

Screening for Vitamin D Deficiency in Adults: U.S. Preventive Services Task Force Recommendation Statement

Michael L. LeFevre, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

Description: New USPSTF recommendation on screening for vitamin D deficiency in adults.

Methods: The USPSTF reviewed the evidence on screening for and treatment of vitamin D deficiency, including the benefits and harms of screening and early treatment.

Population: This recommendation applies to community-dwelling, nonpregnant adults aged 18 years or older who are seen in primary care settings and are not known to have signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended.

Recommendation: 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. (I statement)

Ann Intern Med. doi:10.7326/M14-2450

For author affiliation, see end of text.

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

This article was published online first at www.annals.org on 25 November 2014.

www.annals.org

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care 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 RECOMMENDATION AND EVIDENCE

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. (I statement)

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

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

See also:

Related article: Ann Intern Med.M14-1659. 1
Editorial comment 2
Summary for Patients 3

Web-Only
CME quiz

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

No consensus exists on the definition of vitamin D deficiency or the optimal level of total serum 25-hydroxyvitamin D [25-(OH)D] (the major form of vitamin D that circulates in the body). Depending on which cut point is used (usually <50 or <75 nmol/L [<20 or <30 ng/mL]), some studies have shown that low levels of vitamin D are associated with increased risk for fractures, functional limitations, cancer, diabetes, cardiovascular disease, depression, and death (1-3).

Detection

Many testing methods are available that measure total serum 25-(OH)D levels. However, the accuracy of these tests to detect vitamin D deficiency is difficult to determine because of the lack of studies that use an internationally recognized reference standard and the lack of consensus on the laboratory values that define vitamin D deficiency. The USPSTF found evidence suggesting that results vary by testing method and between laboratories using the same testing methods.

Benefits of Detection and Early Treatment

The USPSTF found no studies that evaluated the direct benefit of screening for vitamin D deficiency in adults. The USPSTF found adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on cancer, type 2 diabetes mellitus, risk for death in community-dwelling adults, and risk for frac-



U.S. Preventive Services
TASK FORCE

www.USPreventiveServicesTaskForce.org

© 2015 American College of Physicians 1

Figure. Screening for Vitamin D Deficiency in Adults: U.S. Preventive Services Task Force Recommendation Statement**Annals of Internal Medicine**

Population	Community-dwelling, nonpregnant, asymptomatic adults aged ≥ 18 y
Recommendation	No recommendation. Grade: I statement (insufficient evidence)
Risk Assessment	Persons with low vitamin D intake, decreased vitamin D absorption, and little or no sun exposure (for example, due to the winter season, high latitude, or physical sun avoidance) may be at increased risk for vitamin D deficiency. Obesity and darker skin pigmentation may be associated with low levels of serum 25-hydroxyvitamin D (25-[OH]D), but it is not clear whether low levels in these populations reflect vitamin D deficiency or are associated with adverse clinical outcomes.
Screening Tests	Numerous testing methods to measure serum 25-(OH)D are available. However, their accuracy is difficult to determine because of the lack of studies that use an internationally recognized reference standard and the lack of consensus on the laboratory values that define vitamin D deficiency.
Treatment and Interventions	Oral vitamin D is the most common treatment for vitamin D deficiency; available forms include vitamin D ₃ (cholecalciferol) and vitamin D ₂ (ergocalciferol). Other treatment options include increasing dietary vitamin D intake or sun exposure, although sun exposure is not generally recommended because it can increase the risk for skin cancer.
Balance of Benefits and Harms	The current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.
Other Relevant USPSTF Recommendations	The USPSTF has recommendations on the use of vitamin D supplementation for the prevention of falls and fractures and vitamin supplementation for the prevention of cardiovascular disease or cancer. These recommendations are available on the USPSTF Web site (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.

tures in persons not selected on the basis of being at high risk for fractures. The USPSTF found inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including psychosocial and physical functioning. Although the evidence is adequate for a few limited outcomes, the overall evidence on the early treatment of asymptomatic, screen-detected vitamin D deficiency in adults to improve overall health outcomes is inadequate.

