

# Vitamin, Mineral, and Multivitamin Supplementation to Prevent Cardiovascular Disease and Cancer

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** According to National Health and Nutrition Examination Survey data, 52% of surveyed US adults reported using at least 1 dietary supplement in the prior 30 days and 31% reported using a multivitamin-mineral supplement. The most commonly cited reason for using supplements is for overall health and wellness and to fill nutrient gaps in the diet. Cardiovascular disease and cancer are the 2 leading causes of death and combined account for approximately half of all deaths in the US annually. Inflammation and oxidative stress have been shown to have a role in both cardiovascular disease and cancer, and dietary supplements may have anti-inflammatory and antioxidative effects.

**OBJECTIVE** To update its 2014 recommendation, the US Preventive Services Task Force (USPSTF) commissioned a review of the evidence on the efficacy of supplementation with single nutrients, functionally related nutrient pairs, or multivitamins for reducing the risk of cardiovascular disease, cancer, and mortality in the general adult population, as well as the harms of supplementation.

**POPULATION** Community-dwelling, nonpregnant adults.

**EVIDENCE ASSESSMENT** The USPSTF concludes with moderate certainty that the harms of beta carotene supplementation outweigh the benefits for the prevention of cardiovascular disease or cancer. The USPSTF also concludes with moderate certainty that there is no net benefit of supplementation with vitamin E for the prevention of cardiovascular disease or cancer. The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer. Evidence is lacking and the balance of benefits and harms cannot be determined. The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with single or paired nutrients (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. Evidence is lacking and the balance of benefits and harms cannot be determined.

**RECOMMENDATION** The USPSTF recommends against the use of beta carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamin supplements for the prevention of cardiovascular disease or cancer. (I statement) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement)

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**Group Information:** A complete list of the members of the US Preventive Services Task Force appears at the end of this article.

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JAMA. 2022;327(23):2326-2333. doi:10.1001/jama.2022.8970

## Summary of Recommendation

Community-dwelling, nonpregnant adults	The USPSTF recommends against the use of beta carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer.	D
Community-dwelling, nonpregnant adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamin supplements for the prevention of cardiovascular disease or cancer. See the Practice Considerations section for additional information regarding the I statement.	I
Community-dwelling, nonpregnant adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. See the Practice Considerations section for additional information regarding the I statement.	I

USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation Figure.

## Importance

According to 2011-2014 National Health and Nutrition Examination Survey (NHANES) data, 52% of surveyed US adults (n = 11 024) reported using at least 1 dietary supplement in the prior 30 days and 31% reported using a multivitamin-mineral supplement.<sup>1</sup> The most commonly cited reason for using supplements is for overall health and wellness and to fill nutrient gaps in the diet. Cardiovascular disease and cancer are the 2 leading causes of death and combined account for approximately half of all deaths in the US annually.<sup>2</sup> Inflammation and oxidative stress have been shown to play a role in both cardiovascular disease and cancer, and dietary supplements may have anti-inflammatory and antioxidative effects. This has served as a rationale for proposing dietary supplements as a means to prevent both cardiovascular disease and cancer.

tion **outweigh the benefits** for the prevention of cardiovascular disease or cancer. The USPSTF also concludes with moderate certainty that there is **no net benefit** of supplementation with vitamin E for the prevention of cardiovascular disease or cancer.

The USPSTF concludes that the **evidence is insufficient** to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer. Evidence is lacking and the balance of benefits and harms cannot be determined.

The USPSTF concludes that the **evidence is insufficient** to determine the balance of benefits and harms of supplementation with single or paired nutrients (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. Evidence is lacking and the balance of benefits and harms cannot be determined.

See the **Table** for more information on the USPSTF recommendation rationale and assessment and the **eFigure** in the Supplement for information on the recommendation grade. See the **Figure** for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.<sup>3</sup>

## USPSTF Assessment of Magnitude of Net Benefit

The US Preventive Services Task Force (USPSTF) concludes with moderate certainty that the **harms** of beta carotene supplementa-

