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

Elizabeth A. O'Connor, PhD; Corinne V. Evans, MPP; Ilya Ivlev, MD, PhD, MBI; Megan C. Rushkin, MPH; Rachel G. Thomas, MPH; Allea Martin, MPH; Jennifer S. Lin, MD, MCR

IMPORTANCE Cardiovascular disease and cancer are the 2 leading causes of death in the US, and vitamin and mineral supplementation has been proposed to help prevent these conditions.

OBJECTIVE To review the benefits and harms of vitamin and mineral supplementation in healthy adults to prevent cardiovascular disease and cancer to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed (publisher-supplied records only), Cochrane Library, and Embase (January 2013 to February 1, 2022); prior reviews.

STUDY SELECTION English-language randomized clinical trials (RCTs) of vitamin or mineral use among adults without cardiovascular disease or cancer and with no known vitamin or mineral deficiencies; observational cohort studies examining serious harms.

DATA EXTRACTION AND SYNTHESIS Single extraction, verified by a second reviewer. Quantitative pooling methods appropriate for rare events were used for most analyses.

MAIN OUTCOMES AND MEASURES Mortality, cardiovascular disease events, cancer incidence, serious harms.

RESULTS Eighty-four studies (N=739 803) were included. In pooled analyses, multivitamin use was significantly associated with a lower incidence of any cancer (odds ratio [OR], 0.93 [95% CI, 0.87-0.99]; 4 RCTs [n=48 859]; absolute risk difference [ARD] range among adequately powered trials, −0.2% to −1.2%) and lung cancer (OR, 0.75 [95% CI, 0.58-0.95]; 2 RCTs [n=36 052]; ARD, 0.2%). However, the evidence for multivitamins had important limitations. Beta carotene (with or without vitamin A) was significantly associated with an increased risk of lung cancer (OR, 1.20 [95% CI, 1.01-1.42]; 4 RCTs [n=94 830]; ARD range, −0.1% to 0.6%) and cardiovascular mortality (OR, 1.10 [95% CI, 1.02-1.19]; 5 RCTs [n=94 506] ARD range, −0.8% to 0.8%). Vitamin D use was not significantly associated with all-cause mortality (OR, 0.96 [95% CI, 0.91-1.02]; 27 RCTs [n=117 082]), cardiovascular disease (eg, composite cardiovascular disease event outcome: OR, 1.00 [95% CI, 0.95-1.05]; 7 RCTs [n=74 925]), or cancer outcomes (eg, any cancer incidence: OR, 0.98 [95% CI, 0.92-1.03]; 19 RCTs [n=86 899]). Vitamin E was not significantly associated with all-cause mortality (OR, 1.02 [95% CI, 0.97-1.07]; 9 RCTs [n=107 772]), cardiovascular disease events (OR, 0.96 [95% CI, 0.90-1.04]; 4 RCTs [n=62 136]), or cancer incidence (OR, 1.02 [95% CI, 0.98-1.08]; 5 RCTs [n=76 777]). Evidence for benefit of other supplements was equivocal, minimal, or absent. Limited evidence suggested some supplements may be associated with higher risk of serious harms (hip fracture [vitamin A], hemorrhagic stroke [vitamin E], and kidney stones [vitamin C, calcium]).

CONCLUSIONS AND RELEVANCE Vitamin and mineral supplementation was associated with little or no benefit in preventing cancer, cardiovascular disease, and death, with the exception of a small benefit for cancer incidence with multivitamin use. Beta carotene was associated with an increased risk of lung cancer and other harmful outcomes in persons at high risk of lung cancer.

Cardiovascular disease and cancer are the 2 leading causes of death in the US. Vitamin and mineral supplementation has been proposed as a preventive strategy for both diseases because of shared disease pathways involving oxidative stress, inflammation, and methionine metabolism. Further, observational evidence has suggested associations between higher plasma levels of various vitamins and minerals and lower rates of cardiovascular disease and cancer. Vitamin and mineral supplements are commonly used in the US, with estimates in 2011 to 2014 showing that 52% of adults reported having recently used at least 1 dietary supplement.