Harms of Detection and Early Treatment

The USPSTF found no studies that evaluated the direct harms of screening for vitamin D deficiency. The USPSTF found adequate evidence that the harms of treatment of vitamin D deficiency are small to none. No studies reporting on the harms of treatment of vitamin D deficiency identified a significant increase in total adverse events, hypercalcemia, kidney stones, or gastrointestinal symptoms.

USPSTF Assessment

The USPSTF concludes that the evidence on screening for vitamin D deficiency in asymptomatic adults to improve health outcomes is insufficient and that the balance of benefits and harms of screening and early intervention cannot be determined.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to community-dwelling, nonpregnant adults aged 18 years or older

who are seen in primary care settings and are not known to have signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended. This recommendation focuses on screening (that is, testing for vitamin D deficiency in asymptomatic adults and treating those who are found to have a deficiency), which is different from other USPSTF recommendation statements on supplementation (that is, recommending preventive medication for patients at increased risk for a specific negative health outcome, such as falls, regardless of whether they have a deficiency).

The USPSTF recognizes that there is no consensus on how to define vitamin D deficiency and does not endorse the use of a specific threshold to identify it. The evidence reviewed by the USPSTF used varying cut points. For the purposes of this recommendation statement, the term "vitamin D deficiency" is used to reflect evidence from study populations generally representing total serum 25-(OH)D levels of 75 nmol/L (30 ng/mL) or less or subpopulations of studies with levels less than 50 nmol/L (<20 ng/mL).

Suggestions for Practice Regarding the I Statement

Potential Preventable Burden

Given the lack of consensus on how to define and assess vitamin D deficiency, its precise prevalence estimates are difficult to determine. To collect precise estimates, accurate assay methods, an internationally recognized reference standard, and a specific cut point for

defining vitamin D deficiency need to be established. Reported estimates of the prevalence of vitamin D deficiency vary widely depending on the period, cut point, study population, study design, and testing method. Estimates range from as low as 19% using a statistical modeling approach (4) to as high as 77% based on NHANES (National Health and Nutrition Examination Survey) data from 2001 to 2004 (using a cut point of <75 nmol/L [<30 ng/mL]) (5).

The effect of vitamin D levels on health outcomes is difficult to evaluate. Lower vitamin D levels have been reported to increase risk for fractures, falls, functional limitations, some types of cancer, diabetes, cardiovascular disease, depression, and death. However, observations of these associations are inconsistent and may vary by the cut point used to define low vitamin D levels and by subpopulation (defined by race or institutionalization). For example, African Americans have paradoxically lower reported rates of fractures despite having increased prevalence of low vitamin D levels than white persons.

If a threshold total serum 25-(OH)D level could be established to define vitamin D deficiency and if testing assays could be standardized, the goal of screening for vitamin D deficiency would be to identify and treat it before associated adverse clinical outcomes occur. However, current evidence is inadequate to determine whether screening for and treatment of asymptomatic low 25-(OH)D levels improve clinical outcomes in community-dwelling adults.

Potential Harms

Screening may misclassify persons with a vitamin D deficiency because of the uncertainty about the cut point for defining deficiency and the variability of available testing assays. Misclassification may result in overdiagnosis (which may lead to nondeficient persons receiving unnecessary treatment) or underdiagnosis (which may lead to deficient persons not receiving treatment).

A rare but potential harm of treatment with oral vitamin D is toxicity, which may lead to hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone, and hypercalciuria. However, the 25-(OH)D level associated with toxicity (often defined as >500 nmol/L [>200 ng/mL]) (6) is well above the level considered to be sufficient. Treatment with vitamin D plus calcium may also be associated with increased risk for kidney stones; vitamin D alone does not seem to increase this risk. In general, treatment with oral vitamin D does not seem to be associated with serious harms. Treatment with increased sun exposure (specifically ultraviolet B [UVB] radiation) may increase risk for skin cancer. Because of this concern, increased sun exposure is generally not recommended as treatment of vitamin D deficiency.

Costs

Several vitamin D testing methods are available; the cost of screening varies.

