JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Vitamin D Deficiency in Adults
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Vitamin D is a fat-soluble vitamin that performs an important role in calcium homeostasis and bone metabolism and also affects many other cellular regulatory functions outside the skeletal system. Vitamin D requirements may vary by individual; thus, no one serum vitamin D level cutpoint defines deficiency, and no consensus exists regarding the precise serum levels of vitamin D that represent optimal health or sufficiency.

OBJECTIVE To update its 2014 recommendation, the US Preventive Services Task Force (USPSTF) commissioned a systematic review on screening for vitamin D deficiency, including the benefits and harms of screening and early treatment.

POPULATION Community-dwelling, nonpregnant adults who have no signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended.

EVIDENCE ASSESSMENT The USPSTF concludes that the overall evidence on the benefits of screening for vitamin D deficiency is lacking. Therefore, the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults cannot be determined.

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)

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

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Summary of Recommendation

Asymptomatic, community-dwelling, nonpregnant adults	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

See the Figure for a more detailed summary of the recommendations for clinicians. See the Practice Considerations section for additional information regarding the I statement. USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation figure.

Importance

Vitamin D is a fat-soluble vitamin that performs an important role in calcium homeostasis and bone metabolism and also affects many other cellular regulatory functions outside the skeletal system.[1-3] Vitamin D requirements may vary by individual; thus, no one serum vitamin D level cutpoint defines deficiency, and no consensus exists regarding the precise serum levels of vitamin D that represent optimal health or sufficiency. According to the National Academy of Medicine, an estimated 97.5% of the population will have their vitamin D needs met at a serum level of 20 ng/mL (49.9 nmol/L) and risk for deficiency, relative to bone health, begins to occur at levels less than 12 to 20 ng/mL (29.9-49.9 nmol/L).[1,4] A report based on data from the 2014 National Health and Nutrition Examination Survey found that 5% of the population 1 year or older had very low 25-hydroxyvitamin D (25[OH]D) levels (<12 ng/mL) and 18% had levels between 12 and 19 ng/mL.[5]

USPSTF Assessment of Magnitude of Net Benefit

The US Preventive Services Task Force (USPSTF) concludes that the overall evidence on the benefits of screening for vitamin D deficiency is lacking. Therefore, the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults cannot be determined (**Table**).

See the **Figure**, Table, and eFigure in the Supplement for more information on the USPSTF recommendation rationale and

Table. Summary of USPSTF Rationale

Rationale	Assessment
Detection	• Vitamin D requirements may vary by individual, and there is no one 25(OH)D level that defines deficiency for all individuals. • Total 25(OH)D levels are currently considered the best marker of vitamin D status; however, levels are difficult to measure accurately. • Evidence suggests that results vary by testing method and between laboratories using the same testing methods.
Benefits of early detection and intervention and treatment	• No direct evidence on the benefits of screening for vitamin D deficiency. • Adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on mortality, risk for fractures in persons selected solely on the basis of low vitamin D levels (as opposed to clinical risks such as low bone density), or incidence of type 2 diabetes mellitus. • Inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including falls, cancer, cardiovascular events, depression, infection, or physical functioning. • Despite adequate evidence to conclude no benefit for a few health outcomes, evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults for other health outcomes remains inadequate. The overall evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults is inadequate.
Harms of early detection and intervention and treatment	• No direct evidence on the harms of screening for vitamin D deficiency. • Adequate evidence that the harms of treatment of vitamin D deficiency are small to none.
USPSTF assessment	The overall evidence on the benefits of screening for vitamin D deficiency is lacking. Therefore, the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults cannot be determined.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; USPSTF, US Preventive Services Task Force.

Figure. Clinician Summary: Screening for Vitamin D Deficiency in Adults

What does the USPSTF recommend?	**For asymptomatic, community-dwelling, nonpregnant adults:** The USPSTF found that the **evidence is insufficient** to assess the balance of benefits and harms of screening for vitamin D deficiency. More research is needed. **I statement**
To whom does this recommendation apply?	Community-dwelling, nonpregnant adults who have no signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended. It does not apply to persons who are hospitalized or living in institutions such as nursing homes.
What's new?	This recommendation is consistent with the 2014 USPSTF statement.
How to implement this recommendation?	There is insufficient evidence to recommend for or against screening for vitamin D deficiency.
Where to read the full recommendation statement?	Visit the USPSTF website (https://www.uspreventiveservicestaskforce.org) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

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.

USPSTF indicates US Preventive Services Task Force.

assessment. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.[6]

Practice Considerations

Patient Population Under Consideration

This recommendation applies to community-dwelling, nonpregnant adults who have no signs or symptoms of vitamin D deficiency, such as bone pain or muscle weakness, or conditions for which vitamin D treatment is recommended. This recommendation focuses on screening (ie, testing for vitamin D deficiency in asymptomatic adults and treating those found to have a deficiency), which differs from USPSTF recommendation statements on supplementation.