In 2014, the US Preventive Services Task Force (USPSTF) recommended against the use of beta carotene or vitamin E to prevent cardiovascular disease and cancer and concluded that the evidence was insufficient to assess net benefit for multivitamins or the use of single- or paired-nutrient supplements. This systematic review was conducted to provide current evidence on the benefits and harms of vitamin and mineral supplementation in healthy adults without known vitamin or mineral deficiencies to inform an updated recommendation by the USPSTF.

Methods

Scope of Review

Figure 1 displays the a priori–developed analytic framework and 4 key questions (KQs) that guided this review, which was posted on the AHRQ website on September 5, 2019. Methodological details and findings for the B and C vitamins, folic acid, magnesium, selenium, and zinc are available in the full evidence report.

Data Sources and Searches

MEDLINE, PubMed (publisher-supplied records only), Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, and Embase were searched for relevant English-language articles published after the 2014 review for the USPSTF (January 1, 2013, through February 1, 2022 [eMethods in the Supplement]). All studies in the prior review were also evaluated, as well as reference lists of relevant systematic reviews. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for relevant ongoing trials.

Study Selection

Titles, abstracts, and full-text articles were reviewed by investigators against prespecified eligibility criteria (eTable 1 in the Supplement). Discrepancies were resolved by consensus. English-language fair- and good-quality randomized clinical trials (RCTs) were included that evaluated multivitamins/minerals (KQ1 and KQ2), and single nutrients or functionally related nutrient pairs (KQ3 and KQ4) compared with placebo or no intervention and reported cardiovascular disease, cancer, mortality, serious harms, or nonserious adverse events reported by at least 5% of the intervention group. For serious harms, comparative observational studies (cohort or case-control) or postmarket surveillance data were also eligible. A stated study aim of cardiovascular disease or cancer prevention was not required for inclusion; thus, trials of supplements designed to prevent other conditions were included if outcomes of interest were reported. A minimum of 1-year follow-up was required for all-cause mortality, and no minimum follow-up was required for all other outcomes. Studies were required to be conducted in countries classified as “very high” on the 2017 Human Development Index. Eligible populations included community-dwelling adults 18 years or older without chronic disease and without vitamin, mineral, or nutritional deficiencies. Studies among persons with cardiovascular disease risk factors, a history of colorectal adenoma, or previous nonmelanoma skin cancer were included.

Data Extraction and Quality Assessment

Data were extracted from each included study into standardized evidence tables by 1 investigator. Data accuracy was confirmed by a second investigator. Study characteristics, dosing details, participant demographics, and results for mortality, cardiovascular disease, cancer, and harms were extracted. Only published data were extracted; investigators were not contacted to supply missing fields. The quality of each study was assessed by 2 reviewers who independently applied USPSTF design-specific criteria (eTable 2 in the Supplement). Each study was assigned a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were resolved by consensus. Studies rated as poor quality were excluded.

Data Synthesis and Analysis

Summary tables for all KQs were created for each supplement. Quantitative pooling was conducted when at least 3 studies of the same supplement reported the same outcome. A single effect per study was included in each meta-analysis, preferentially selecting the time point corresponding with the end of supplement use. Data for beta carotene and vitamin A are summarized together because beta carotene is a vitamin A precursor. Peto odds ratios (ORs) with a restricted maximum likelihood (REML) model were used when events occurred in less than 5% of the sample for most studies in the analysis. When events typically occurred in 5% to 10% of the sample, a fixed-effects Mantel-Haenszel model was used as the primary analysis. When events had a higher incidence, standard ORs using a REML model were pooled, adding the Knapp-Hartung correction for pooling a small number of studies. Because absolute event rates were highly variable for most analyses, sensitivity analyses using alternative pooling methods were conducted (see full report). The presence of statistical heterogeneity among the studies was assessed using the $I^2$ statistic. $I^2$ values were not generated for fixed-effects models, so $I^2$ from random-effects sensitivity analyses are reported, if available.

