of Patients With Kidney Stones/Total No. (%)		Risk Ratio (95% CI)	Absolute Risk Difference, % (95% CI)
	Supplement	Placebo		
Calcium				
Lappe et al,[21] 2007	3/445 (0.7)	1/288 (0.4)	1.94 (0.20-18.57)	0.33 (-0.69 to 1.35)
Riggs et al,[20] 1998	0/119 (0)	1/117 (0.9)	0.33 (0.01-7.97)	-0.85 (-3.18 to 1.47)
Reid et al,[22] 2008	0/191 (0)	1/99 (1.0)	0.17 (0.01-4.22)	-1.01 (-3.50 to 1.48)
Subtotal: I^2 = 0.0%; P = .42			0.68 (0.14-3.36)	0.00 (-0.88 to 0.87)
Vitamin D with calcium				
Lappe et al,[21] 2007	1/446 (0.2)	1/288 (0.4)	0.65 (0.04-10.28)	-0.12 (-0.93 to 0.69)
WHI,[27] 2011	449/18 176 (2.5)	381/18 106 (2.1)	1.17 (1.03-1.34)	0.37 (0.06 to 0.67)
Lappe et al,[25] 2017	16/1102 (1.5)	10/1095 (0.9)	1.59 (0.72-3.49)	0.54 (-0.36 to 1.44)
Subtotal: I^2 = 0.0%; P = .69			1.18 (1.04-1.35)	0.88 (0.05 to 0.80)



WHI indicates Women's Health Initiative.

combined with calcium, 2 RCTs were eligible. One RCT reported 7 deaths (0.6%) in the vitamin D with calcium group and 9 deaths (0.8%) in the placebo group over 4 years (ARD, −0.19% [95% CI, −0.90% to 0.52%]; RR, 0.77 [95% CI, 0.29 to 2.07]).[25] The WHI CaD trial reported 744 deaths (4.1%) in the vitamin D with calcium group over 7 years, compared with 807 deaths (4.5%) in the placebo group (ARD, −0.36% [95% CI, −0.78% to 0.05%]; HR, 0.91 [95% CI, 0.83 to 1.01]).[29]

Kidney Stones

Five RCTs examined the effect of supplementation with calcium alone[20-22] or vitamin D combined with calcium[24,25,27,28] on incident kidney stones. No studies evaluating the effects of vitamin D alone on incident kidney stones were identified. Findings are summarized in **Figure 4**. For calcium alone compared with placebo, the pooled ARD for incident kidney stones over 2 to 4 years was 0.00% (95% CI, −0.88% to 0.87%) and the pooled RR was 0.68 (95% CI, 0.14 to 3.36; I^2 = 0.0%; 3 RCTs [1259 participants]), suggesting no association. For vitamin D combined with calcium compared with placebo, a statistically significant association for increase in incidence was found (pooled ARD, 0.33% [95% CI, 0.06% to 0.60%]; pooled RR, 1.18 [95% CI, 1.04 to 1.35]; I^2 = 0.0%; 3 RCTs [39 213 participants]).

Cardiovascular Disease

Five RCTs examined the effect of supplementation with vitamin D alone,[14,16-18] calcium alone,[22] or vitamin D with calcium[24,29-32] on cardiovascular disease outcomes. For vitamin D alone compared with placebo, 3 RCTs were eligible, and none found significant findings for any outcome. One RCT reported myocardial infarction incidence over 3.3 years in 28 participants (1.1%) in the vitamin D group and 31 participants (1.2%) in the placebo group (ARD, −0.12%, [95% CI, −0.71% to 0.47%]; HR, 0.90 [95% CI, 0.54 to 1.50]).[17] Similar, nonsignificant findings were found for stroke, venous thromboembolism, and heart failure outcomes. Another RCT reported incident ischemic heart disease over 5 years in 224 participants (16.7%) assigned to vitamin D vs 233 participants (17.4%) assigned to placebo (ARD, −0.72% [95% CI, −3.56 to 2.12]; age-adjusted RR, 0.94 [95% CI, 0.77 to 1.15]).[16] For incident cerebrovascular disease, 105 participants (7.8%) in the vitamin D group vs 101 (7.5%) in the placebo group experienced events (ARD, 0.27% [95% CI, −1.74% to 2.29%]; age-adjusted RR, 1.02 [95% CI, 0.77 to 1.36]). Cardiovascular disease events in the third RCT were rare; 1 woman experienced a myocardial infarction and 1 underwent coronary artery bypass graft surgery in the vitamin D group, and no cardiovascular events were reported in the placebo group.[14]

