

Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: New U.S. Preventive Services Task Force (USPSTF) recommendation statement on vitamin D and calcium supplementation to prevent fractures in adults.

Methods: The USPSTF commissioned 2 systematic evidence reviews and a meta-analysis on vitamin D supplementation with or without calcium to assess the effects of supplementation on bone health outcomes in community-dwelling adults, the association of vitamin D and calcium levels with bone health outcomes, and the adverse effects of supplementation.

Population: These recommendations apply to noninstitutionalized or community-dwelling asymptomatic adults without a history of fractures. This recommendation does not apply to the treatment of persons with osteoporosis or vitamin D deficiency.

Recommendation: The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms

of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D₃ and greater than 1000 mg of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. (I statement)

The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D₃ and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. (D recommendation)

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For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the **Appendix** (available at www.annals.org).

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific clinical preventive services for patients without 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.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

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

The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D₃ and greater than 1000 mg of calcium for the

primary prevention of fractures in noninstitutionalized postmenopausal women. (I statement)

The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D₃ and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. (D recommendation)

The USPSTF has previously concluded in a separate recommendation that vitamin D supplementation is effective in preventing falls in community-dwelling adults aged 65 years or older who are at increased risk for falls. (B recommendation)

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

See also:

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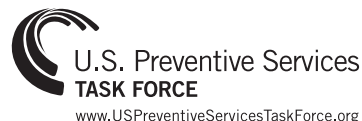
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Summary for Patients. I-36

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Figure. Vitamin D and calcium supplementation to prevent fractures in adults: clinical summary of U.S. Preventive Services Task Force recommendation.

Annals of Internal Medicine



**VITAMIN D AND CALCIUM SUPPLEMENTATION TO PREVENT FRACTURES IN ADULTS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

Population	Men or premenopausal women	Community-dwelling postmenopausal women at doses of >400 IU of vitamin D ₃ and >1000 mg of calcium	Community-dwelling postmenopausal women at doses of ≤400 IU of vitamin D ₃ and ≤1000 mg of calcium
Recommendation	No recommendation. Grade: I statement	No recommendation. Grade: I statement	Do not supplement. Grade: D

Preventive Medications	<p>Appropriate intake of vitamin D and calcium are essential to overall health. However, there is inadequate evidence to determine the effect of combined vitamin D and calcium supplementation on the incidence of fractures in men or premenopausal women.</p> <p>There is adequate evidence that daily supplementation with 400 IU of vitamin D₃ and 1000 mg of calcium has no effect on the incidence of fractures in postmenopausal women.</p> <p>There is inadequate evidence regarding the effect of higher doses of combined vitamin D and calcium supplementation on fracture incidence in community-dwelling postmenopausal women.</p>		
Balance of Benefits and Harms	Evidence is lacking regarding the benefit of daily vitamin D and calcium supplementation for the primary prevention of fractures, and the balance of benefits and harms cannot be determined.	Evidence is lacking regarding the benefit of daily supplementation with >400 IU of vitamin D ₃ and >1000 mg of calcium for the primary prevention of fractures in postmenopausal women, and the balance of benefits and harms cannot be determined.	Daily supplementation with ≤400 IU of vitamin D ₃ and ≤1000 mg of calcium has no net benefit for the primary prevention of fractures.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for osteoporosis and vitamin D supplementation to prevent falls in community-dwelling older adults. These recommendations are available at www.uspreventiveservicestaskforce.org .		

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

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

RATIONALE

Importance

Fractures, particularly hip fractures, are associated with chronic pain and disability, loss of independence, decreased quality of life, and increased mortality (1). One half of all postmenopausal women will have an osteoporosis-related fracture during their lifetime.

Appropriate intake of vitamin D and calcium are essential to overall health. The Institute of Medicine has published recommended dietary allowances (**Table**). However, the benefits and harms of daily supplementation with

greater than 400 IU of vitamin D₃ and greater than 1000 mg of calcium to prevent fractures are not clearly understood.

Benefits of Preventive Medication

In premenopausal women and in men, there is inadequate evidence to determine the effect of combined vitamin D and calcium supplementation on the incidence of fractures. In postmenopausal women, there is adequate evidence that daily supplementation with 400 IU of vitamin D₃ combined with 1000 mg of calcium has no effect on the incidence of fractures. However, there is inadequate evidence about the effect of higher doses of combined vitamin D and calcium supplementation on fracture incidence in noninstitutionalized postmenopausal women.