Current Practice

Testing rates for vitamin D levels seem to be increasing, despite the uncertainty about the definition of deficiency. Although estimates of screening rates in primary care settings are not available, a recent study evaluating data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey found that the annual rate of outpatient visits associated with a diagnosis code for vitamin D deficiency more than tripled between 2008 and 2010 (1177 visits per 100 000 population in 2010) (7). In addition, according to a 2009 survey, total serum 25-(OH)D testing increased by at least 50% compared with the previous year in more than half of the clinical laboratories surveyed (8).

Assessment of Risk

Although there is not enough evidence to support screening for vitamin D deficiency, some evidence suggests factors that may increase risk for vitamin D deficiency. Persons with low vitamin D intake, decreased vitamin D absorption, and little or no sun exposure (for example, due to the winter season, high latitude, or physical sun avoidance) may be at increased risk for vitamin D deficiency (1, 2). Obesity and darker skin pigmentation may also be associated with low levels of total serum 25-(OH)D, but whether these factors reflect vitamin D deficiency or increase the risk for adverse clinical outcomes is unclear. Obesity may allow for greater sequestration of vitamin D into adipose tissue; however, this vitamin D may still be bioavailable (1, 2). Increased skin pigmentation reduces the skin's ability to produce vitamin D in response to UVB exposure. Prevalence rates of low total serum 25-(OH)D are 2 to 9 times higher in African Americans and 2 to 3 times higher in Hispanics than in white persons (1), yet the risk for fractures in African Americans is half that in white persons (9). Other factors, such as body composition and calcium economy, have been proposed to explain this paradox (10); however, a recent study suggests that although total serum 25-(OH)D levels in African Americans may be low, the concentration of bioavailable 25-(OH)D may not be (1, 11). Some evidence suggests that older age and female sex may also be associated with increased risk for vitamin D deficiency; however, these findings are inconsistent (1).

Screening Tests

Current vitamin D assays measure total serum 25-(OH)D levels to determine vitamin D status (that is, whether a person is considered to have or not have a deficiency). Many testing methods are available, including competitive protein binding, immunoassay, high-performance liquid chromatography, and combined high-performance liquid chromatography and mass spectrometry. However, the sensitivity and specificity of these tests are unknown because of the lack of studies that use an internationally recognized reference standard. Variability between assay methods and between laboratories using the same methods may range from 10% to 20%, and classification of samples as "deficient" or "nondeficient" may vary by 4% to 32%, depending

CLINICAL GUIDELINE

Screening for Vitamin D Deficiency in Adults

on which assay is used (1, 2). Another factor that may complicate interpretation is that 25-(OH)D may act as a negative acute-phase reactant, and its levels may decrease in response to inflammation. Lastly, whether common laboratory reference ranges are appropriate for all ethnic groups is unclear.

Treatment and Interventions

Oral vitamin D is most often used to treat vitamin D deficiency; other treatment options include increasing dietary vitamin D intake or UVB exposure. Commonly available forms of oral vitamin D include vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol).

Additional Approaches to Prevention

According to the Institute of Medicine, daily dietary vitamin D intake of 600 IU in adults aged 18 to 70 years and 800 IU in adults older than 70 years should be sufficient to meet the needs of 97.5% of the adult population (12). Ultraviolet B exposure may also increase vitamin D levels; however, several variables (such as the time of day, season, cloud cover, skin pigmentation, and sunscreen use) can affect the length of exposure needed to attain sufficient vitamin D levels. Sun exposure to prevent vitamin D deficiency is not generally recommended because it increases the risk for skin cancer associated with UVB radiation.

Useful Resources

The USPSTF has published recommendations on the use of vitamin D supplementation for the prevention of falls and fractures and vitamin supplementation for the prevention of cardiovascular disease or cancer (available at www.uspreventiveservicestaskforce.org). These recommendations differ from the current recommendation statement in that they address vitamin D supplementation in certain populations at high risk for falls, fractures, cardiovascular disease, or cancer without first determining a patient's vitamin D status.