Stata version 16 (StataCorp) was used for all quantitative analyses. All significance testing was 2-sided, and results were considered statistically significant at $P < .05$.

Results

A total of 84 studies (N = 739 803) (eTable 3 in the Supplement) were included, comprising 78 RCTs (N = 324 837) and 6 cohort studies (N = 390 689) after review of 17 459 unique citations and 379 full-text articles (Figure 2). Fifty-two of the included studies were newly identified since the last review. The included studies addressed multivitamins; vitamins A, B₁, B₆, B₁₂, C, D, and E; beta carotene; folic acid; calcium; magnesium; selenium; and zinc. The evidence for the B and C vitamins, folic acid, magnesium, selenium, and...
Figure 1. Analytic Framework: Vitamin and Mineral Supplements for Primary Prevention of Cardiovascular Disease and Cancer

Multivitamin/mineral supplementation or single nutrients or functionally related pairs

1. Health outcomes
   Cardiovascular disease incidence and events
   Cancer incidence
   Mortality (all-cause, disease-specific)

2. Harms of supplementation

Community-dwelling adults 18 y or older without known nutritional deficiencies

Key questions

1. What is the efficacy of multivitamin supplementation for reducing cardiovascular disease, cancer, and mortality in the general adult population?
2. What are the harms of multivitamin supplementation in the general adult population?
3. What is the efficacy of supplementation with single nutrients or functionally related nutrient pairs for reducing cardiovascular disease, cancer, and mortality in the general adult population?
4. What are the harms of supplementation with single nutrients in the general adult population?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. For additional information see the USPSTF Procedure Manual.9

Benefits of Multivitamin Supplementation

Key Question 1. What is the efficacy of multivitamin supplementation for reducing cardiovascular disease, cancer, and mortality in the general adult population?

Nine RCTs addressed KQ1 (n = 51,945) (eTable 4 in the Supplement).16,26,31,43,54,70,72,81,93 Three large studies had primary aims of cardiovascular disease and cancer prevention, were all rated as good quality, and comprised most of the evidence for this KQ.16,26,93 These were the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (n = 13,017),16 which examined use of an antioxidant-focused supplement among adults aged 35 to 60 years; the Physicians’ Health Study II (PHS-II) examined use of an antioxidant-focused supplement among adults aged 35 to 60 years (men) or 65 years or older (women).93 The other 6 RCTs were small, with a variety of other aims, and 5 of these did not report a robust ascertainment process for the all-cause mortality, cardiovascular disease, or cancer outcomes. The evidence suggested small to no benefit of multivitamin use for all-cause mortality, no benefit for cardiovascular disease, and a possible small benefit for cancer outcomes (Figure 3). In pooled analyses, the association with all-cause mortality was not statistically significant (OR, 0.94 [95% CI, 0.87-1.01]; 9 RCTs [n = 51,550]; I² = 0%). The largest trial, COSMOS, reported that 3.4% of participants taking a multivitamin had died after a median of 3.6 years of follow-up, compared with 3.6% who were taking a placebo (hazard ratio [HR], 0.93 [95% CI, 0.81-1.08] [n = 21,442]),93 and effect sizes were very similar in the other 2 trials. The pooled effect sizes were also similar for cancer mortality (OR, 0.94 [95% CI, 0.81-1.09]; 4 RCTs [n = 37,400]; I² = 28.9%) and cancer incidence (OR, 0.93 [95% CI, 0.87-0.99]; 4 RCTs [n = 48,859]; I² = 0%; absolute risk difference range among adequately powered trials, −0.2% to −1.2%). For cancer incidence, which showed a statistically significant pooled effect, 4.8% of participants in COSMOS taking a multivitamin had developed invasive cancer after 3.6 years, compared with 5.0% taking placebo (HR, 0.97 [95% CI, 0.86-1.09]; [n = 21,442]).50,93 The pooled effect size was also statistically significant for lung cancer, an outcome reported only by COSMOS and PHS-II (OR, 0.75 [95% CI, 0.58-0.95]; 2 RCTs [n = 36,052]; I² = 30%; absolute risk difference, −0.2% in both studies).

