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Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: US Preventive Services Task Force Recommendation Statement

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### Authors

Grossman, David C  
Curry, Susan J  
Owens, Douglas K  
et al.

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

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Because of the aging population, osteoporotic fractures are an increasingly important cause of morbidity and mortality in the United States. Approximately 2 million osteoporotic fractures occurred in the United States in 2005, and annual incidence is projected to increase to more than 3 million fractures by 2025. Within 1 year of experiencing a hip fracture, many patients are unable to walk independently, more than half require assistance with activities of daily living, and 20% to 30% of patients will die.






**OBJECTIVE** To update the 2013 US Preventive Services Task Force (USPSTF) recommendation on vitamin D supplementation, with or without calcium, to prevent fractures.

**EVIDENCE REVIEW** The USPSTF reviewed the evidence on vitamin D, calcium, and combined supplementation for the primary prevention of fractures in community-dwelling adults (defined as not living in a nursing home or other institutional care setting). The review excluded studies conducted in populations with a known disorder related to bone metabolism (eg, osteoporosis or vitamin D deficiency), taking medications known to be associated with osteoporosis (eg, long-term steroids), or with a previous fracture.

**FINDINGS** The USPSTF found inadequate evidence to estimate the benefits of vitamin D, calcium, or combined supplementation to prevent fractures in community-dwelling men and premenopausal women. The USPSTF found adequate evidence that daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium has no benefit for the primary prevention of fractures in community-dwelling, postmenopausal women. The USPSTF found inadequate evidence to estimate the benefits of doses greater than 400 IU of vitamin D or greater than 1000 mg of calcium to prevent fractures in community-dwelling postmenopausal women. The USPSTF found adequate evidence that supplementation with vitamin D and calcium increases the incidence of kidney stones.

**CONCLUSIONS AND RECOMMENDATION** The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in community-dwelling, asymptomatic men and premenopausal women. (I statement) The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (I statement) The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (D recommendation) These recommendations do not apply to persons with a history of osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency.

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**Author/Group Information:** The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.

**Corresponding Author:** David C. Grossman, MD, MPH ([chair@uspstf.net](mailto:chair@uspstf.net))

**T**he US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

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## Summary of Recommendations and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women (I statement) (Figure 1).

The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (I statement)

The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (D recommendation)

See the Clinical Considerations section for suggestions for practice regarding the I statements.

These recommendations apply to community-dwelling, asymptomatic adults. "Community-dwelling" is defined as not living in a nursing home or other institutional care setting. These recommendations do not apply to persons with a history of osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency.

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## Rationale

### Importance

Approximately 2 million osteoporotic fractures occurred in the United States in 2005.<sup>1,2</sup> Within 1 year of experiencing a hip fracture, many patients are unable to walk independently, more than half require assistance with activities of daily living,<sup>3,4</sup> and 20% to 30% of patients will die.<sup>5</sup>

### Benefits of Preventive Medication

The USPSTF found inadequate evidence to determine the effects of vitamin D and calcium supplementation, alone or combined, on the incidence of fractures in men and premenopausal women. The USPSTF found adequate evidence that daily supplementation with 400 IU or less of vitamin D combined with 1000 mg or less of calcium has no effect on the incidence of fractures in community-dwelling, postmenopausal women. The USPSTF found inadequate

evidence regarding the effects of higher doses of vitamin D and calcium supplementation, alone or combined, on the incidence of fractures in community-dwelling, postmenopausal women.

### Harms of Preventive Medication

The USPSTF found adequate evidence that supplementation with vitamin D and calcium increases the incidence of kidney stones. The USPSTF assessed the magnitude of this harm as small. The USPSTF found a few studies evaluating supplementation with vitamin D alone that suggested no increase in incident cardiovascular disease.

### USPSTF Assessment

#### Community-Dwelling, Postmenopausal Women

The USPSTF concludes that the evidence on the benefit of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women is lacking, and the balance of benefits and harms cannot be determined.

The USPSTF concludes with moderate certainty that daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium has no net benefit for the primary prevention of fractures in community-dwelling, postmenopausal women.

#### Men and Premenopausal Women

The USPSTF concludes that the evidence on the benefit of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women is lacking, and the balance of benefits and harms cannot be determined.