OTHER CONSIDERATIONS

Research Needs and Gaps

The lack of an accurate screening strategy to identify vitamin D deficiency, especially in important subpopulations (such as African Americans), is a critical gap in the evidence. Further research is needed to determine the cut point that defines vitamin D deficiency, the sensitivity and specificity of various assays using an internationally accepted reference standard, and whether total serum 25-(OH)D is the best measure of vitamin D deficiency in all populations. The possible effects of acute inflammation on vitamin D levels also needs further investigation. More studies are also needed to evaluate which treatment regimens may benefit specific vitamin D-deficient populations, such as men and non-Caucasian ethnic groups, who are absent from the evidence base. Lastly, further studies are needed to evaluate the harms of screening for and treatment of vitamin D deficiency. One ongoing trial, VITAL (VITamin D and Omega-3 Trial), may provide some answers in the near future. This large random-

ized, double-blind, placebo-controlled trial is designed to evaluate the effect of vitamin D supplementation on the prevention of cancer and cardiovascular disease in a multiethnic study population. Furthermore, because a large portion of the study population will have baseline 25-(OH)D levels measured, the study may provide information on whether supplementation in vitamin D-deficient populations is beneficial.

DISCUSSION

Burden of Disease

Vitamin D is a fat-soluble vitamin that helps regulate calcium homeostasis and bone health. Important sources of vitamin D include diet (such as fatty fish, cod liver oil, dairy products, fortified beverages and foods, and supplements) and endogenous synthesis triggered by UVB exposure. Inadequate dietary vitamin D intake, decreased vitamin D absorption, and limited UVB exposure can all decrease vitamin D levels, but the exact threshold that defines vitamin D deficiency is not well-established. Furthermore, the association between vitamin D status and health outcomes is unclear.

Severe and prolonged vitamin D deficiency can cause bone mineralization diseases, such as rickets in children and osteomalacia in adults. Other health effects caused by more moderate decreases in vitamin D levels, which were the focus of the current evidence review, are difficult to determine. Studies have evaluated the association between vitamin D status and health outcomes, such as fractures, falls, cancer, cardiovascular disease, death, functional limitations, diabetes, and depression. Results have varied depending on the cut point used to define deficiency, population, and setting (1, 2). Overall, studies have suggested a decreased risk for colorectal cancer with higher 25-(OH)D levels and either an inverse or a U-shaped relationship with mortality. Studies on risk for fractures, falls, and cardiovascular disease have been less consistent; most often, white populations showed an increased risk for fractures and cardiovascular disease, and institutionalized populations showed an increased risk for falls. Few studies have evaluated associations with functional limitations, diabetes, or depression, but these studies have generally suggested an increased risk with lower 25-(OH)D levels (1, 2).

Childhood rickets has become relatively rare in the United States since vitamin D-fortified milk was introduced in the 1930s. Prevalence rates of less clinically overt vitamin D deficiency are much more difficult to characterize given the uncertainty about how to define adequate levels of vitamin D and which cut point defines deficiency. In addition, the lack of a reference standard for vitamin D testing until recently has further complicated accurate measurement of vitamin D deficiency prevalence rates.

A recent study using a statistical probability approach estimated that 19% of the U.S. population is at risk for vitamin D inadequacy (4). On the basis of NHANES data, 33% of the U.S. population had 25-(OH)D levels at 50 nmol/L (20 ng/mL) or less from 2001

to 2006 (13) and 77% had levels less than 75 nmol/L (<30 ng/mL) from 2001 to 2004 (5).

Commonly reported risk factors for low 25-(OH)D levels are decreased dietary vitamin D intake, absorption, or synthesis due to decreased sun exposure or darker skin pigmentation; older age; inflammatory bowel disease, malabsorptive conditions, or history of gastric bypass; being homebound or institutionalized; routinely wearing clothing that prevents sun exposure on most of the skin; and living at high latitudes (14).