Harms of Multivitamin Supplementation

Key Question 2. What are the harms of multivitamin supplementation in the general adult population?

Harms of multivitamin use were reported in 9 RCTs (n = 51,614) (eTable 4 in the Supplement)16,26,31,43,54,70,72,81 and 3 cohort studies (n = 188,027).94,96,99 Among the 4 trials reporting any adverse effects,54,83 serious adverse effects,31 or withdrawals due to adverse effects,48 no group differences were found, although there were very few serious adverse effects or withdrawals due to adverse effects. With regard to specific adverse effects, PHS-II found an increased risk of rash (29.0% among multivitamin users, 27.3%
among nonusers; OR, 1.06 [95% CI, 1.01-1.12]) and nosebleeds (21.6% among multivitamin users, 19.8% among nonusers; OR, 1.09 [95% CI, 1.02-1.16]). Small increases in cataracts44,49,99 and hip fractures44 reported by cohort studies were not statistically significant and were not reported by any of the trials. None of the harms were replicated in COSMOS, which also found very few group differences among many other assessed potential adverse effects.93

Benefits of Single-Nutrient or Nutrient-Pair Supplementation

Key Question 3. What is the efficacy of supplementation with single nutrients or functionally related nutrient pairs for reducing cardiovascular disease, cancer, and mortality in the general adult population?

Beta Carotene and Vitamin A

Six RCTs addressed KQ3 for beta carotene and vitamin A (eTable 5 and eTable 6 in the Supplement). These studies evaluated the use of 20 to 50 mg/d of beta carotene (n = 112 820)17,21,32, 1 trial (n = 18 314) examined the combined use of beta carotene and 25 000 IU/d of vitamin A.18 Two of these studies—the original Physicians’ Health Study (PHS-I)20 and the Women’s Health Study (WHS)18—had broad cancer and cardiovascular disease prevention aims in men20 or women.18 Both were factorial design trials that also evaluated aspirin, as well as vitamin E in the WHS. Two trials, the Alpha-Tocopherol Beta Carotene Cancer Prevention (ATBC) trial21 and the Beta-Carotene and Retinol Efficacy Trial (CARET),19 had primary aims of lung cancer prevention and evaluated beta carotene supplementation in high-risk populations such as smokers and asbestos-exposed workers. ATBC was multifactorial, with additional randomization to 50 mg/d of vitamin E. The other 2 beta carotene studies were more narrowly aimed at primary37 or secondary32 prevention of skin cancer. One additional RCT examined the effect of 25 000 IU of vitamin A among adults with moderate risk for new nonmelanoma skin cancer (n = 2297).33

Pooled estimates showed statistically significant paradoxical harm associated with beta carotene use (Figure 3). The most pronounced risk increase was for lung cancer, with the pooled estimate showing a statistically significantly increased risk over 3.7 to 12 years of follow-up (OR, 1.20 [95% CI, 1.01-1.42]; 4 RCTs [n = 94 830]; I² = 38.8%). Absolute risk differences in individual trials ranged from −0.1% to 0.6%. These estimates included trials in general populations and those at high risk of lung cancer, and the strongest evidence was from the trials of people at high risk of lung cancer. Cardiovascular disease mortality similarly showed an increased risk (OR, 1.10 [95% CI, 1.02-1.19]; 5 RCTs [n = 94 506]; I² = 0%).
Absolute risk differences in individual trials ranged from −0.8% to 0.8%. In pooled analyses, the OR for all-cause mortality associated with beta carotene use was 1.06 (95% CI, 1.00-1.12; 6 RCTs [n = 112 820]; I² = 6.4%). When the study of vitamin A supplementation (alone) was included in the meta-analysis, 33 the all-cause mortality finding became statistically significant (OR, 1.06 [95% CI, 1.01-1.12]; 7 RCTs [n = 115 117]).