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## Clinical Considerations

### Patient Population Under Consideration

These recommendations apply to community-dwelling, asymptomatic adults (Figure 2). "Community-dwelling" is defined as not living in a nursing home or other institutional care setting. These recommendations do not apply to persons with a history of osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency.

### Suggestions for Practice Regarding the I Statements

#### Potential Preventable Burden

Approximately 2 million osteoporotic fractures occurred in the United States in 2005.<sup>2</sup> The health burden of fractures is substantial in the older adult population. Twenty percent to 30% of patients die within 1 year of a hip fracture, with significantly higher mortality rates in men than in women.<sup>5</sup> Nearly 40% of persons who experience a fracture are unable to walk independently at 1 year, and 60% require assistance with at least 1 essential activity of daily living.<sup>3,4</sup>

Low bone mass, older age, and history of falls are major risk factors for incident osteoporotic fractures.<sup>1,6</sup> Ten percent to 15% of falls result in fractures,<sup>6</sup> and nearly all hip fractures are related to a fall.<sup>7</sup> Other risk factors for low bone mass and fractures include female sex, smoking, use of glucocorticoids, and use of other medications that impair bone metabolism (eg, aromatase inhibitors).<sup>8-11</sup> Most fractures (71%) occur among women,<sup>2</sup> and an estimated 74% of all fractures that occur in women are among those 65 years or older.<sup>6</sup> Although the risk for fractures in premenopausal women

Figure 1. US Preventive Services Task Force (USPSTF) Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit	
Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

increases with lower peak bone mass, absolute fracture risk in premenopausal women is very low compared with that in postmenopausal women.<sup>12</sup> Although fractures occur more frequently in women, mortality rates after a hip fracture are significantly higher in men than in women.<sup>2,13</sup>

The large Women's Health Initiative (WHI) trial (n = 36 282), which studied daily supplementation with 400 IU of vitamin D<sub>3</sub> (cholecalciferol) and 1000 mg of calcium, reported no significant reduction in any fracture outcome<sup>14</sup>; thus, the USPSTF concluded that supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium does not prevent fractures. Studies of supplementation with higher doses of vitamin D and calcium (alone or combined) showed inconsistent results and were frequently underpow-

ered to detect differences; thus, the USPSTF concluded that the evidence on supplementation with higher doses of vitamin D and calcium to prevent fractures is inadequate.

#### Potential Harms

The WHI trial found a statistically significant increase in the incidence of kidney stones in women taking vitamin D and calcium compared with women taking placebo.<sup>14</sup> For every 273 women who received supplementation over a 7-year follow-up period, 1 woman was diagnosed with a urinary tract stone. In addition, a recent study<sup>15</sup> of combined vitamin D and calcium supplementation found findings consistent with those from the WHI trial, although the increase was not statistically significant. Another recent study<sup>16,17</sup> found

Figure 2. Clinical Summary: Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

Population	Men and premenopausal women	>400 IU of vitamin D and >1000 mg of calcium in postmenopausal women	≤400 IU of vitamin D and ≤1000 mg of calcium in postmenopausal women
Recommendation	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)	Do not recommend. Grade: D

<b>Risk Assessment</b>	Low bone mass, older age, and history of falls are major risk factors for incident osteoporotic fractures. Other risk factors for low bone mass and fractures include female sex, smoking, use of glucocorticoids, and use of other medications that impair bone metabolism (eg, aromatase inhibitors). Absolute fracture risk is very low in premenopausal women compared with postmenopausal women.
<b>Preventive Medication</b>	The recommendation against supplementation at lower doses was based on an overall assessment that supplementation at low doses provides no benefit. Evidence on the effect of supplementation on fractures at higher doses is conflicting, with some studies showing a reduction in certain fractures at higher doses and others showing no reduction or even an increase. More studies are needed to more clearly determine if supplementation with vitamin D, calcium, or both consistently prevents fractures. If future evidence shows a benefit, the magnitude of that benefit will need to be weighed against the magnitude of harms caused by supplementation (kidney stones).
<b>Other Relevant USPSTF Recommendations</b>	The USPSTF recommends against vitamin D supplementation to prevent falls in community-dwelling adults 65 years or older. The USPSTF recommends exercise interventions to prevent falls in community-dwelling older adults at increased risk for falls; multifactorial interventions may also be effective in some persons as well. The USPSTF recommends screening for osteoporosis in women 65 years or older and in younger women at increased risk. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <https://www.uspreventiveservicestaskforce.org>.