Assessment of Risk

Although there is insufficient evidence to recommend for or against screening for vitamin D deficiency, several factors are associated with lower vitamin D levels. Low dietary vitamin D intake may be associated with lower 25(OH)D levels.[7] Little or no UV B exposure (eg, because of winter season, high latitude, or sun avoidance) and older age are also associated with an increased risk for low vitamin D levels.[8-12] Obesity is associated with lower 25(OH)D levels,[13] and people who are obese have a 1.3- to 2-fold increased risk of being vitamin D–deficient, depending on the threshold used to define deficiency.[8,9,13,14] The exact mechanism for this finding is not completely understood.

Depending on the serum threshold used to define deficiency, the prevalence of vitamin D deficiency is 2 to 10 times higher in non-Hispanic Black persons than in non-Hispanic White persons, likely related to differences in skin pigmentation.[7-9,14] However, these prevalence estimates are based on total 25(OH)D levels, and controversy remains about whether this is the best measure of vitamin D status among different racial and ethnic groups.

A significant proportion of the variability in 25(OH)D levels among individuals is not explained by the risk factors noted

above, which seem to account for only 20% to 30% of the variation in 25(OH)D levels.[11,15]

Treatment and Interventions

Vitamin D deficiency is usually treated with oral vitamin D. There are 2 commonly available forms of vitamin D—vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Both are available as either a prescription medication or an over-the-counter dietary supplement.

Suggestions for Practice Regarding the I Statement

Potential Preventable Burden

The prevalence of vitamin D deficiency varies based on how deficiency is defined. According to data from the 2011 to 2014 National Health and Nutrition Examination Survey, which used the liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay to measure 25(OH)D levels, 5% of the population 1 year or older had very low 25(OH)D levels (<12 ng/mL) and 18% had levels between 12 and 19 ng/mL.[5] (To convert 25[OH]D values to nmol/L, multiply by 2.496.)

In some observational studies, lower vitamin D levels have been associated with risk for fractures, falls, functional limitations, some types of cancer, diabetes, cardiovascular disease, depression, and death.[16,17] However, observations of these associations are inconsistent. This inconsistency may be because of different studies using different cutoffs to define a low vitamin D level or because vitamin D requirements and the optimal cutoff that defines a low vitamin D level or vitamin D deficiency may vary by individual or by subpopulation. For example, non-Hispanic Black persons have lower reported rates of fractures[18] despite having increased prevalence of lower vitamin D levels than White persons.[7-9,14] Further, it is unknown whether these associations are linked to causality.

The goal of screening for vitamin D deficiency would be to identify and treat it before associated adverse clinical outcomes occur. Total 25(OH)D level is currently considered the best marker of vitamin D status.[4,19] A variety of assays can be used to measure 25(OH)D levels; however, levels can be difficult to measure accurately, and assays may underestimate or overestimate 25(OH)D levels. Additionally, the 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 cutoff for defining deficiency and the variability of available testing assays. Misclassification may result in overdiagnosis (leading to nondeficient persons receiving unnecessary treatment) or underdiagnosis (leading to deficient persons not receiving treatment).

A rare but potential harm of treatment with vitamin D is toxicity, which is characterized by marked hypercalcemia as well as hyperphosphatemia and hypercalciuria. However, the 25(OH)D level associated with toxicity (typically >150 ng/mL)[20] is well above the level considered to be sufficient. In general, treatment with oral vitamin D does not seem to be associated with serious harms.

Current Practice

The prevalence of screening for vitamin D deficiency by primary care clinicians in the US has not been well studied. Data suggest that laboratory testing for vitamin D levels has increased greatly over the last several years or longer. One study reported a more than 80-fold increase in Medicare reimbursement volumes for vitamin D testing from 2000 to 2010.[21]

Other Related USPSTF Recommendations

The USPSTF has published recommendations on the use of vitamin D supplementation for the prevention of falls[22] and fractures[23] and vitamin supplementation for the prevention of cardiovascular disease or cancer.[24] These recommendations differ from the current recommendation statement in that they address vitamin D supplementation without first determining a patient's vitamin D status (ie, regardless of whether they have a deficiency).

Update of Previous USPSTF Recommendation

This recommendation updates the 2014 USPSTF recommendation statement on screening for vitamin D deficiency in asymptomatic adults. In 2014, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency.[25] For the current recommendation statement, the USPSTF again concludes that the evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

Supporting Evidence

Scope of Review

To update its 2014 recommendation statement, the USPSTF commissioned a systematic review[26,27] of the evidence on screening for vitamin D deficiency, including the benefits and harms of screening and early treatment. The review focused on asymptomatic, community-dwelling, nonpregnant adults 18 years or older who do not have clinical signs of vitamin D deficiency or conditions that could cause vitamin D deficiency, or for which vitamin D treatment is recommended, and who were seen in primary care settings.