Harms of Preventive Medication

Adequate evidence indicates that supplementation with 400 IU or less of vitamin D₃ and 1000 mg or less of

calcium increases the incidence of renal stones. The USPSTF assessed the magnitude of this harm as small.

USPSTF Assessment

Noninstitutionalized, Community-Dwelling Postmenopausal Women

The USPSTF concludes that evidence is lacking about the benefit of daily supplementation with greater than 400 IU of vitamin D₃ and greater than 1000 mg of calcium for the primary prevention of fractures, 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 D₃ and 1000 mg or less of calcium has no net benefit for the primary prevention of fractures.

Men and Premenopausal Women

The USPSTF concludes that evidence is lacking about the benefit of vitamin D supplementation with or without calcium for the primary prevention of fractures, and the balance of benefits and harms cannot be determined.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to noninstitutionalized or community-dwelling asymptomatic adults without a history of fractures. "Community-dwelling" is defined as not living in an assisted living facility, nursing home, or other institutional care setting. This recommendation does not apply to persons with osteoporosis or vitamin D deficiency.

Considerations for Practice Regarding the I Statements

Potential Preventable Burden

The health burden of fractures is substantial in the older adult population.

Potential Harms

In the Women's Health Initiative (WHI), a statistically increased incidence of renal stones occurred in women taking supplemental vitamin D and calcium. One woman was diagnosed with a urinary tract stone for every 273 women who received supplementation over a 7-year follow-up.

Costs

Vitamin D and calcium supplements are inexpensive and readily available without a prescription.

Current Practice

Vitamin D and calcium supplementation are often recommended for women, especially postmenopausal women, to prevent fractures. Surveys estimate that 56% of women aged 60 years or older take supplemental vitamin

Table. Institute of Medicine 2011 Recommended Dietary Allowances for Vitamin D and Calcium*

Population	Recommended Daily Dose	
	Vitamin D, IU	Calcium, mg
Women		
Aged 19–50 y	600	1000
Aged 51–70 y	600	1200
Aged >70 y	800	1200
Pregnant women		
Aged <18 y	600	1300
Aged >18 y	600	1000
Breastfeeding women		
Aged <18 y	600	1300
Aged >18 y	600	1000
Men		
Aged 19–50 y	600	1000
Aged 51–70 y	600	1000
Aged >70 y	800	1200

* Data from references 11 and 12.

D and 60% take a supplement containing calcium. The exact dosage is not well-known (2).

Other Approaches to Prevention

The USPSTF recommends screening for osteoporosis in women aged 65 years or older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors. This recommendation statement is available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).

The USPSTF recommends vitamin D supplementation (the median dose of vitamin D in available studies was 800 IU) to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls because of a history of recent falls or vitamin D deficiency (B recommendation). This recommendation statement is available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).

OTHER CONSIDERATIONS

Research Needs and Gaps

Research is needed to determine whether daily supplementation with greater than 400 IU of vitamin D₃ and greater than 1000 mg of calcium reduces fracture incidence in postmenopausal women or older men. The comparative effectiveness of different preparations of vitamin D (for example, D₂ vs. D₃) or different calcium formulations should be evaluated. Prospective studies should assess the potential benefits of vitamin D and calcium supplementation in early adulthood on fracture incidence later in life. Studies are 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 are done in this population and it is difficult to extrapolate results to nonwhite populations.

DISCUSSION

Burden of Disease

Each year, approximately 1.5 million osteoporotic fractures occur in the United States. Nearly half of all women older than 50 years will have an osteoporosis-related fracture during their lifetime. Fractures are associated with chronic pain, disability, and decreased quality of life. Hip fractures significantly increase illness and death. During the first 3 months after a hip fracture, a person's mortality risk is 2.8 to 4 times that of a person of similar age living in the community without a fracture. Nearly 20% of patients with hip fracture are subsequently institutionalized in long-term care facilities (3).

Scope of Review

The USPSTF used 2 systematic evidence reviews and an updated meta-analysis on vitamin D supplementation with or without calcium (4–6) to assess the effects of supplementation on bone health outcomes in community-dwelling adults, the association of vitamin D and calcium levels with bone health outcomes, and the adverse effects of supplementation. The USPSTF did not consider questions relating to adequate daily intake of calcium and vitamin D, nor did it examine the effect of calcium supplementation alone. The systematic reviews did not examine other health outcomes, such as pregnancy complications, prevention of falls, cardiovascular disease, or overall mortality.