USPSTF indicates US Preventive Services Task Force.

no increase in incident cardiovascular disease with high-dose vitamin D supplementation.

In a separate recommendation statement,<sup>18</sup> the USPSTF found that vitamin D supplementation does not reduce the number of falls or the number of persons who experience a fall. A single study suggested that an annual high dose of vitamin D (500 000 IU) may even be associated with a greater number of injurious falls and a greater number of persons experiencing falls and fractures.<sup>19</sup> The USPSTF now recommends against vitamin D supplementation to prevent falls in community-dwelling older adults.<sup>18</sup>

#### Current Practice

Vitamin D and calcium supplementation are often recommended for women, especially postmenopausal women, to prevent fractures, although actual use is uncertain. Based on 2011-2012 data from the National Health and Nutrition Examination Survey, an estimated 27% of men and 35% of women older than 20 years take a vitamin D supplement, and 26% of men and 33% of women take a calcium supplement.<sup>20</sup> The exact dosage of supplementation is not known.

#### Other Approaches to Prevention

The USPSTF recommends screening for osteoporosis in women 65 years or older and in younger women at increased risk.<sup>21</sup> The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.<sup>22</sup>

The USPSTF recently updated its recommendation on interventions to prevent falls in community-dwelling older adults.<sup>18</sup> The USPSTF assessed the effect of vitamin D to prevent falls in older adults at average and increased risk for falls without vitamin D insufficiency or deficiency. The USPSTF found adequate evidence that vitamin D supplementation does not prevent falls. The USPSTF also found that exercise can prevent falls in community-dwelling older adults at increased risk for falls; multifactorial interventions may also be effective in some persons as well.<sup>18,19</sup>

#### Other Considerations

##### Research Needs and Gaps

Research is needed to determine whether daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium reduces fracture incidence in postmenopausal women and in older men. Prospective studies should assess the potential benefits of vitamin D and calcium supplementation in premenopausal women on fracture incidence later in life. Studies need to be adequately powered and should evaluate consistent fracture outcomes. Studies are also needed to evaluate the effects of vitamin D supplementation on diverse populations. Because white women have the highest risk for osteoporotic fractures, most fracture prevention studies have been conducted in this population, and it is difficult to extrapolate results to nonwhite populations. In addition,

more studies evaluating the potential harms of supplementation are needed, particularly studies on calcium and potential adverse cardiovascular outcomes.

## Discussion

### Burden of Disease

Because of the aging population, osteoporotic fractures are an increasingly important cause of morbidity and mortality in the United States. Approximately 2 million osteoporotic fractures occurred in the United States in 2005, and annual incidence is projected to increase to more than 3 million fractures by 2025.<sup>2</sup> Nearly half of all women older than 50 years will experience an osteoporotic fracture during their lifetime.<sup>23</sup> Fractures are associated with chronic pain, disability, and decreased quality of life. Hip fractures significantly increase morbidity and mortality. From 2004-2014, hip fractures alone accounted for approximately 300 000 hospitalizations annually in the United States.<sup>24</sup> During the first 3 months after a hip fracture, a patient's mortality risk is 5 to 8 times that of a similarly aged person living in the community without a fracture.<sup>25</sup> Nearly 20% of patients with hip fracture subsequently receive care in a long-term care facility.<sup>23</sup>

### Scope of Review

The USPSTF commissioned a systematic evidence review on vitamin D, calcium, and combined supplementation for the primary prevention of fractures in community-dwelling adults.<sup>1,26</sup> The review excluded studies conducted in populations with a known disorder related to bone metabolism (eg, osteoporosis or vitamin D deficiency), taking medications known to be associated with osteoporosis (eg, long-term steroids), or with a previous fracture. The review also excluded studies that recruited participants based on a history of falls or high risk for falls, because these populations are covered in a separate evidence review, and studies conducted in institutional care settings, such as long-term care facilities, because persons living in these settings are often at a very increased risk for falls. Evaluating evidence on the use of vitamin D to treat vitamin D deficiency or to treat osteoporosis is beyond the scope of this review.