**Table. Summary of USPSTF Rationale**

Rationale	Assessment
Benefits of preventive medication	<ul style="list-style-type: none"> <li>Adequate evidence that supplementation with beta carotene provides no benefit in preventing cardiovascular disease or cancer.</li> <li>Adequate evidence that supplementation with vitamin E provides no benefit in preventing cardiovascular disease or cancer.</li> <li>Inadequate evidence on the benefits of supplementation with multivitamins in preventing cardiovascular disease or cancer.</li> <li>Inadequate evidence on the benefits of supplementation with single or paired nutrients (other than beta carotene and vitamin E) in preventing cardiovascular disease or cancer.</li> </ul>
Harms of preventive medication	<ul style="list-style-type: none"> <li>Adequate evidence that beta carotene causes small harms in increasing the risk for lung cancer in persons at increased risk.</li> <li>Adequate evidence that vitamin E causes at most small harms.</li> <li>Adequate evidence that multivitamins cause at most small harms.</li> <li>Inadequate evidence on the harms of supplementation with single or paired nutrients (other than beta carotene or vitamin E).</li> </ul>
USPSTF assessment	<ul style="list-style-type: none"> <li>The USPSTF concludes with moderate certainty that the harms of beta carotene supplementation for the prevention of cardiovascular disease or cancer outweigh the benefits.</li> <li>The USPSTF concludes with moderate certainty that there is no net benefit of supplementation with vitamin E for the prevention of cardiovascular disease or cancer.</li> <li>The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer.</li> <li>The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with single or paired nutrients (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer.</li> </ul>

Abbreviation: USPSTF, US Preventive Services Task Force.

Figure. Clinician Summary

<b>What does the USPSTF recommend?</b>	The USPSTF recommends against the use of beta carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. <b>Grade: D</b> The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamin supplements, or single- or paired-nutrient supplements (other than beta carotene and vitamin E), for the prevention of cardiovascular disease or cancer. <b>Grade: I statement</b>
<b>To whom does this recommendation apply?</b>	<ul style="list-style-type: none"> <li>This recommendation applies to community-dwelling, nonpregnant adults. It does not apply to children, persons who are pregnant or may become pregnant, or persons who are chronically ill, are hospitalized, or have a known nutritional deficiency.</li> <li>The USPSTF separately recommends that all persons who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid.</li> </ul>
<b>What's new?</b>	This recommendation is consistent with the 2014 USPSTF recommendation statement on vitamin, mineral, and multivitamin supplements to prevent cardiovascular disease and cancer.
<b>How to implement this recommendation?</b>	<ul style="list-style-type: none"> <li>Do not use beta carotene or vitamin E supplements to prevent cardiovascular disease or cancer.</li> <li>The evidence is insufficient to recommend for or against the use of multivitamin supplements, or single- or paired-nutrient supplements (other than beta carotene and vitamin E), to prevent cardiovascular disease or cancer. Clinicians should use their clinical judgement to determine whether vitamin supplements should be recommended for an individual patient.</li> </ul>
<b>What additional information should clinicians know about this recommendation?</b>	<ul style="list-style-type: none"> <li>For many vitamins and nutrients, there was little evidence of serious harms. However, an important harm of increased lung cancer incidence was reported with the use of beta carotene by persons who smoke tobacco or have occupational exposure to asbestos.</li> <li>Excessive doses of vitamin supplements can cause adverse effects.</li> <li>It is uncertain whether there might be heterogeneity across populations or by baseline nutrient level, or by socioeconomic factors such as food insecurity, in the effects of vitamin, mineral, and multivitamin supplementation on cardiovascular disease and cancer outcomes.</li> </ul>
<b>Why is this recommendation and topic important?</b>	<ul style="list-style-type: none"> <li>Cardiovascular disease and cancer are the 2 leading causes of mortality in the US.</li> <li>In 2015-2018, 26.1 million persons in the US had some form of cardiovascular disease (excluding hypertension), and in 2021 an estimated 1.9 million persons were diagnosed with cancer in the US.</li> <li>According to National Health and Nutrition Examination Survey data, more than half of surveyed US adults reported using at least 1 dietary supplement in the prior 30 days.</li> </ul>
<b>Where to read the full recommendation statement?</b>	Visit the USPSTF website ( <a href="https://www.uspreventiveservicestaskforce.org/uspstf/">https://www.uspreventiveservicestaskforce.org/uspstf/</a> ) or the JAMA website ( <a href="https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force">https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force</a> ) 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.

## Practice Considerations

### Patient Population Under Consideration

This recommendation applies to community-dwelling, nonpregnant adults. This recommendation does not apply to children, persons who are pregnant or may become pregnant, or persons who are chronically ill, are hospitalized, or have a known nutritional deficiency.