For calcium alone compared with placebo, 1 RCT reported no cardiovascular disease events in the placebo group, 1 event in the 600-mg calcium group (ARD, 1.02% [95% CI, −1.75% to 3.80%]; RR, 3.03 [95% CI, 0.12 to 73.49]), and 2 events in the 1200-mg calcium group (ARD, 2.15% [95% CI, −1.38% to 5.68%]; RR, 5.32 [95% CI, 0.26 to 109.35]).[22]

For vitamin D combined with calcium, the WHI CaD trial reported myocardial infarction in 411 participants (2.3%) in the vitamin D and calcium group compared with 390 participants (2.2%) in the placebo group at 7 years (ARD, 0.11% [95% CI, −0.20% to 0.41%]; HR, 1.03 [95% CI, 0.90 to 1.19]).[29] Similar findings for stroke, venous thromboembolism, and hospitalization for heart failure were also reported (stroke: ARD, −0.09% [95% CI, −0.38% to 0.20%] and HR, 0.95 [95% CI, 0.82 to 1.10]; venous thromboembolism: ARD, −0.16% [95% CI, −0.44% to 0.12%] and HR, 0.92 [95% CI, 0.79 to 1.07]; heart failure: ARD, −0.11% [95% CI, −0.40% to 0.18%] and HR, 0.95 [95% CI, 0.82 to 1.09]).[31,32]

Cancer

Four RCTs examined the effect of supplementation with vitamin D alone,[14,16,33] calcium alone,[21] or vitamin D with calcium[24,28,29,34-37] on incident cancer. For vitamin D alone compared with placebo, 1 RCT reported incident cancer in 188 participants (14%) in the vitamin D group compared with 173 (13%) in the placebo group (ARD, 1.08% [95% CI, −1.50% to 3.66%]; age-adjusted RR, 1.09 [95% CI, 0.86 to 1.36]).[16] A second RCT conducted among a younger study population reported a lower overall incidence of cancer: 2 participants (1.8%) in the vitamin D group and 3 participants (2.6%) in the placebo group (ARD, −0.82% [95% CI, −4.63% to 2.99%]; RR, 0.68 [95% CI, 0.12 to 4.02]).[33] For calcium alone compared with

placebo, 1 RCT reported incident nonskin cancer in 17 women (3.8%) who took calcium compared with 20 (6.9%) who took placebo (ARD, −3.12% [95% CI, −6.56% to 0.31%]; RR, 0.55 [95% CI, 0.29 to 1.03]).[21] For vitamin D combined with calcium compared with placebo, pooled estimates found no significant association for total incident cancer (pooled RR, 0.73 [95% CI, 0.49 to 1.10]; I^2 = 75.8%; pooled ARD, −1.48% [95% CI, −3.32% to 0.35%]; I^2 = 70.9%; 3 RCTs [39 213 participants]) (eFigures 5 and 6 in the Supplement). Similar findings were reported for breast cancer (pooled RR, 0.82 [95% CI, 0.56 to 1.19]; I^2 = 39.5%) and colon cancer (pooled RR, 1.07 [95% CI, 0.87 to 1.33]; I^2 = 0.0%).

Discussion

The evidence reviewed to inform an updated USPSTF recommendation is summarized in **Table 2**. Among the community-dwelling populations without prior history of fractures or known vitamin D deficiency or osteoporosis, the preponderance of the evidence suggests no decreased fracture risk from supplementation with vitamin D with or without calcium, although the strength of evidence was graded as low. This finding is consistent with the findings of the prior review on behalf of the USPSTF,[5] since only 2 new studies evaluating vitamin D supplementation (with or without calcium) were identified. Limited evidence was found in this update to draw conclusions regarding the effect of calcium alone on fracture prevention; calcium-alone interventions were not included in the prior review.