Populations with darker skin pigmentation, such as African Americans, Hispanics, and Asians, have been found to have lower 25-(OH)D levels than white populations. According to the Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population (based on NHANES data from 2003 to 2006), 21.7% of white persons had 25-(OH)D levels of 50 nmol/L (20 ng/mL) or less compared with 70.6% of African Americans and 44.2% of Hispanics; further, the geometric mean of 25-(OH)D levels in adults aged 20 years or older ranged from 57.5 to 64 nmol/L (23.0 to 25.6 ng/mL) in white persons, 32.5 to 36.25 nmol/L (13.0 to 14.5 ng/mL) in African Americans, and 44.5 to 46.5 nmol/L (17.8 to 18.6 ng/mL) in Hispanics. However, it is unclear if low 25-(OH)D levels are associated with adverse clinical outcomes in these populations. For example, the increased risk for fractures and cardiovascular disease observed in some studies of white persons has not been found in African Americans (1). A recent study suggests that although total serum 25-(OH)D levels may be lower in African Americans than in white persons, the concentration of bioavailable 25-(OH)D may be similar between the 2 populations when vitamin D-binding protein is considered (11). If substantiated, this finding could potentially explain why higher rates of low total serum 25-(OH)D levels have been reported in African Americans without an associated risk for fractures and question the use of total serum 25-(OH)D measurements to identify vitamin D deficiency in all populations.

Populations with obesity have been found to have lower 25-(OH)D levels; however, this may be due to either increased vitamin D requirements or greater sequestration of vitamin D into adipose tissue. It is not clear whether low 25-(OH)D levels in persons who are obese are associated with negative clinical outcomes (1, 12, 14).

Scope of Review

This is a new topic for the USPSTF. The USPSTF commissioned a review of the evidence on screening for vitamin D deficiency, including the benefits and harms of screening and early treatment. The review focused on community-dwelling, nonpregnant adults aged 18 years or older who do not have clinical signs of vitamin D deficiency or conditions that could cause vitamin D deficiency and were seen in primary care settings. Populations with certain conditions, such as (but not limited to) bone, endocrine, or autoimmune diseases were excluded because vitamin D testing in

these populations could be considered management of a condition rather than general screening. Similarly, because of the unique and increased nutritional demands during pregnancy, vitamin D testing in pregnant women is considered outside the scope of general screening. Although breastfeeding women were not excluded, the review identified no studies of breastfeeding women that met inclusion criteria. For treatment, the review included only oral vitamin D formulations; treatment with nonoral vitamin D therapies or UVB exposure was excluded.

Accuracy of Screening Tests

Despite the availability of many tests that measure total serum 25-(OH)D levels, their sensitivities and specificities are currently unknown given the lack of studies that use an internationally recognized, commutable reference standard. In addition, determining the accuracy of 25-(OH)D assays is complicated by an unclear understanding of how consistently (within a given assay and between assays) 25-(OH)D is displaced from vitamin D-binding protein to be measured and the effect of possible interference from other heterophilic antibodies that may bind and cause inaccurate measurements (15). Studies report testing variability between methods and between laboratories using the same method and that classification of patient samples as deficient or nondeficient can vary by 4% to 32%, depending on which assay is used (1, 2).

Recognizing the need for standardization of vitamin D measurement, a few organizations recently initiated programs to improve testing accuracy. The National Institute of Standards and Technology developed a standard reference material for 25-(OH)D in 2009 that seems to improve testing accuracy of high-performance liquid chromatography and mass spectrometry, but it has limited effects on improving accuracy of immunoassay methods. Since 2010, the Vitamin D Standardization Program (16) has sought to standardize the laboratory measurement of vitamin D status through international collaboration and coordination and has developed standardized procedures for measuring total serum 25-(OH)D for the NHANES. However, these protocols are not yet available for commercial or research laboratory use. The Centers for Disease Control and Prevention offers the Vitamin D Standardization Certification Program, which is a nonregulatory program that helps laboratories maintain and enhance the quality and comparability of measurement results (17). Several external accuracy-based testing systems are available for commercial and research laboratory use, such as the Vitamin D Metabolites Quality Assurance Program (established by the National Institute of Standards and Technology and the National Institutes of Health) and the Vitamin D External Quality Assurance Scheme (1).