The USPSTF separately recommends that all persons who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid.<sup>4</sup>

### Treatment and Interventions

Vitamins (eg, vitamins A, C, D, E, and K and the B vitamins) are groups of chemically diverse organic compounds that are essential to maintaining normal metabolism.<sup>5</sup> Minerals (eg, calcium, iron, and zinc) are inorganic substances that humans also need to maintain function.<sup>6</sup> Vitamins and minerals can be combined, with or

without other substances, in multivitamin or multimineral supplements.

### Suggestions for Practice Regarding the I Statement

#### Potential Preventable Burden

Cardiovascular disease and cancer are the 2 leading causes of death and combined account for approximately half of all deaths in the US annually.<sup>2</sup> According to 2015-2018 NHANES data, 26.1 million persons in the US have some form of cardiovascular disease (excluding hypertension).<sup>7</sup> Cardiovascular disease accounted for 803 191 deaths in the US in 2018, approximately 30% of all deaths.<sup>2</sup> Heart disease and stroke are most common among older adults, male individuals, and persons with low socioeconomic status and vary across racial and ethnic groups. The prevalence rates of cardiovascular disease, and notably stroke, are particularly high among Black persons and American Indian/Alaska Native persons compared with other races and ethnicities.<sup>7,8</sup>

In 2021, an estimated 1.9 million persons were diagnosed with cancer in the US.<sup>9</sup> Cancer is the second leading cause of death in the

US and accounted for 599 274 deaths (21.1% of all deaths) in 2018.<sup>2</sup> Black males have the highest rates of cancer incidence of any sex and racial and ethnic group, and Black persons have the highest total cancer mortality and the highest mortality rates for most major cancer types.<sup>10</sup> Although the causes for this are not certain, it is likely because of social factors (eg, environmental exposures, systemic racism, disparities in access to care, and disparities in treatment).<sup>11</sup> It is not known what proportion of cardiovascular disease and cancer might be potentially preventable with vitamin or mineral supplementation.

### Potential Harms

For many of the vitamins and nutrients reviewed, there was little evidence of serious harms. However, an important harm of increased lung cancer incidence was reported with the use of beta carotene by persons who smoke tobacco or have occupational exposure to asbestos.

Excessive doses of vitamin supplements can cause several known adverse effects; for example, moderate doses of vitamin A supplements may reduce bone mineral density, and high doses may be hepatotoxic or teratogenic. Vitamin D has potential harms, such as a risk of hypercalcemia and kidney stones, when given at high doses. The potential for harm from other supplements at high doses should be carefully considered.

### Current Practice

Contemporary data on the prevalence with which health care professionals recommend vitamins and minerals for cardiovascular disease and cancer prevention are limited. Older data suggest that it was common for health care professionals to recommend vitamin and mineral supplements to their patients for a variety of reasons such as overall health, bone health, musculoskeletal pain, or viral infections and immune health.<sup>12,13</sup>

### Other Related USPSTF Recommendations

The USPSTF has published several recommendations for prevention of cardiovascular disease and cancer, including recommendations for smoking cessation,<sup>14</sup> screening for hypertension,<sup>15</sup> statin use to prevent cardiovascular disease,<sup>16</sup> aspirin use to prevent cardiovascular disease,<sup>17</sup> interventions to prevent obesity-related morbidity and mortality,<sup>18</sup> behavioral counseling to prevent cardiovascular disease in adults with risk factors,<sup>19</sup> medication use to reduce breast cancer risk,<sup>20</sup> behavioral counseling to decrease risk of skin cancer,<sup>21</sup> screening for breast,<sup>22</sup> cervical,<sup>23</sup> colorectal,<sup>24</sup> lung,<sup>25</sup> and prostate cancer,<sup>26</sup> and risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.<sup>27</sup> The USPSTF has also published several recommendations related to vitamin and mineral supplementation, including vitamin D, calcium, or combined supplementation to prevent fractures in adults,<sup>28</sup> vitamin D supplementation to prevent falls in community-dwelling older adults,<sup>29</sup> and folic acid to prevent neural tube defects in persons who are planning or capable of pregnancy.<sup>4</sup>

## Update of Previous USPSTF Recommendation

This recommendation replaces the 2014 USPSTF recommendation statement on vitamin, mineral, and multivitamin supplements

to prevent cardiovascular disease and cancer.<sup>30</sup> Although newer evidence was assessed, the USPSTF came to the same conclusions as it did in 2014, and the current recommendation statement is consistent with the 2014 recommendation. The USPSTF again concludes that the evidence is insufficient to assess the balance of benefits and harms of multivitamins and single- or paired-nutrient supplements (except beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. The USPSTF again recommends against the use of beta carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer.