Accuracy of Screening Tests

Total 25(OH)D levels can be measured by both binding and chemical assays. Serum total 25(OH)D levels are difficult to measure accurately, and different immunoassays can lead to underestimation or overestimation of total 25(OH)D levels.[19] LC-MS/MS is considered the reference assay. However, LC-MS/MS is a complicated process and is subject to variation and error, including interference from other chemical compounds.[19]

In 2010, the National Institutes of Health Office of Dietary Supplements, in collaboration with other organizations, initiated the Vitamin D Standardization Program.[28,29] The primary goal of the program has been to promote the standardized measurement of 25(OH)D levels. Most of the trials reviewed for this recommendation precede this standardization program. When

previously banked samples have been reassayed using these standardized methods, both upward and downward revisions of 25(OH)D levels have been observed, depending on the original assay that was used.[19,30,31]

Benefits of Early Detection and Treatment

The USPSTF found no studies that directly evaluated the benefits of screening for vitamin D deficiency. The USPSTF did find 26 randomized clinical trials (RCTs) and 1 nested case-control study that reported on the effectiveness of treatment of vitamin D deficiency (variably defined as a level <20 ng/mL to <31.2 ng/mL) on a variety of health outcomes, including all-cause mortality, fractures, incidence of diabetes, cardiovascular events and cancer, falls, depression, physical function, and infection.[26,27]

Eight RCTs and 1 nested case-control study reported on all-cause mortality in community-dwelling adults. Study duration ranged from 16 weeks to 7 years. In a pooled analysis of the 8 trials (n = 2006), there was no difference in all-cause mortality in persons randomized to vitamin D treatment compared with controls (relative risk [RR], 1.13 [95% CI, 0.39-3.28]).[26,27] In the Women's Health Initiative (WHI) Calcium–Vitamin D nested case-control study, there was no association between treatment with vitamin D and calcium and all-cause mortality among participants with baseline vitamin D levels between 14 and 21 ng/mL and among participants with baseline levels less than 14 ng/mL.[32,33]

Six RCTs reported on fracture outcomes in community-dwelling adults. Study duration ranged from 12 weeks to 7 years. A pooled analysis of the 6 trials (n = 2186) found no difference in the incidence of fractures among those randomized to vitamin D treatment compared with placebo (RR, 0.84 [95% CI, 0.58-1.21]).[26] The USPSTF found only 1 trial reporting on hip fracture in community-dwelling adults. In that study, only 1 hip fracture occurred, leading to a very imprecise effect estimate.[34] In the WHI Calcium–Vitamin D nested case-control study, there was no association between treatment with vitamin D and calcium and clinical fracture or hip fracture incidence.[32]

Five RCTs reported on incident diabetes. Study duration ranged from 1 year to 7 years. A pooled analysis of the 5 trials (n = 3356) found no difference in the incidence of diabetes among participants randomized to vitamin D treatment compared with placebo (RR, 0.96 [95% CI, 0.80-1.15]).[26]

For several outcomes, the USPSTF found inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency. Limitations of the following evidence include few studies reporting certain outcomes and, for some outcomes, variable methods of ascertainment, variable reporting of outcomes, small study size, or short duration of follow-up.

Two trials, the Vitamin D and Omega-3 Trial (VITAL) (n = 2001 in trial subgroup)[35] and the Vitamin D Assessment Study (ViDA) (n = 1270 in trial subgroup),[36] reported on cardiovascular events. Both trials observed no statistically significant differences in cardiovascular events between the treatment and placebo groups among the subgroup of participants with serum vitamin D levels less than 20 ng/mL at baseline. VITAL had 5.3 years of follow-up, while the ViDA trial had only 3.3 years of follow-up. The ViDA trial also used a heterogeneous definition of cardiovascular events, which included venous thromboembolism, pulmonary embolism, inflammatory cardiac conditions, arrhythmias, and conduction disorders.

Two trials, VITAL[35] and a post hoc analysis of the ViDA trial,[37] and the WHI nested case-control study[38,39] reported on the effect of vitamin D treatment on the incidence of cancer. Both trials reported no difference in cancer incidence between participants randomized to treatment and placebo among the subgroup of participants with serum 25(OH)D levels less than 20 ng/mL at baseline. The ViDA trial had only 3 years of follow-up, which may be a short period to detect an effect on cancer incidence. In the WHI Calcium–Vitamin D nested case-control study, the adjusted odds ratios (ORs) for incident breast or colorectal cancer over 7 years of follow-up did not demonstrate a statistically significant association between exposure to active treatment and incidence of cancer among participants with vitamin D deficiency at baseline.[38,39]