### Effectiveness of Preventive Medication

The USPSTF reviewed evidence from 8 randomized clinical trials (RCTs) on vitamin D, calcium, or combined supplementation for the primary prevention of fractures; 4 trials evaluated vitamin D supplementation (n = 10 606), 2 trials evaluated calcium supplementation (n = 339), and 2 trials evaluated combined vitamin D and calcium supplementation (n = 36 727).<sup>1,26</sup> Four studies included men (representing data from 5900 men) and 4 studies were conducted exclusively in women (total of 41 772 women across all 8 studies). The mean age of study participants ranged from 53 to 80 years. In the 5 studies reporting race/ethnicity, 83% to 100% of participants were white; the remaining 3 studies did not report this information. Four of the studies were conducted in the United States, while 4 were conducted in the United Kingdom, Finland, the Netherlands, and New Zealand. Fracture outcomes varied and included total fractures, hip fractures, major osteoporotic fractures, nonvertebral fractures, vertebral fractures (clinical, morphometric, or both), upper extremity fractures, lower arm/wrist fractures, and peripheral fractures.

Four studies reported on the effect of vitamin D supplementation on fracture prevention.<sup>1</sup> Two studies evaluated daily doses of 400 IU or less (n = 2810)<sup>27,28</sup> and did not find any significant difference in any fracture outcome. The primary aim of the larger study (n = 2578)<sup>28</sup> was reduction in incidence of hip and other osteoporotic fractures. Two studies evaluated higher doses of vitamin D: a loading dose of 200 000 IU followed by 100 000 IU monthly (n = 5110)<sup>16,17</sup> and 100 000 IU every 4 months (n = 2686).<sup>29</sup> These 2 studies reported inconsistent findings. The larger study did not find any significant difference in nonvertebral fractures (absolute risk difference [ARD], 0.75% [95% CI, -0.51% to 2.04%]; adjusted hazard ratio [HR], 1.19 [95% CI, 0.94 to 1.50]); however, the primary outcome of the study was not fracture prevention.<sup>1,16</sup> The smaller study found a reduction in total fractures (ARD, -2.26% [95% CI, -4.53% to 0.00%]; age-adjusted relative risk [RR], 0.78 [95% CI, 0.61 to 0.99]) but nonsignificant reductions in hip fractures (ARD, -0.23% [95% CI, -1.20% to 0.74%]; age-adjusted RR, 0.85 [95% CI, 0.47 to 1.53]) and clinical vertebral fractures (ARD, -0.75% [95% CI, -1.73% to 0.23%]; age-adjusted RR, 0.63 [95% CI, 0.35 to 1.14]).<sup>1,29</sup>

Two studies reported on the effect of calcium supplementation on fracture prevention (n = 339).<sup>1,30,31</sup> The studies evaluated daily doses of 1200 and 1600 mg. Neither study found a significant difference in fracture outcomes with calcium supplementation, although neither study was adequately powered to detect differences.

Two studies evaluated the effect of combined vitamin D and calcium supplementation on fracture prevention (n = 36 727).<sup>1,14,32</sup> The much larger WHI trial (n = 36 282), which evaluated a daily dose of 400 IU of vitamin D with 1000 mg of calcium compared with placebo, was adequately powered to detect the effect of combined vitamin D and calcium supplementation on risk for hip fractures and found no statistically significant difference between groups (ARD, -0.14% [95% CI, -0.34% to 0.07%]; HR, 0.88 [95% CI, 0.72 to 1.08]).<sup>14</sup> The WHI trial also did not find any statistically significant difference in total fractures (ARD, -0.35% [95% CI, -1.02% to 0.31%]; HR, 0.96 [95% CI, 0.91 to 1.02]) or clinical vertebral fractures (ARD, -0.09% [95% CI, -0.30% to 0.12%]; HR, 0.90 [95% CI, 0.74 to 1.10]). However, this trial allowed participants to use calcium and vitamin D supplements outside of the study protocol, which may have biased results toward a null effect. The other, much smaller trial (n = 445) evaluated 700 IU of vitamin D with 500 mg of calcium daily compared with placebo and did not find any significant difference in hip fractures (ARD, -0.50% [95% CI, -1.88% to 0.78%]; RR, 0.36 [95% CI, 0.01 to 8.78]). This trial found a reduction in nonvertebral fractures with vitamin D and calcium supplementation, which was one of its primary aims (ARD, -6.99% [95% CI, -12.71% to -1.27%]; RR, 0.46 [95% CI, 0.23 to 0.90]).<sup>32</sup>