## Supporting Evidence

### Scope of Review

To update its 2014 recommendation statement, the USPSTF commissioned a systematic review<sup>31,32</sup> of the evidence on the efficacy of supplementation with single nutrients, functionally related nutrient pairs, or multivitamins for reducing the risk of cardiovascular disease, cancer, and mortality in the general adult population, as well as the harms of supplementation. The review focused on community-dwelling, nonpregnant adults 18 years or older without known cardiovascular disease or chronic disease (other than hypertension, overweight, or obesity) or nutritional deficiencies.

### Benefits of Supplementation

#### Beta Carotene With or Without Vitamin A

The USPSTF found 6 randomized clinical trials (RCTs) reporting on health outcomes associated with beta carotene supplementation.<sup>31,32</sup> One of these trials studied beta carotene plus vitamin A supplementation.<sup>33</sup> A pooled analysis assessing association with beta carotene use showed an increased risk that was not statistically significant for all-cause mortality associated with beta carotene use over 4 to 12 years of follow-up (odds ratio [OR], 1.06 [95% CI, 1.00-1.12]; 6 RCTs; n = 112 820). A pooled analysis of 5 studies showed a statistically significant increased risk for cardiovascular disease mortality associated with beta carotene supplementation at 4 to 12 years of follow-up (Peto OR, 1.10 [95% CI, 1.02-1.19]; 5 RCTs; n = 94 506).<sup>31</sup> Two trials conducted in persons who smoke or were exposed to asbestos in the workplace found a significantly increased risk of lung cancer with beta carotene supplementation (risk ratio [RR], 1.18 [95% CI, 1.03-1.36])<sup>34</sup> and beta carotene plus vitamin A supplementation (adjusted RR, 1.28 [95% CI, 1.04-1.57]).<sup>33</sup>

#### Vitamin A

One RCT reported no association between vitamin A supplementation and all-cause mortality (OR, 1.16 [95% CI, 0.80-1.69]).<sup>31,35</sup> The effects of vitamin A and beta carotene combined on lung cancer risk in persons at high risk<sup>33</sup> are noted above.

#### Vitamin E

Nine RCTs reported on health outcomes associated with vitamin E supplementation.<sup>31,32</sup> Pooled analyses demonstrated no benefit associated with vitamin E use on all-cause mortality (OR, 1.02 [95% CI, 0.97-1.07]; 9 RCTs; n = 107 772) after 3 to 10 years of follow-up or on the composite outcome of any cardiovascular disease event (OR, 0.96 [95% CI, 0.90-1.04]; 4 RCTs; n = 62 136) or cardiovascular disease mortality (OR, 0.88 [95% CI, 0.74-1.04]; 6 RCTs;

n = 77 114). Pooled analyses also showed no benefit associated with vitamin E use on incidence of or mortality from any cancer.<sup>31</sup>

### Multivitamins

The USPSTF found 9 RCTs that reported on health outcomes associated with multivitamin supplementation.<sup>31,32</sup> A pooled analysis of these studies showed no association between multivitamin supplementation and all-cause mortality (OR, 0.94 [95% CI, 0.87-1.01]; 9 RCTs; n = 51 550). The largest trial, COSMOS (Cocoa Supplement and Multivitamin Outcomes Study; n = 21 442), also found no effect of multivitamin supplementation on all-cause mortality after a median of 3.6 years of follow-up (3.4% of participants taking a multivitamin had died compared with 3.6% who were taking a placebo; hazard ratio, 0.93 [95% CI, 0.81-1.08]).<sup>36</sup> Pooled analyses of 4 studies demonstrated no association between multivitamin use and cardiovascular disease mortality (OR, 0.94 [95% CI, 0.83-1.06]; 4 RCTs; n = 37 400) or cancer mortality (OR, 0.94 [95% CI, 0.81 to 1.09]; 4 RCTs; n = 37 400),<sup>30</sup> although a pooled analysis of 4 trials found a small decrease in cancer incidence (OR, 0.93 [95% CI, 0.87-0.99]; 4 RCTs; n = 48 859).<sup>31</sup> The body of evidence on the effects of multivitamin supplementation on mortality, CVD, and cancer outcomes has several limitations. As described above, multivitamin supplementation was not associated with an effect for most outcomes, and the effects on cancer incidence and mortality were not concordant. Of the 3 largest trials of vitamin supplementation (and the only trials to specifically focus on cardiovascular disease and cancer prevention), 2 focused on broad-spectrum multivitamins and 1 focused on antioxidants.<sup>36-38</sup> Additionally, 1 of these trials (PHS II, n = 14 641) was limited to male physicians.<sup>38</sup> Also, the largest of these trials (COSMOS, n = 21 442) had a median follow-up of only 3.6 years,<sup>36</sup> which may be too short for assessing cardiovascular disease and cancer outcomes. All of these factors limit the ability to determine whether supplementation may or may not have a benefit.