In addition to the uncertain accuracy of total serum 25-(OH)D tests, it is unclear if total serum 25-(OH)D is the best indicator of vitamin D status or if bioavailable 25-(OH)D should be used instead. As noted previously, a 2013 study found that although African American

CLINICAL GUIDELINE

Screening for Vitamin D Deficiency in Adults

study participants had lower total serum 25-(OH)D levels than white study participants, both groups had similar concentrations of bioavailable 25-(OH)D. This study highlights the difficulty of using a universal total serum 25-(OH)D cut point to define deficiency across different races. However, more research is needed before this can be confirmed, and commercial testing of bioavailable 25-(OH)D levels is not currently available.

Effectiveness of Early Detection and Treatment

Overall, the USPSTF reviewed 16 trials and 1 nested case-control study that evaluated the effects of treatment of vitamin D deficiency on health outcomes in populations not selected on the basis of signs or symptoms of vitamin D deficiency (1, 2). In general, studies included older adults (most studies had a mean study age >65 years) who were predominantly women (12 studies included women only) and community-dwelling, although 4 studies were conducted in exclusively institutionalized settings. All studies were done in the United States or Europe, with most conducted exclusively in Europe. Studies used vitamin D₃ in doses of 400 to 4800 IU/d or 8400 to 50 000 IU/wk, and 5 studies included treatment with calcium. Follow-up ranged from 2 months to 7 years.

No studies directly assessed the effectiveness of screening for vitamin D deficiency. The USPSTF identified 17 studies that assessed the effectiveness of oral vitamin D treatment on various health outcomes (such as death, falls, fractures, cancer, diabetes, and physical and psychosocial functioning) in participants with vitamin D deficiency who were not selected on the basis of signs or symptoms of deficiency (1, 2). Three studies conducted in Europe reported results suggesting a benefit on mortality in older institutionalized patients who were treated for vitamin D deficiency. However, meta-analysis of 8 studies limited to community-dwelling populations showed no benefit (1, 2). Studies on vitamin D treatment and falls reported mixed results. Five studies evaluated the effect of treatment of vitamin D deficiency on risk for fractures, and no studies, either individually or aggregated in meta-analysis, found a benefit on fracture risk (1, 2). Few studies evaluated the effect of treatment of vitamin D deficiency on risk for cancer or diabetes or physical or psychosocial functioning, but they generally reported no association (1, 2).

Potential Harms of Screening and Treatment

No studies directly assessed the harms of screening for vitamin D deficiency. The USPSTF identified 24 studies (1, 2) that reported on the adverse effects of vitamin D treatment; however, most trials were not designed to assess harms, and reporting of adverse events was generally suboptimal. Study participants were predominantly women, although 2 studies were done exclusively in men. The mean age of study participants ranged from 31 to 85 years, and most studies were conducted in Europe. Five studies were conducted exclusively in institutionalized settings. Vitamin D doses ranged from 400 to 7000 IU/d and 8400 to

54 000 IU/wk, and 5 studies included treatment with vitamin D and calcium. Follow-up ranged from 6 weeks to 4 years.

No significant difference in rates of serious adverse events or withdrawals due to adverse events was reported by any study, either individually or aggregated in meta-analysis (1, 2). Seventeen trials evaluated the risk for hypercalcemia with vitamin D treatment. No individual studies reported a significantly higher incidence of hypercalcemia; overall, 1.7% of treated participants versus 1.3% of control participants had hypercalcemia in trials that reported at least 1 case of hypercalcemia. However, the overall number of cases of hypercalcemia was low, and 7 trials reported no cases. Seven trials reported on risk for kidney stones, 2 of which included treatment with vitamin D and calcium; none reported kidney stones in any participants.