### Potential Harms of Preventive Medication

The USPSTF evaluated evidence from 9 RCTs on the harms of vitamin D, calcium, or combined supplementation.<sup>1,26</sup> Four studies reported on harms of vitamin D supplementation alone (n = 10 599) (the same 4 studies mentioned previously), 3 studies reported on the harms of calcium supplementation alone (n = 1292), and 3 studies (including 1 of the studies reporting on harms of calcium supplementation alone) reported on harms of combined vitamin D and calcium supplementation (n = 39 659). One study was conducted in men only, and 3 other studies included men (total of 5991 men across studies). The mean age of study participants ranged from 53 to 80



years. In the 4 studies that reported race/ethnicity, 83% to 100% of study participants were white; the remaining 5 studies did not report this information. Four of the studies were conducted in the United States; the other 5 studies were conducted in Finland, the Netherlands, the United Kingdom, and New Zealand (2 studies). The USPSTF particularly sought evidence on the outcomes of all-cause mortality, cardiovascular disease, cancer, and kidney stones.<sup>1</sup>

Vitamin D, with or without calcium, had no statistically significant effect on all-cause mortality or incident cardiovascular disease compared with placebo. Four studies ( $n = 10\,599$ ) reported on mortality outcomes with vitamin D supplementation alone; the pooled ARD was  $-0.74\%$  (95% CI,  $-0.80\%$  to  $0.32\%$ ), and the pooled RR was  $0.91$  (95% CI,  $0.82$  to  $1.01$ ). Two studies reported on mortality outcomes with combined vitamin D and calcium supplementation, including the large WHI trial; ARDs were  $-0.19\%$  and  $-0.36\%$ , with 95% CIs spanning the null effect. However, none of these studies were adequately powered to detect mortality differences. Three studies reported on incident cardiovascular outcomes with vitamin D supplementation, including 1 good-quality study ( $n = 5110$ ) in which cardiovascular disease incidence was the primary outcome.<sup>16,17</sup> Various outcomes were reported, including ischemic heart disease, myocardial infarction, cerebrovascular disease, and stroke. ARDs ranged from  $-0.72\%$  to  $1.79\%$ , with all 95% CIs spanning the null effect. The WHI trial also reported on incident cardiovascular outcomes with combined vitamin D and calcium supplementation and found no significant increase in myocardial infarction, coronary heart disease, stroke, venous thromboembolism, deep vein thrombosis, pulmonary embolism, or hospitalizations for heart failure; ARDs ranged from  $-0.16\%$  to  $0.12\%$ , with all 95% CIs including zero. The evidence on calcium supplementation alone suggested no increased incidence of all-cause mortality or cardiovascular disease but was limited to 1 study.<sup>33</sup>

Evidence on the effects of vitamin D or calcium supplementation alone on cancer incidence was inconsistent and imprecise. Combined vitamin D and calcium supplementation did not increase cancer incidence; the pooled ARD from 3 RCTs ( $n = 39\,213$ ) was  $-1.5\%$  (95% CI,  $-3.3\%$  to  $0.4\%$ ).<sup>1</sup>

Calcium supplementation alone for 2 to 4 years did not increase the incidence of kidney stones; the pooled ARD from 3 RCTs ( $n = 1259$ ) was  $0.00\%$  (95% CI,  $-0.88\%$  to  $0.87\%$ ), and the pooled RR was  $0.68$  (95% CI,  $0.14$  to  $3.40$ ). Based on evidence from 3 RCTs ( $n = 39\,659$ ), combined vitamin D and calcium supplementation for 4 to 7 years increased the incidence of kidney stones; the pooled ARD was  $0.33\%$  (95% CI,  $0.06\%$  to  $0.60\%$ ), and the pooled RR was  $1.18$  (95% CI,  $1.04$  to  $1.35$ ).<sup>1</sup>