### Vitamin D With or Without Calcium

Thirty-two RCTs reported on health outcomes associated with vitamin D with or without calcium supplementation; overall, results were very similar in studies examining the effects of vitamin D without calcium and those examining vitamin D and calcium combined.<sup>31,32</sup> A pooled analysis of 27 studies found no difference in all-cause mortality associated with vitamin D use (OR, 0.96 [95% CI, 0.91-1.02]; 27 RCTs; n = 117 082) after 6 months to 7 years of follow-up. Pooled analyses showed no between-group differences for cardiovascular disease mortality (OR, 0.96 [95% CI, 0.87-1.06]; 9 trials; n = 98 422), the composite outcome of any cardiovascular disease event (OR, 1.00 [95% CI, 0.95-1.05]; 7 RCTs; n = 74 925), or myocardial infarction or stroke. Pooled analyses also showed that vitamin D supplementation was not associated with any difference in cancer mortality (pooled OR, 0.94 [95% CI, 0.86-1.03]; 9 RCTs; n = 100 465) or cancer incidence (OR for any cancer, 0.98 [95% CI, 0.92-1.03]; 19 RCTs; n = 86 899) compared with placebo.<sup>31</sup> However, the 2 largest trials of vitamin D supplementation (VITAL, n = 25 871 and D-Health, 21 310) that reported on cancer mortality had point estimates for effect size that were on opposite sides of null (ORs, 0.82 and 1.15).<sup>39,40</sup> It is unclear whether the effect of vitamin D on health outcomes might vary based on patient population characteristics (eg, baseline vitamin D level or diet quality) or an unidentified factor. Additionally, the trials that reported on can-

cer mortality ranged from 3.3 to 7 years of follow-up,<sup>31</sup> which may be too short to detect an effect on cancer-specific mortality. These factors limit the ability to determine with certainty the effect of vitamin D on cancer incidence and mortality.

### Calcium

Seven RCTs reported on health outcomes associated with calcium supplementation. Pooled analyses found no difference in all-cause mortality, cardiovascular disease events, cardiovascular disease mortality, or any incidence of cancer in persons taking calcium, although the number of pooled trials was small and heterogeneity was high for some of these outcomes.<sup>31,32</sup>

### Folic Acid With or Without Vitamin B<sub>12</sub>

The USPSTF found 5 RCTs that reported on health outcomes associated with folic acid in nonpregnant adults,<sup>31,32</sup> with 1 trial studying folic acid plus vitamin B<sub>12</sub> supplementation.<sup>41</sup> A pooled analysis showed no association between folic acid supplementation and all-cause mortality over 2 to 6.5 years. Event rates for cardiovascular disease mortality and cardiovascular disease events were too low to draw conclusions.<sup>31</sup> In a pooled analysis, folic acid either alone<sup>42,43</sup> or with vitamin B<sub>12</sub><sup>41</sup> was associated with higher rates of any cancer incidence at 2 to 6 years of follow-up.<sup>31</sup> However, 1 trial was limited to adults with moderately elevated homocysteine levels,<sup>41</sup> and the others were limited to adults with a history of colorectal adenomas.<sup>42,43</sup> Thus, the generalizability of this finding to the general population is uncertain.

### Vitamin C

Two RCTs<sup>44-46</sup> suggested that vitamin C supplementation has no effect on all-cause mortality, cardiovascular disease events, or cardiovascular disease mortality, although 1 of these trials was small and not powered for these outcomes. One trial<sup>46</sup> suggested that vitamin C supplementation has no effect on cancer incidence or mortality.