This review included evidence on 4 harms: all-cause mortality, kidney stones, cardiovascular disease, and cancer. The evidence suggests that vitamin D with calcium increases the incidence of kidney stones, and this evidence was graded as moderate. The strength of evidence for no harm for all other interventions and outcomes was graded as either insufficient or low. Cohort and case-control studies of supplementation were eligible for the review of harms, but all were excluded for poor quality because of many methodologic limitations also noted by others.[38,39]

Because this review was narrower in scope than other published reviews of vitamin D (with or without calcium), the conclusions may differ from the conclusions drawn from other reviews with a broader scope. As an example, a 2014 Cochrane review evaluated vitamin D and vitamin D analogues for preventing fractures and, similar to this review, found no benefit for vitamin D alone; however, they concluded that vitamin D with calcium may prevent fracture.[40] The study populations considered in the Cochrane review included participants with osteoporosis, institutionalized participants, and secondary prevention populations. The fracture benefits overall appear to be largely attributable to benefits among the high-risk populations, with little to no benefit in lower-risk populations (1 fewer hip fracture per 1000 community-dwelling adults per year [95% CI, 0 to 2]). Similar to this review, the Cochrane review concluded that vitamin D with calcium was associated with increased renal disease (defined as renal calculi or insufficiency) but did not adversely affect the risk of death. Bolland and Grey discussed the issue of discordant results from different meta-analyses on the same topic using vitamin D supplementation and fracture as an example.[41] In their analysis, differences in trial selection, outcome definitions used, and analytic approaches explain the majority of differences in findings. Across a body of evidence of 25 trials, they found strong statements concluding both benefit and no benefit of supplementation. Thus, it is important to consider the scope of the populations and interventions included when drawing conclusions from the body of evidence in this review to avoid inappropriate comparisons to reviews with a different scope.

Limitations

This review and the body of evidence included in this review has several limitations. For applicability to primary care populations, the review was scoped to focus on community-dwelling populations not known to have vitamin D deficiency, osteoporosis, high risk for falls, or prior history of fracture. As such, this review cannot address the effect of supplementation in higher-risk, selected populations. Several studies did not report the proportion of participants with a history of prior osteoporotic fracture; study authors were contacted to determine whether such data were available, and, in most cases, data were not available. These studies were ultimately included in this review because the reported baseline characteristics were similar to characteristics reported in the studies largely focused on primary prevention. The review was limited to oral or injectable vitamin D and oral calcium preparations that are available as dietary supplements and did not consider vitamin D analogues or formulations typically dispensed with a prescription.

Most studies included in this review were not powered for the fracture or harm outcomes considered; thus, small sample sizes and low event rates resulted in imprecise effect estimates. Some studies, notably the WHI CaD trial, allowed for use of personal calcium and vitamin D supplements during the study, and some have suggested this design feature as an explanation for the nonsignificant intention-to-treat analysis findings reported by the WHI CaD trial.[42] Heterogeneity in outcome specification is another limitation of this body of evidence. The anatomical sites contributing to "total fracture" varied across studies and included both traumatic and osteoporotic fractures in most studies. Studies evaluating harms varied in specificity of definition or rigor of harm outcome ascertainment, some relying on self-report to identify cases and others relying on adverse event reporting during study monitoring or on secondary data sources (registries, claims, death certificates). Although some evidence on men exists, the majority of this body of evidence is applicable to postmenopausal, white women. In addition, only a few studies evaluated vitamin D doses higher than 800 IU per day, and the evidence on calcium was limited to doses ranging from 400 mg to 1600 mg per day.

Conclusions

Vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence among community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture. Vitamin D with calcium was associated with an increase in the incidence of kidney stones.

Table 2. Summary of Evidence for Supplementation With Vitamin D, Calcium, or Both on Primary Prevention of Fracture and Harms