The assessment of vitamin D supplementation with or without calcium to prevent cancer was removed from this recommendation statement and will be incorporated into a separate, upcoming recommendation statement.

Effectiveness of Preventive Medication

Sixteen randomized, controlled trials with considerable heterogeneity in populations, settings, and interventions examined the effect of vitamin D supplementation with or without calcium on fracture incidence in adults (6). Postmenopausal women represented the largest group of participants in the trials; no trials included women of childbearing age or men younger than 50 years. Almost all trial participants were white. Six trials reported a history of fractures in 10.6% to 26% of participants. Two trials included only adults with a history of fractures, and 5 trials included only elderly institutionalized adults.

Vitamin D doses ranged from 300 to 1370 IU daily, although most trials used at least 800 IU daily. Five trials compared vitamin D with placebo or no treatment, 8 trials compared vitamin D and calcium with placebo or no treatment, 4 trials compared vitamin D and calcium with calcium alone, and 1 trial compared vitamin D and calcium with vitamin D alone; 1 trial had several comparisons.

Most of the trials used vitamin D₃ as the intervention, but 3 used vitamin D₂. Calcium supplementation also varied. Most trials used calcium carbonate, whereas others used citrate-, lactate-, or phosphate-based preparations. Methods for fracture ascertainment included self-report, radiograph confirmation, administrative data, physician verification, or some combination.

The USPSTF considered 6 randomized trials evaluating the use of vitamin D and calcium supplementation within the scope of this recommendation. These trials were conducted in community-dwelling adults, and fewer than 26% had a history of fractures. No statistically significant reduction in fractures was observed in these studies (pooled relative risk, 0.89 [95% CI, 0.76 to 1.04]). The largest trial of fracture outcomes included in the meta-analysis was the WHI trial (7), which enrolled 36 282 healthy postmenopausal women aged 50 to 79 years. Approximately 83% of enrolled women were white, 9% were black, 4% were Hispanic, and 4% were of other races. The intervention group received 400 IU of vitamin D₃ and 1000 mg of calcium daily; the control group received placebo. This study reported no statistically significant reduction in hip fracture (hazard ratio, 0.88 [CI, 0.72 to 1.08]) or total fractures (hazard ratio, 0.96 [CI, 0.91 to 1.02]). However, the USPSTF could not generalize the results of the WHI trial beyond the specific dose, preparation, and population studied. Nearly 30% of study participants were already taking 500 mg or more of calcium daily before the start of the trial.

Trials of vitamin D supplementation alone showed no statistical difference (pooled relative risk, 1.03 [CI, 0.84 to 1.26]). Of the 12 trials reporting baseline levels of vitamin D, 5 reported mean vitamin D levels less than 30 nmol/L, a level considered to be vitamin D–deficient. However, neither baseline vitamin D status nor supplement dose correlated with supplement efficacy.

An individual patient data meta-analysis (8) published after the USPSTF's review included 31 022 persons aged 65 years or older from 11 trials, many of which were included in the USPSTF review. The meta-analysis concluded that fractures may be reduced for persons taking higher doses of vitamin D (≥ 800 IU daily). The effect was seen in both institutionalized and community-dwelling adults. The subgroup thresholds were not predefined by the original trial authors, and the reduction was not considered statistically significant when adjusted for several subgroup analyses. Therefore, any positive findings should be viewed with caution.

Potential Harms of Preventive Medication

Reporting of adverse outcomes in clinical trials and observational studies of vitamin D and calcium supplementation is limited. The WHI trial (9) reported an increased risk for nephrolithiasis (hazard ratio, 1.17 [CI, 1.02 to 1.34]). The absolute risk was 2.5% in the intervention group and 2.1% in the placebo group, with a number

needed to harm of 273. It is uncertain if this adverse effect occurs in vitamin D–deficient populations. A meta-analysis of calcium supplementation (10) suggests an association between calcium use and increased risk for cardiovascular disease, but the link has not been consistently demonstrated. The effect was primarily seen in persons taking calcium alone and not in combination with vitamin D. None of the studies reviewed by the USPSTF reported this adverse effect.