### Vitamins B<sub>3</sub> and B<sub>6</sub>

The USPSTF found insufficient evidence to assess the effects of these vitamins on all-cause mortality, cardiovascular disease outcomes, or cancer outcomes.<sup>31,32</sup>

### Selenium

Although some individual studies showed conflicting results, the limited overall evidence suggests that selenium supplementation has no effect on all-cause mortality, cardiovascular disease mortality, cardiovascular disease events, or cancer mortality.<sup>31,32</sup>

### Harms of Supplementation

The USPSTF also reviewed the evidence on the harms of vitamin and mineral supplements. For many supplements there was little to no evidence of serious harms.<sup>31,32</sup>

The most serious harm identified was increased cardiovascular disease mortality and increased risk of lung cancer in persons who smoke or had workplace asbestos exposure, associated with beta carotene supplementation at doses of 30 and 20 mg/d.<sup>33,34</sup> One of these trials also co-administered vitamin A at a dose of 25 000 IU/d,<sup>33</sup> which exceeds the current tolerable upper intake level for vitamin A in adults.<sup>47</sup> A minor harm of beta carotene was orange discolor-



ation of the skin.<sup>31</sup> Two cohort studies in women showed a statistically nonsignificant increased risk of hip fracture associated with vitamin A supplementation.<sup>48,49</sup> Two trials<sup>34,45</sup> showed an increased risk of hemorrhagic stroke associated with vitamin E supplementation at doses of 111 and 200 IU daily, and 1 cohort study found that a high intake of vitamin B<sub>6</sub> ( $\geq 35$  mg/d) was associated with an increased risk of hip fracture compared with a low intake ( $< 2$  mg/d).<sup>50</sup>

One trial and 2 cohort studies reported an increased risk of kidney stones in persons taking vitamin D.<sup>31</sup> In the cohort studies, this risk was only associated with vitamin D doses of 1000 IU/d or more. Two cohort studies in men suggest an association between vitamin C supplementation and kidney stones.<sup>31</sup> The evidence on an association between calcium use and kidney stones was mixed.<sup>31</sup>

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from May 4 to June 1, 2021. In response to comments, the USPSTF specified the doses of beta carotene, vitamin A, and vitamin E used in trials reporting harms from these vitamins. Some comments requested that persons with chronic conditions or who are hospitalized be included in this recommendation. In response, the USPSTF wants to clarify that its recommendations apply to community-dwelling individuals without known underlying health conditions. Persons who have an acute or chronic illness may require additional vitamin, mineral, or multivitamin supplementation as part of management of their condition, which goes beyond supplementation for the prevention purposes addressed by this recommendation. Some comments requested additional detailed information from included studies. More information can be found in the accompanying evidence summary<sup>32</sup> and evidence report.<sup>31</sup> In addition, the USPSTF clarified that persons who experience food insecurity are among the populations of interest for the research gap on whether the effects of vitamin, mineral,

and multivitamin supplementation on cardiovascular disease and cancer outcomes differ across specific populations.

### Research Needs and Gaps

Studies are needed that provide more information on the following.

- The effects of vitamin, mineral, and multivitamin supplementation on cardiovascular disease and cancer outcomes. Studies need to be of sufficient duration to detect an effect on these outcomes.
- Whether vitamin D supplementation has an effect on cancer mortality. Studies need to be of sufficient duration to detect an effect on this outcome.
- Whether there is heterogeneity across specific populations, or by baseline nutrient level or socioeconomic factors such as food insecurity, in the effects of vitamin, mineral, and multivitamin supplementation on cardiovascular disease and cancer outcomes, especially in persons with no known deficiencies and low prevalence of supplement use and in racially and ethnically diverse populations.

### Recommendations of Others

The US Department of Health and Human Services 2020-2025 dietary guidelines suggest that nutritional needs should be met primarily from foods and beverages—specifically, nutrient-dense foods and beverages.<sup>51</sup> The American Heart Association recommends that healthy persons receive adequate nutrients by eating a variety of foods in moderation, rather than by taking supplements.<sup>52</sup>

#### ARTICLE INFORMATION

**Accepted for Publication:** May 12, 2022.

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**Author Contributions:** Dr Mangione had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The USPSTF members contributed equally to the recommendation statement.

**Conflict of Interest Disclosures:** Authors followed the policy regarding conflicts of interest described at <https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/conflict-interest-disclosures>. All members of the USPSTF receive travel reimbursement and an honorarium for participating in USPSTF meetings.

**Funding/Support:** The USPSTF is an independent, voluntary body. The US Congress mandates that the Agency for Healthcare Research and Quality (AHRQ) support the operations of the USPSTF.

**Role of the Funder/Sponsor:** AHRQ staff assisted in the following: development and review of the research plan, commission of the systematic evidence review from an Evidence-based Practice Center, coordination of expert review and public comment of the draft evidence report and draft recommendation statement, and the writing and preparation of the final recommendation statement and its submission for publication. AHRQ staff had

no role in the approval of the final recommendation statement or the decision to submit for publication. Recommendations made by the USPSTF are independent of the US government. They should not be construed as an official position of AHRQ or the US Department of Health and Human Services.