Intervention	No. of Studies (Participants Analyzed)	Summary of Findings	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality, No. of RCTs	EPC Assessment of Strength of Evidence
KQ1: Benefits Related to Prevention of Fractures								
Vitamin D alone	4 RCTs (n = 10 606)	Over 3.3 to 5 y: total fracture (1 RCT, n = 2686): ARD, −2.26% (95% CI, −4.53% to 0.00%); RR, 0.78 (95% CI, 0.61 to 0.99)[a] Hip fracture (3 RCTs, n = 5496; I^2 = 0.0%): pooled ARD, −0.01% (95% CI, −0.80% to 0.78%); pooled RR, 1.08 (95% CI, 0.79 to 1.48) Nonvertebral fracture (2 RCTs, n = 5340): smaller study (n = 232): ARD, −3.45% (95% CI, −11.55% to 4.66%); RR, 0.64 (95% CI, 0.29 to 1.42); larger study (n = 5108): ARD, 0.77% (95% CI, −0.51% to 2.04%); adjusted HR, 1.19 (95% CI, 0.94 to 1.50) Clinical vertebral fracture (1 RCT, n = 2686): ARD, −0.75% (95% CI, −1.73% to 0.23%); RR, 0.63 (95% CI, 0.35 to 1.14)	Consistent, imprecise	Undetected	Studies not powered for fracture outcomes; variability in populations and outcome specification and ascertainment; not enough studies to evaluate the influence of dose, route, or frequency on incidence	Three of the 4 studies included men; studies conducted outside of United States but likely applicable to US settings; doses include 300 IU/d and 400 IU/d, 100 000 IU every 4 mo, and 100 000 IU every mo (after an initial 200 000-IU loading dose)	Fair: 3 Good: 1	Low for no benefit
Calcium alone	2 RCTs (n = 339)	Over 4 y: nonvertebral fracture (1 RCT, n = 236): ARD, −1.01% (95% CI, −8.58% to 6.56%); RR, 0.90 (95% CI, 0.41 to 1.96) Morphometric vertebral fracture (2 RCTs, n = 339): ARDs, 7.26% (95% CI, −9.84% to 24.36%) and −0.97% (95% CI, −7.57% to 5.63%); RRs, 1.34 (95% CI, 0.68 to 2.64) and 0.87 (95% CI, 0.35 to 2.19)	Inconsistent, imprecise	Detected[b]	Studies not powered for fracture outcomes; limited fracture outcomes reported; not enough studies to evaluate the influence of dose, route, or frequency on incidence	Postmenopausal women in United States; doses included 1200 mg/d and 1600 mg/d	Fair	Insufficient
Vitamin D with calcium	2 RCTs (n = 36 671)	Over 3 to 7 y: total fracture (1 RCT, n = 36 282): ARD, −0.35% (95% CI, −1.02% to 0.31%); HR, 0.96 (95% CI, 0.91 to 1.02) Hip fracture (2 RCTs, n = 36 671): from larger trial[c]: ARD, −0.14% (95% CI, −0.34% to 0.07%); HR, 0.88 (95% CI, 0.72 to 1.08) Nonvertebral fractures (1 RCT, n = 389): ARD, −6.99% (95% CI, −12.71% to −1.27%); RR, 0.46 (95% CI, 0.23 to 0.90) Clinical vertebral fracture (1 RCT, n = 36 282): ARD, −0.09% (95% CI, −0.30% to 0.12%); HR, 0.90 (95% CI, 0.74 to 1.10)	Inconsistent, imprecise	Detected[b]	Not enough studies to evaluate the influence of dose, route, or frequency on incidence; participants allowed to take personal vitamin D and calcium supplements during the trial in the larger of the 2 trials	Postmenopausal women in United States; the smaller of the 2 trials included men; vitamin D doses were 400 IU/d and 700 IU/d; calcium doses were 500 mg/d and 1000 mg/d	Fair	Low for no benefit[d]
KQ2: All-Cause Mortality								
Vitamin D alone	4 RCTs (n = 10 599)	Over 3.3 to 5 y: pooled ARD, −0.74% (95% CI, −1.80% to 0.32%); I^2 = 19.6%; pooled RR, 0.91 (95% CI, 0.82 to 1.01); I^2 = 0.0%	Consistent, imprecise	Undetected	Studies not powered to assess all-cause mortality	Older men and postmenopausal women in non-US countries, although likely applicable to United States; doses were 300 IU/d and 400 IU/d and 100 000 IU every mo or 4 mo	Fair: 3 Good: 1	Low for no harm

(continued)

Table 2. Summary of Evidence for Supplementation With Vitamin D, Calcium, or Both on Primary Prevention of Fracture and Harms (continued)