The most commonly reported other adverse event associated with supplementation was constipation; however, this was not consistently reported across studies. A few studies reported on other serious adverse events, but these events were rare and noted by the authors to be unrelated to the study medication. In a separate evidence review commissioned by the USPSTF on interventions to prevent falls in community-dwelling older adults,<sup>19</sup> 1 study ( $n = 2256$ ) reported an increase in the number of persons experiencing a fall with a very high dose of vitamin D (500 000 IU per year) (adjusted incidence rate ratio,  $1.16$  [95% CI,  $1.03$  to  $1.31$ ]).<sup>19,34</sup>

### Estimate of Magnitude of Net Benefit

The USPSTF found inadequate evidence to estimate the benefits of vitamin D, calcium, or combined supplementation to prevent frac-

tures in community-dwelling men and premenopausal women. The USPSTF concludes that there is insufficient evidence to estimate the net benefit of vitamin D, calcium, or combined supplementation to prevent fractures in community-dwelling men and premenopausal women. Because of the lack of effect on fracture incidence and the increased incidence of kidney stones in intervention groups, the USPSTF concludes with moderate certainty that daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium has no net benefit for the primary prevention of fractures in community-dwelling, postmenopausal women. Although women enrolled in the WHI trial were predominately white, the lower risk for fractures in nonwhite women makes it very unlikely that a benefit would exist in this population. The USPSTF found inadequate evidence on calcium supplementation alone, as well as on supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium in postmenopausal women. The USPSTF concludes that there is insufficient evidence to estimate the net benefit of supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium in postmenopausal women.

### How Does Evidence Fit With Biological Understanding?

Calcium contributes to bone growth, and vitamin D helps bones absorb calcium. Normal, healthy bones turn over calcium constantly, replacing calcium loss with new calcium. The human body has 2 main sources of vitamin D. Cholecalciferol (vitamin D<sub>3</sub>), the larger source of vitamin D, is synthesized in the skin by UVB rays from the sun. Vitamin D<sub>3</sub> is converted to its active form through enzymatic processes in the liver and kidney. Ergocalciferol (vitamin D<sub>2</sub>) is consumed in the diet and can be found naturally in a few foods, such as mushrooms and egg yolks, but is more commonly consumed as a supplement or in fortified foods and beverages, such as milk, yogurt, and orange juice.<sup>35</sup> Most cells contain specific receptors for the active form of vitamin D. Stimulation of skeletal muscle receptors promotes protein synthesis, and vitamin D has a beneficial effect on muscle strength and balance. Vitamin D controls calcium absorption in the small intestines, interacts with parathyroid hormone to help maintain calcium homeostasis between the blood and bones, and is essential for bone growth and maintaining bone density. Obtaining insufficient amounts of vitamin D through diet or sun exposure can lead to inadequate levels of the hormone calcitriol (the active form of vitamin D), which in turn can lead to impaired absorption of dietary calcium. Consequently, the body uses calcium from skeletal stores, which can weaken existing bones.

The current recommendation against supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures is primarily based on the finding of no benefit with supplementation at lower doses. More evidence is needed to determine whether higher doses of supplementation may be more effective at preventing fractures. Although the risk for kidney stones could theoretically increase at higher doses of supplementation, the overall determination of net benefit or net harm will depend on whether a benefit in fracture prevention is also found at higher doses and, if so, what the magnitude of that benefit is.

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from September 26, 2017, to October 24, 2017. To clarify which population the recommendation

applies to, the USPSTF revised the title to "Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults." Some comments expressed concern that the recommendation against supplementation with vitamin D would be misinterpreted by persons with known osteoporosis or vitamin D deficiency. Persons with known osteoporosis or vitamin D deficiency were excluded from the evidence review, and thus are excluded from the recommendation statement, as described in the "Summary of Recommendations and Evidence" and "Patient Population Under Consideration" sections. Other comments requested clarification of the role of vitamin D in persons with known osteoporosis or vitamin D deficiency. This is beyond the scope of the recommendation and has been clarified in the "Scope of Review" section. Some comments also expressed confusion over why a finding of "insufficient evidence" was issued for supplementation at higher doses if the USPSTF recommends against supplementation at lower doses. The recommendation against supplementation at lower doses was based on an overall assessment that supplementation at low doses provides no benefit. Evidence on the effect of supplementation on fractures at higher doses is conflicting, with some studies showing a reduction in certain fracture types at higher doses, and others showing no reduction or even an increase. More studies are needed to more clearly determine if supplementation with vitamin D, calcium, or both consistently prevents fractures. If future evidence shows a benefit, the magnitude of that benefit will need to be weighed against the magnitude of harms caused by supplementation (kidney stones).