**Additional Contributions:** We thank Howard Tracer, MD (AHRQ), who contributed to the writing of the manuscript, and Lisa Nicoletta, MA (AHRQ), who assisted with coordination and editing.

**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. Published by JAMA®—Journal of the American Medical Association under arrangement with the Agency for Healthcare Research and Quality (AHRQ). ©2022 AMA and

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## REFERENCES

- Cowan AE, Jun S, Gahche JJ, et al. Dietary supplement use differs by socioeconomic and health-related characteristics among US adults, NHANES 2011-2014. *Nutrients*. 2018;10(8):1114. doi:10.3390/nu10081114
- Murphy SL, Xu J, Kochanek KD, Arias E, Tejada-Vera B. Deaths: final data for 2018. *Natl Vital Stat Rep*. 2021;69(13):1-83.
- US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Published May 2021. Accessed May 3, 2022. <https://uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual>
- US Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;317(2):183-189. doi:10.1001/jama.2016.19438
- Fairfield KM. Vitamin supplementation in disease prevention. Updated May 21, 2021. Accessed May 3, 2022. <https://www.uptodate.com/contents/vitamin-supplementation-in-disease-prevention>
- National Center for Complementary and Integrative Health, National Institutes of Health. Vitamins and minerals. Updated February 2018. Accessed May 3, 2022. <https://www.nccih.nih.gov/health/vitamins>
- Tsao CW, Aday AW, Almarazooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052
- National Center for Health Statistics. National Health Interview Survey, 2018: Table A-1a: age-adjusted percentages (with standard errors) of selected circulatory diseases among adults aged 18 and over, by selected characteristics: United States, 2018. Centers for Disease Control and Prevention. Accessed May 3, 2022. [https://ftp.cdc.gov/pub/Health\\_Statistics/NCHS/NHIS/SHS/2018\\_SH5\\_Table\\_A-1.pdf](https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SH5_Table_A-1.pdf)
- SEER Cancer Statistics Review, 1975-2018: Table 1.1: estimated new cancer cases and deaths for 2021: all races, by sex. National Cancer Institute. Accessed May 3, 2022. [https://seer.cancer.gov/archive/csr/1975\\_2018/browse\\_csr.php?sectionSEL=1&pageSEL=sect\\_01\\_table.01](https://seer.cancer.gov/archive/csr/1975_2018/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01)
- Henley SJ, Ward EM, Scott S, et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. *Cancer*. 2020;126(10):2225-2249. doi:10.1002/cncr.32802
- Doubeni CA, Simon M, Krist AH. Addressing systemic racism through clinical preventive service recommendations from the US Preventive Services Task Force. *JAMA*. 2021;325(7):627-628. doi:10.1001/jama.2020.26188
- Dickinson A, Bonci L, Boyon N, Franco JC. Dietitians use and recommend dietary supplements: report of a survey. *Nutr J*. 2012;11:14. doi:10.1186/1475-2891-11-14
- Dickinson A, Boyon N, Shao A. Physicians and nurses use and recommend dietary supplements: report of a survey. *Nutr J*. 2009;8:29. doi:10.1186/1475-2891-8-29
- US Preventive Services Task Force. Interventions for tobacco smoking cessation in adults, including pregnant persons: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;325(3):265-279. doi:10.1001/jama.2020.25019
- Siu AL; US Preventive Services Task Force. Screening for high blood pressure in adults: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163(10):778-786. doi:10.7326/M15-2223
- US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(19):1997-2007. doi:10.1001/jama.2016.15450
- US Preventive Services Task Force. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;327(16):1577-1584. doi:10.1001/jama.2022.4983
- US Preventive Services Task Force. Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(11):1163-1171. doi:10.1001/jama.2018.13022
- US Preventive Services Task Force. Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: US Preventive Services Task Force recommendation statement. *JAMA*. 2020;324(20):2069-2075. doi:10.1001/jama.2020.21749
- US Preventive Services Task Force. Medication use to reduce risk of breast cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322(9):857-867. doi:10.1001/jama.2019.11885
- US Preventive Services Task Force. Behavioral counseling to prevent skin cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(11):1134-1142. doi:10.1001/jama.2018.1623
- Siu AL; US Preventive Services Task Force. Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164(4):279-296. doi:10.7326/M15-2886
- US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686. doi:10.1001/jama.2018.10897
- US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315(23):2564-2575. doi:10.1001/jama.2016.5989
- US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(10):962-970. doi:10.1001/jama.2021.1117
- US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901-1913. doi:10.1001/jama.2018.3710
- US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322(7):652-665. doi:10.1001/jama.2019.10987
- US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(15):1592-1599. doi:10.1001/jama.2018.3185
- US Preventive Services Task Force. Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(16):1696-1704. doi:10.1001/jama.2018.3097
- Moyer VA; US Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(8):558-564. doi:10.7326/M14-0198
- O'Connor EA, Evans CV, Ivliv I, et al. *Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: A Systematic Evidence Review for the US Preventive Services Task Force. Evidence Synthesis No. 209*. Agency for Healthcare Research and Quality; 2022. AHRQ publication 21-05278-EF-1.
- O'Connor EA, Evans CV, Ivliv I, et al. Vitamin and mineral supplements for the primary prevention of cardiovascular disease and cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. Published June 21, 2022. doi:10.1001/jama.2021.15650
- Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996;334(18):1150-1155. doi:10.1056/NEJM199605023341802
- Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330(15):1029-1035. doi:10.1056/NEJM199404143301501
- Moon TE, Levine N, Cartmel B, et al; Southwest Skin Cancer Prevention Study Group. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. *Cancer Epidemiol Biomarkers Prev*. 1997;6(11):949-956.
- Sesso HD, Manson JE, Aragaki AK, et al; COSMOS Research Group. Effect of cocoa flavanol supplementation for prevention of cardiovascular disease events: the COSMOS randomized clinical trial. *Am J Clin Nutr*. Published online March 16, 2022. doi:10.1093/ajcn/nqac055
- Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164(21):2335-2342. doi:10.1001/archinte.164.21.2335
- Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;