Intervention	No. of Studies (Participants Analyzed)	Summary of Findings	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality, No. of RCTs	EPC Assessment of Strength of Evidence
Calcium alone	1 RCT (n = 290)	Over 2 y: ARD, 0.01% (95% CI, −2.29% to 2.32%); RR, 1.01 (95% CI, 0.09 to 11.06)	Unknown consistency (single study), very imprecise[e]	Undetected	Study not powered to assess all-cause mortality; no reporting of how mortality ascertained	Predominantly white men (≥40 y) in New Zealand, although likely applicable to United States; doses included 600 mg/d and 1200 mg/d	Fair	Insufficient
Vitamin D with calcium	2 RCTs (n = 38 479)	Over 4 y (smaller trial, n = 2303): ARD, −0.19% (95% CI, −0.90% to 0.52%); RR, 0.77 (95% CI, 0.29 to 2.07) Over 7 y (larger trial, n = 36 282): ARD, −0.36% (95% CI, −0.78% to 0.05%); HR, 0.91 (95% CI, 0.83 to 1.01)	Consistent, imprecise	Undetected	Studies not powered to assess all-cause mortality; participants allowed to take personal vitamin D and calcium supplements in larger trial	Postmenopausal women in United States; vitamin D dose 400 IU/d or 2000 IU/d; calcium dose 1000 mg/d to 1500 mg/d	Fair	Low for no harm
KQ2: Incident Kidney Stones								
Vitamin D alone	0 (NA)	NA	NA	NA	NA	NA	NA	Insufficient
Calcium alone	3 RCTs (n = 1259)	Over 2 to 4 y: pooled ARD, 0.00% (95% CI, −0.88% to 0.87%); I^2 = 0.0%; pooled RR, 0.68 (95% CI, 0.14 to 3.36); I^2 = 0.0%	Consistent, imprecise	Undetected	Studies not powered to assess incident kidney stones; limited information on outcome specification and ascertainment	Postmenopausal women in United States and New Zealand; doses ranging from 600 mg/d to 1600 mg/d	Fair	Low for no harm
Vitamin D with calcium	3 RCTs (n = 39 213)	Pooled ARD, 0.33% (95% CI, 0.06% to 0.60%); I^2 = 0.0%; pooled RR, 1.18 (95% CI, 1.04 to 1.35); I^2 = 0.0%	Consistent, precise (primarily considering the larger 2 trials)[f]	Undetected	Studies not powered to assess incident kidney stones; participants allowed to take personal vitamin D and calcium supplements during largest trial	Postmenopausal women in United States; vitamin D dose 400 IU/d, 1000 IU/d, and 2000 IU/d; calcium dose 1000 mg/d and 1400 to 1500 mg/d	Fair	Moderate for harm
KQ2: Incident Cardiovascular Disease								
Vitamin D alone	3 RCTs (n = 8021)	Over 3.3 to 5 y in the 2 larger trials (n = 2686 and n = 5108)[g]: myocardial infarction: ARD, −0.72% (95% CI, −3.56% to 2.12%); RR, 0.94 (95% CI, 0.77 to 1.15) and ARD, −0.12% (95% CI, −0.71% to 0.47%); HR, 0.90 (95% CI, 0.54 to 1.50) Cerebrovascular disease/stroke: ARD, 0.27% (95% CI, −1.74% to 2.29%); RR, 1.02 (95% CI, 0.77 to 1.36) and ARD, −0.04% (95% CI, −0.60% to 0.51%); HR, 0.95 (95% CI, 0.55 to 1.62)	Consistent, imprecise	Undetected	Only 1 study powered for cardiovascular disease events; varying control event rates suggest heterogeneity in populations, outcome specifications, and ascertainment methods	Postmenopausal women and men in United States, United Kingdom, and New Zealand; doses included 300 IU/d and 100 000 IU every 1 to 4 mo	Fair: 2 Good: 1	Low for no harm
Calcium alone	1 RCT (n = 290)	Over 2 y: myocardial infarction: 600-mg dose: ARD, 1.02% (95% CI, −1.75% to 3.80%); RR, 3.03 (95% CI, 0.12 to 73.49) 1200-mg dose: ARD, 2.15% (95% CI, −1.38% to 5.68%); RR, 5.32 (95% CI, 0.26 to 109.35)	Unknown consistency (single study), very imprecise[h]	Undetected	Study not powered for cardiovascular disease events.	Predominantly white men (≥40 y) in New Zealand, although likely applicable to United States; doses included 600 mg/d and 1200 mg/d	Fair	Insufficient

(continued)

Table 2. Summary of Evidence for Supplementation With Vitamin D, Calcium, or Both on Primary Prevention of Fracture and Harms (continued)