Estimate of Magnitude of Net Benefit

Except for postmenopausal women, there is inadequate evidence to estimate the benefits of vitamin D or calcium supplementation to prevent fractures in noninstitutionalized adults. Due to the lack of effect on fracture incidence and the increased incidence of nephrolithiasis in the intervention group of the WHI trial, the USPSTF concludes with moderate certainty that daily supplementation with 400 IU of vitamin D₃ and 1000 mg of calcium has no net benefit for the primary prevention of fractures in noninstitutionalized, postmenopausal women. Although women enrolled in WHI were predominately white, the lower risk for fractures in nonwhite women makes it very unlikely that a benefit would exist in this population.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 12 June to 10 July 2012. The USPSTF received more than 40 comments. In response, information was added to the Rationale section to reinforce the basic dietary requirements for vitamin D and calcium. Several recently published studies on the benefits and harms of vitamin D and calcium supplementation were reviewed, and their results were highlighted in the Discussion section. The dose of calcium used in the WHI trial was clarified throughout the statement.

How Does Evidence Fit With Biological Understanding?

Calcium is one of the main building blocks of bone growth. Vitamin D helps bones absorb calcium. Normal healthy bones turn over calcium constantly, replacing calcium loss with new calcium received from dietary intake. There are 2 main sources of vitamin D in the human body. Ergocalciferol, or vitamin D₂, is consumed in the diet, mainly in the form of fatty fish. Fortified foods, such as milk, yogurt, and orange juice, provide other dietary sources of vitamin D. Cholecalciferol, or vitamin D₃, is synthesized in the skin by ultraviolet B rays from the sun. Vitamin D₃ is converted to its active form by means of enzymatic processes in the liver and kidney. 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. Insufficient amounts of vitamin D obtained through the 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 dietary calcium absorption. Subsequently, the body uses calcium from skeletal stores, which can weaken existing bones.

RECOMMENDATIONS OF OTHERS

The Institute of Medicine (Table) (11) and the World Health Organization (12) have recommended standards for adequate daily intake of calcium and vitamin D as a part of overall health. Neither organization has made 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.

From the U.S. Preventive Services Task Force, Rockville, Maryland.

Disclaimer: Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Financial Support: The USPSTF is an independent, voluntary body. The U.S. Congress mandates that the Agency for Healthcare Research and Quality support the operations of the USPSTF.

Potential Conflicts of Interest: None disclosed. Disclosure forms from USPSTF members can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0215.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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The screenshot shows the homepage of the Annals of Internal Medicine website. At the top, it says 'ACP AMERICAN COLLEGE OF PHYSICIANS' and 'ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS'. The main navigation bar includes links for Home, Current Issue, All Issues, Online First, Collections, In the Clinic, Journal Club, CME, Audio & Video, My Account, and Submit. A search bar is located in the top right corner. The main content area features a large article preview for 'Preventing Falls' with a sub-headline: 'The US Preventive Services Task Force recommends exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling older adults at increased risk for falls.' Below this, there are sections for 'Online First' (Most Recent Posts, RSS, Email Alert, Online First Index), 'Current Issue' (7 Aug 2012 | Vol. 157, No. 3, RSS, Email Alert, Table of Contents), and 'Original Research' (Should the HbA_{1c} Diagnostic Cutoff Differ Between Blacks and Whites?). On the right side, there is a 'Sign In' section with options for individual or institutional login, and a 'Most Read This Week' section listing several articles. At the bottom right, there is a 'COLLECTIONS' section with links to Guidelines, End-of-Life Care, and Rheumatology.

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APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (Baylor College of Medicine, Houston, Texas); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); and Douglas K. Owens, MD, MS (Veteran Affairs Palo Alto Health Care System, Palo Alto, California, and Stanford University, Stanford, California). Former USPSTF members who contributed to the development of this recommendation are Diana Pettiti, MD, MPH; Timothy J. Wilt, MD, MPH; and Bernadette Melnyk, PhD, RN.

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. 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/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/provide this service.
C	<i>Note: The following statement is undergoing revision.</i> Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms, there is likely to be only a small benefit from this service.	Offer/provide this service only if other considerations support offering or providing the service in an individual patient.
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 measured.	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.

Appendix Table 2. 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; and 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 that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an 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 on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.