10(2):125-134. doi:10.1016/S1047-2797(99)00042-3

- 39.** Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380(1):33-44. doi:10.1056/NEJMoa1809944
- 40.** Neale RE, Baxter C, Romero BD, et al. The D-Health trial: a randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol.* 2022;10(2):120-128. doi:10.1016/S2213-8587(21)00345-4
- 41.** van Wijngaarden JP, Swart KM, Enneman AW, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. *Am J Clin Nutr.* 2014;100(6):1578-1586. doi:10.3945/ajcn.114.090043
- 42.** Cole BF, Baron JA, Sandler RS, et al; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA.* 2007;297(21):2351-2359. doi:10.1001/jama.297.21.2351
- 43.** Wu K, Platz EA, Willett WC, et al. A randomized trial on folic acid supplementation and risk of

recurrent colorectal adenoma. *Am J Clin Nutr.* 2009;90(6):1623-1631. doi:10.3945/ajcn.2009.28319

- 44.** Salonen JT, Nyyssönen K, Salonen R, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. *J Intern Med.* 2000;248(5):377-386. doi:10.1046/j.1365-2796.2000.00752.x
- 45.** Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA.* 2008;300(18):2123-2133. doi:10.1001/jama.2008.600
- 46.** Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA.* 2009;301(1):52-62. doi:10.1001/jama.2008.862
- 47.** National Institutes of Health, Office of Dietary Supplements. Vitamin A and carotenoids: fact sheet for health professionals. Updated March 23, 2022. Accessed May 3, 2022. <https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/>

**48.** Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. *JAMA.* 2002;287(1):47-54. doi:10.1001/jama.287.1.47

- 49.** Lim LS, Harnack LJ, Lazovich D, Folsom AR. Vitamin A intake and the risk of hip fracture in postmenopausal women: the Iowa Women's Health Study. *Osteoporos Int.* 2004;15(7):552-559. doi:10.1007/s00198-003-1577-y
- 50.** Meyer HE, Willett WC, Fung TT, Holvik K, Feskanich D. Association of high intakes of vitamins B<sub>6</sub> and B<sub>12</sub> from food and supplements with risk of hip fracture among postmenopausal women in the Nurses' Health Study. *JAMA Netw Open.* 2019;2(5):e193591. doi:10.1001/jamanetworkopen.2019.3591
- 51.** US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025.* 9th ed. US Department of Health and Human Services; 2020.
- 52.** American Heart Association. Vitamin supplements: hype or help for healthy eating. Reviewed February 1, 2014. Accessed May 3, 2022. <https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/vitamin-supplements-hype-or-help-for-healthy-eating>