Intervention	No. of Studies (Participants Analyzed)	Summary of Findings	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality, No. of RCTs	EPC Assessment of Strength of Evidence
Vitamin D with calcium	1 RCT (n = 36 282)	Over 7 y: myocardial infarction: ARD, 0.11% (95% CI, −0.20% to 0.41%); HR, 1.03 (95% CI, 0.90 to 1.19) Stroke: ARD, −0.09% (95% CI, −0.38% to 0.20%); HR, 0.95 (95% CI, 0.82 to 1.10) Venous thromboembolism: ARD, −0.16% (95% CI, −0.44% to 0.12%); HR, 0.92 (95% CI, 0.79 to 1.07) Heart failure hospitalization: ARD, −0.11% (95% CI, −0.40% to 0.18%); HR, 0.95 (95% CI, 0.82 to 1.09)	Unknown consistency (single study), precise	Undetected	Study not powered for cardiovascular disease events; participants allowed to take personal vitamin D and calcium supplements during the trial in the larger of the 2 trials	Postmenopausal women in United States; vitamin D dose 400 IU/d; calcium dose 1000 mg/d	Fair	Low for no harm
KQ2: Incident Cancer								
Vitamin D alone	2 RCTs (n = 2918)	Over 5 y: any incident cancer: ARDs, 1.08% (95% CI, −1.50% to 3.66%) and −0.82% (95% CI, −4.63% to 2.99%); RRs, 1.09 (95% CI, 0.86 to 1.36) and 0.68 (95% CI, 0.12 to 4.02)	Inconsistent, imprecise	Undetected	Studies not powered for cancer outcomes; no validation of self-reported cancers	Older men and postmenopausal women; doses included 300 IU/d and 100 000 IU every 4 mo	Fair	Insufficient
Calcium alone	1 RCT (n = 733)	Over 4 y: any incident nonskin cancer: ARD, −3.12% (95% CI, −6.56% to 0.31%); RR, 0.55 (95% CI, 0.29 to 1.03)	Unknown consistency (single study), imprecise	Undetected	Study not powered for cancer outcomes	Postmenopausal women in the United States without a recent history of cancer; dose 1400 to 1500 mg/d	Good	Insufficient
Vitamin D with calcium	3 RCTs (n = 39 213)	Over 4 to 7 y: total (nonskin cancer): pooled ARD, −1.48% (95% CI, −3.32% to 0.35%); I^2 = 70.9%; pooled RR, 0.73 (95% CI, 0.49 to 1.10); I^2 = 75.8%	Inconsistent, precise (primarily considering the largest of the trials)	Undetected	Largest study not powered for cancer outcomes; participants allowed to take personal vitamin D and calcium supplements during the trials	Postmenopausal women in United States; vitamin D dose 400 IU/d, 1000 IU/d, 2000 IU/d; calcium dose 1000 mg/d, 1400 to 1500 mg/d	Fair: 2 Good: 1	Low for no harm

Abbreviations: ARD, absolute risk difference; EPC, Evidence-based Practice Center; HR, hazard ratio; KQ, key question; NA, not applicable; RCT, randomized clinical trial; RR, relative risk ratio.

[a] Adjusted estimate reported by the study; unadjusted estimate based on raw data in article was 0.80 (95% CI, 0.63 to 1.00).

[b] One RCT was identified that was registered with a primary study aim of evaluating the effect of calcium alone and vitamin D with calcium supplementation on fracture incidence. According to the study's corresponding author, alendronate became available during the study and about 20% of the study population started it; the trial found no significant differences with respect to fracture incidence, and findings were not published (Joan Lappe, written communication, December 22, 2016).

[c] Only 1 hip fracture (in control group) occurred in the smaller of the 2 trials.[23]

[d] Although findings between trials were inconsistent, the larger trial (Women's Health Initiative Calcium and Vitamin D trial) was primarily relied on to derive the strength of evidence assessment.

[e] Reflects effect estimates of the 600-mg or 1200-mg calcium dose compared with placebo. This trial is considered very imprecise because the outcome was very rare; only 1 participant in each active study group died.

[f] The smaller trial (n = 734) was considered very imprecise because the outcome was very rare; only 1 participant in each study group had kidney stones.[21]

[g] The smallest trial (n = 232) reported 1 myocardial infarction and 1 coronary artery bypass graft surgery in treatment group; no events in control group.[14]

[h] This trial is considered very imprecise because the outcome was rare; no participants in the control group had any events, 1 participant in the 600-mg group had an event, and 2 participants in the 1200-mg group had an event.[22]

ARTICLE INFORMATION

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Author Contributions: Dr Kahwati had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kahwati, Weber, Gourlay, LeBlanc, Viswanathan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kahwati, Pan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kahwati, Pan, Viswanathan.
Obtained funding: Viswanathan.
Administrative, technical, or material support: Kahwati, Weber, Pan, Viswanathan.
Supervision: Kahwati, Viswanathan.

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Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

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Additional Information: A draft version of the full evidence report underwent external peer review from 4 content experts (Mei Chung, PhD, Tufts University; Joann Manson, MD, Harvard Medical School; Elizabeth Yetley, PhD, Office of Dietary Supplements, National Institutes of Health; and 1 reviewer who wished to remain anonymous) and 5 federal partner reviewers (Centers for Disease Control and Prevention, Indian Health Service, National Heart, Lung, and Blood Institute [2 reviewers], National Institute of Diabetes and Digestive and Kidney Diseases). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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