## Update of Previous USPSTF Recommendation

This recommendation is consistent with the 2013 USPSTF recommendation on vitamin D supplementation, with or without cal-

cium, to prevent fractures.<sup>36</sup> The USPSTF added evidence on calcium supplementation alone to the evidence review for this recommendation; however, the evidence was too limited to make a separate recommendation about calcium supplementation alone. Evidence from more recent studies confirms that the evidence on fracture prevention with doses of vitamin D greater than 400 IU daily is inconsistent and inadequate, because of underpowering of studies at higher doses. Newer evidence confirms an increased risk for kidney stones with combined vitamin D and calcium supplementation and also suggests no increased incidence of cardiovascular disease with vitamin D supplementation.

## Recommendations of Others

The Institute of Medicine (now the National Academy of Medicine)<sup>37</sup> and the World Health Organization<sup>38</sup> recommend standards for adequate daily intake of calcium and vitamin D as a part of overall health. Neither organization has recommendations specific to fracture prevention. The Institute of Medicine notes the challenge of determining dietary reference intakes given the complex interrelationship between calcium and vitamin D, the inconsistency of studies examining bone health outcomes, and the need to limit sun exposure to minimize skin cancer risk. The National Osteoporosis Foundation supports the Institute of Medicine's recommendations regarding calcium consumption and recommends that adults 50 years or older consume 800 to 1000 IU of vitamin D daily.<sup>39</sup> The Endocrine Society recommends that adults 65 years or older consume 800 IU of vitamin D daily for the prevention of falls and fractures.<sup>40</sup> The American Geriatric Society recommends that adults 65 years or older take daily vitamin D supplementation of at least 1000 IU as well as calcium to reduce the risk for fractures and falls.<sup>41</sup>

### ARTICLE INFORMATION

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#### The US Preventive Services Task Force (USPSTF)

**members:** David C. Grossman, MD, MPH; Susan J. Curry, PhD; Douglas K. Owens, MD, MS; Michael J. Barry, MD; Aaron B. Caughey, MD, PhD; Karina W. Davidson, PhD, MASc; Chyke A. Doubeni, MD, MPH; John W. Epling Jr, MD, MSc; Alex R. Kemper, MD, MPH, MS; Alex H. Krist, MD, MPH; Martha Kubik, PhD, RN; Seth Landefeld, MD; Carol M. Mangione, MD, MSPH; Michael Silverstein, MD, MPH; Melissa A. Simon, MD, MPH; Chien-Wen Tseng, MD, MPH, MSEE.

#### Affiliations of The US Preventive Services Task Force (USPSTF) members:

Kaiser Permanente Washington Health Research Institute, Seattle (Grossman); University of Iowa, Iowa City (Curry); Veterans Affairs Palo Alto Health Care System, Palo Alto, California (Owens); Stanford University, Stanford, California (Owens); Harvard Medical School, Boston, Massachusetts (Barry); Oregon Health & Science University, Portland (Caughey); Columbia University, New York, New York (Davidson); University of Pennsylvania, Philadelphia (Doubeni); Virginia Tech Carilion School of Medicine, Roanoke (Epling); Nationwide Children's Hospital, Columbus, Ohio (Kemper); Fairfax Family Practice Residency, Fairfax, Virginia (Krist); Virginia Commonwealth University, Richmond (Krist); Temple University, Philadelphia,

Pennsylvania (Kubik); University of Alabama at Birmingham (Landefeld); University of California, Los Angeles (Mangione); Boston University, Boston, Massachusetts (Silverstein); Northwestern University, Evanston, Illinois (Simon); University of Hawaii, Honolulu (Tseng); Pacific Health Research and Education Institute, Honolulu, Hawaii (Tseng).

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