Estimate of Magnitude of Net Benefit

Overall, the USPSTF found insufficient evidence on screening for and early treatment of vitamin D deficiency in community-dwelling, U.S. primary care adult populations. No studies specifically evaluated the effect of screening on health outcomes or the treatment of screen-detected vitamin D deficiency. Studies on treatment of asymptomatic vitamin D deficiency used varying testing methods, cut points for vitamin D deficiency, and treatment regimens. Furthermore, most studies were conducted in elderly white (mostly European) and predominantly female populations; thus, applying the evidence to screening in the general U.S. primary care population is difficult. The harms of early treatment of vitamin D deficiency are small to none, and the evidence on the harms of screening is inadequate. Despite the absence of proven harms of screening, the USPSTF did not find sufficient evidence to determine that the benefits of screening outweigh the potential harms.

The USPSTF found evidence suggesting considerable variation in the way vitamin D is measured and great uncertainty about the specific vitamin D level that determines when treatment with vitamin D would improve health. Furthermore, information is lacking on how to measure and treat vitamin D deficiency in specific subpopulations, such as men, nonwhite ethnic groups, persons who are obese, and less elderly populations. On the basis of the current available science, the USPSTF concludes that the evidence on screening for vitamin D deficiency to improve health outcomes is insufficient and that the balance of benefits and harms of screening and early intervention cannot be determined.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 24 June to 21 July 2014. Several comments requested that the scope of the recommendation be expanded to include special populations, such as those with bone, endocrine, and immune conditions. The USPSTF clarified the recommendation to better explain to which populations it applies and why other popula-

tions were not included. A few comments also requested information on risk assessment tools that could be used to stratify patients into high versus low risk for vitamin D deficiency before testing. The systematic review did not evaluate the evidence on risk assessment tools; however, the USPSTF may consider looking at this information in future updates of the topic. Comments also provided information on additional factors that complicate interpretation of vitamin D tests; the USPSTF added discussion of these factors to the Clinical Considerations and Discussion sections.

RECOMMENDATIONS OF OTHERS

No national, primary care professional organization currently recommends population-wide screening for vitamin D deficiency. The American Academy of Family Physicians concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency (18). The Endocrine Society recommends screening for vitamin D deficiency only in persons at risk and states that there is no evidence showing benefits of screening at a population level (19). It defines vitamin D deficiency as total serum 25-(OH)D levels of less than 50 nmol/L (<20 ng/mL) and vitamin D insufficiency as 52.5 to 72.5 nmol/L (21 to 29 ng/mL) and recommends treatment of persons with a vitamin D deficiency.

Other organizations, including the American Congress of Obstetricians and Gynecologists (20), the American Geriatric Society (21), and the National Osteoporosis Foundation (22), recommend testing for vitamin D as part of osteoporosis management or falls prevention.

The Institute of Medicine does not have formal guidelines on screening for vitamin D deficiency, but it has published a report on the recommended dietary allowance (RDA) for vitamin D (12). The RDA is the estimated requirement to meet or exceed the vitamin D needs of 97.5% of the adult population. Assuming minimal sun exposure, the Institute of Medicine's RDA for vitamin D is 600 IU/d for adults aged 19 to 70 years and 800 IU/d for adults older than 70 years. Furthermore, it concluded that total serum 25-(OH)D levels of 40 nmol/L (16 ng/mL) meet the needs of approximately half of the population, and levels of 50 nmol/L (20 ng/mL) or greater meet the needs of nearly all of the population. However, it is not necessary to evaluate 25-(OH)D levels before discussing RDA with patients.

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.

Disclosures: Dr. Gillman reports royalties from Cambridge University Press and UpToDate outside the submitted work. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-2450.