Nine trials reported fall outcomes in community-dwelling adults.[26,27] Some trials reported only falls, others only the number of participants who experienced 1 or more falls (ie, "fallers"), and some trials reported both outcomes. A pooled analysis of 6 trials found no association between vitamin D treatment and number of fallers (RR, 0.90 [95% CI, 0.75-1.08]), while a pooled analysis of 5 trials found a significant association between vitamin D treatment and falls (incidence rate ratio, 0.76 [95% CI, 0.57-0.94]).[26,27] However, heterogeneity was high in both analyses, ascertainment methods for falls and fallers were variable across studies, and the variable reporting of falls, fallers, or both outcomes raises the possibility of selective outcome reporting. One trial reported on the incidence of 2 or more falls, a different definition of "fallers" than in the trials included in the pooled analysis above. It found no significant difference between participants randomized to vitamin D or placebo among the subgroup of participants with baseline vitamin D levels less than 12 ng/mL (adjusted OR, 1.03 [95% CI, 0.59-1.79]) or among those with levels between 12 and 20 ng/mL (adjusted OR, 1.13 [95% CI, 0.87-1.48]).[40]

Three trials reported depression outcomes. One, VITAL-DEP (Depression Endpoint Prevention), was an ancillary study to the VITAL trial. Among the subgroup of participants with baseline serum vitamin D levels less than 20 ng/mL (n = 1328), there was no difference in the change in Personal Health Questionnaire Depression Scale scores between those randomized to vitamin D compared with placebo over a median follow-up of 5.3 years.[41] The other 2 trials were relatively small and of short duration. Both reported no significant difference in depression measures between vitamin D treatment and placebo.[42,43] Two trials reporting on physical functioning measures reported conflicting results.[44,45] An unplanned subgroup analysis of 1 trial conducted in persons with impaired fasting glucose found no difference in incidence of a first urinary tract infection in participants with vitamin D deficiency who were treated with vitamin D compared with placebo.[46]

As noted, the studies comprising the body of evidence cited above did not uniformly define vitamin D deficiency. Different studies enrolled participants with vitamin D levels that ranged from less than 20 ng/mL to less than 31.2 ng/mL. For those outcomes with sufficient data (mortality, fractures, and falls), findings were similar between studies using a lower threshold and studies using a higher threshold.[26,27]

Harms of Screening and Treatment

The USPSTF found no studies that directly evaluated the harms of screening for vitamin D deficiency. The USPSTF found 36 studies that reported adverse events and harms from treatment with vitamin D (with or without calcium) compared with a control group. The absolute incidence of adverse events varied widely across studies; however, the incidence of total adverse events, such as gastrointestinal symptoms, fatigue, musculoskeletal symptoms, and headaches, and serious adverse events was generally similar between treatment and control groups. In the 10 trials that reported incidence of kidney stones, there was only 1 case.[26,27]

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from September 22, 2020, to October 19, 2020. Some comments requested the USPSTF to evaluate the evidence on or make a recommendation regarding vitamin D supplementation. In response, the USPSTF wants to clarify that this recommendation focuses on screening for vitamin D deficiency. The USPSTF does have separate recommendations that address vitamin D supplementation (ie, providing vitamin D to all persons without testing, and regardless of vitamin D level) for a variety of conditions.[22-24] In response to comments, the USPSTF also wants to clarify that this recommendation applies to asymptomatic, community-dwelling adults. It does not apply to persons in institutional or hospital settings, who may have underlying or intercurrent conditions that warrant vitamin D testing or treatment. The USPSTF also wants to clarify that it did not review the emerging evidence on COVID-19, the disease caused by the new coronavirus SARS-CoV-2, and vitamin D.

Research Needs and Gaps

More studies are needed that address the following areas:

- More research is needed to determine whether total serum 25 (OH)D levels are the best measure of vitamin D deficiency and whether the best measure of vitamin D deficiency varies by subgroups defined by race, ethnicity, or sex.
- More research is needed to determine the cutoff that defines vitamin D deficiency and whether that cutoff varies by specific clinical outcome or by subgroups defined by race, ethnicity, or sex.
- When vitamin D deficiency is better defined, studies on the benefits and harms of screening for vitamin D deficiency will be helpful.

Recommendations of Others

No organization recommends population-based screening for vitamin D deficiency, and the American Society for Clinical Pathology recommends against it.[47] The American Academy of Family Physicians supports the USPSTF 2014 recommendation, which states that there is insufficient evidence to recommend screening the general population for vitamin D deficiency.[48] The Endocrine Society[49] and the American Association of Clinical Endocrinologists[50] recommend screening for vitamin D deficiency in individuals at risk. The Endocrine Society does not recommend population screening for vitamin D deficiency in individuals not at risk.[49]

ARTICLE INFORMATION

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Additional Information: The 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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