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

References

1. LeBlanc E, Chou R, Zakher B, Daeges M, Pappas M. Screening for Vitamin D Deficiency: Systematic Review for the U.S. Preventive Services Task Force Recommendation. Evidence synthesis no. 119. AHRQ publication no. 13-05183-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
2. LeBlanc E, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. [Epub ahead of print 25 Nov 2014] doi:10.7326/M14-1659
3. Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). Evidence report/technology assessment no. 217. AHRQ publication no. 14-E004-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
4. Taylor CL, Carriquiry AL, Bailey RL, Sempos CT, Yetley EA. Appropriateness of the probability approach with a nutrient status biomarker to assess population inadequacy: a study using vitamin D. *Am J Clin Nutr*. 2013;97:72-8. [PMID: 23097269] doi:10.3945/ajcn.112.046094
5. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med*. 2009;169:626-32. [PMID: 19307527] doi:10.1001/archinternmed.2008.604
6. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr*. 2008;88:582S-586S. [PMID: 18689406]
7. Huang KE, Milliron BJ, Davis SA, Feldman SR. Surge in US outpatient vitamin D deficiency diagnoses: National Ambulatory Medical Care Survey analysis. *South Med J*. 2014;107:214-7. [PMID: 24937512] doi:10.1097/SMJ.0000000000000085
8. Rollins G. Vitamin D testing—what's the right answer? *Clinical Laboratory News*. 2009;35:1, 6, 8.
9. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, et al. Osteoporosis and fracture risk in women of different ethnic groups. *J Bone Miner Res*. 2005;20:185-94. [PMID: 15647811]
10. Aloia JF. African Americans, 25-hydroxyvitamin D, and osteoporosis: a paradox. *Am J Clin Nutr*. 2008;88:545S-550S. [PMID: 18689399]
11. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med*. 2013;369:1991-2000. [PMID: 24256378] doi:10.1056/NEJMoa1306357
12. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Pr; 2011.
13. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. NCHS Data Brief. 2011;1-8. [PMID: 21592422]
14. National Institutes of Health. Vitamin D: fact sheet for health professionals. Bethesda, MD: National Institutes of Health; 2011. Accessed at <http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional> on 21 October 2014.

CLINICAL GUIDELINE

Screening for Vitamin D Deficiency in Adults

15. **Carter GD.** 25-hydroxyvitamin D: a difficult analyte [Editorial]. *Clin Chem.* 2012;58:486-8. [PMID: 22238254] doi:10.1373/clinchem.2011.180562
16. **National Institutes of Health, Office of Dietary Supplements.** Vitamin D standardization program. Bethesda, MD: National Institutes of Health; 2014. Accessed at <http://ods.od.nih.gov/Research/vdsp.aspx> on 22 October 2014.
17. **Vesper HW, Cook Botelho J.** Vitamin D standardization certification program. Atlanta, GA: Centers for Disease Control and Prevention; 2014. Accessed at www.cdc.gov/labstandards/pdf/hs/Vitamin_D_Protocol.pdf on 21 October 2014.
18. **American Academy of Family Physicians.** Recommendations by type: clinical preventive services. Leawood, KS: American Academy of Family Physicians; 2014. Accessed at www.aafp.org/patient-care/clinical-recommendations/cps.html on 22 October 2014.
19. **Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al; Endocrine Society.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911-30. [PMID: 21646368] doi:10.1210/jc.2011-0385
20. **Committee on Practice Bulletins-Gynecology, The American College of Obstetricians and Gynecologists.** ACOG Practice Bulletin N. 129. Osteoporosis. *Obstet Gynecol.* 2012;120:718-34. [PMID: 22914492] doi:10.1097/AOG.0b013e31826dc446
21. **American Geriatrics Society.** AGS/BGS clinical practice guideline: prevention of falls in older persons. New York: American Geriatrics Society; 2010. Accessed at www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/prevention_of_falls_summary_of_recommendations on 22 October 2014.
22. **National Osteoporosis Foundation.** Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014. Accessed at <http://nof.org/files/nof/public/content/file/2791/upload/919.pdf> on 21 October 2014.

APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Michael L. LeFevre, MD, MSPH, *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); Kirsten Bibbins-Domingo, PhD, MD, MAS, *Co-Vice Chair* (University of California, San Francisco, San Francisco, California); Linda Ciofu Baumann, PhD, RN, APRN (University of Wisconsin, Madison, Wisconsin); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Karina W. Davidson, PhD, MASc (Columbia University, New York, New York); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH (Pima County Department of Health,

Tucson, Arizona); Matthew Gillman, MD, SM (Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Ann E. Kurth, PhD, RN, MSN, MPH (New York University, New York, New York); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); Maureen G. Phipps, MD, MPH (Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/Page/Name/our-members.

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	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/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.

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.