Vitamin E
Nine RCTs addressed KQ3 for vitamin E (n = 116 468) (eTable 7 in the Supplement). 18,21,22,25,26,51,74,77,79 Seven RCTs (n = 86 142) had an explicit aim to prevent cardiovascular disease 18,25,26,51 or related outcomes, 22,74,79 most among adults at increased risk for cardiovascular disease due to either smoking history 21,79 or other cardiovascular disease risk factors. 52,53,74 Three of the trials with cardiovascular disease aims also had a cancer prevention aim. 18,21,25,26 Doses ranged from 50 to 300 mg/d for 3 to 10 years, and follow-up time ranged from 3 to 24 years. One trial (n = 34 888) examined vitamin E with or without 200 μg of selenium daily, 25 and another small trial (n = 520) had a similar design including 500 mg of vitamin C. 22

Evidence indicated that vitamin E had no benefit for mortality, cardiovascular disease, or cancer. For example, pooled evidence demonstrated no statistically significant association between vitamin E use and all-cause mortality (OR, 1.02 [95% CI, 0.97-1.07]; 9 RCTs [n = 107 772]; I² = 0%) or the composite outcome of any cardiovascular disease event (OR, 0.96 [95% CI, 0.90-1.04]; 4 RCTs [n = 62 136]; I² = 0%) or incidence of any cancer (OR, 1.02 [95% CI, 0.98-1.08]; 5 RCTs [n = 76 777]; I² = 0%) (Figure 3). Effect sizes were very similar when vitamin E was used with or without selenium. 25 Additionally, 22,21,26 of 4 trials reporting hemorrhagic stroke or hemorrhagic stroke mortality showed statistically significant increases in these rare outcomes in groups randomized to vitamin E. In PHS-II, 0.5% among those taking vitamin E and 0.3% among those taking placebo experienced a hemorrhagic stroke (HR, 1.74 [95% CI, 1.04-2.90]). In the ATBC study of smokers, risk of hemorrhagic stroke death was similarly elevated (calculated OR, 1.50 [95% CI, 1.03-2.20]; vitamin E: 0.5%; placebo: 0.3%). 21
Vitamin D With or Without Calcium

Thirty-two RCTs addressed KQ3 for vitamin D (n = 123,140) (eTable B in the Supplement).24, 28, 34, 35, 38-41, 47-50, 58-60, 62-64, 66-69, 72, 73, 75, 76, 78, 82, 83, 86-90 Most of the studies had aims related to bone density, fractures, or falls and were primarily limited to adults 55 years or older. However, 5 explicitly aimed to prevent cardiovascular disease,24, 35, 39, 41, 89 and 7 had a cancer prevention aim.24, 28, 35, 38, 40-41, 89 The 3 largest studies were the WHI (n = 36,282)24 which examined the effects of 400 IU vitamin D and 1000 mg calcium use daily; the Vitamin D and Omega-3 Trial (VITAL, n = 25,871),16 which tested the effects of 2000 IU/d of vitamin D, with or without an omega-3 fatty acid supplement; and D-Health, which examined the use of 2000 IU daily.35 Both WHI and VITAL had specific aims of cancer and cardiovascular disease prevention among adults 50 years or older, while mortality reduction among 60- to 84-year-old adults was the aim of D-Health. Among all trials, doses ranged from 20 to 5000 IU/d for 1 month to 7 years and follow-up time ranged from 1 month to 11.9 years. The mean age was 66 years, and an estimated 75% of participants in all trials were women.

Pooling studies of vitamin D with or without calcium co-supplementation showed no significant reduction in all-cause mortality (OR, 0.96 [95% CI, 0.91-1.02]; 27 RCTs [n = 117,082]; I² = 0%), cardiovascular disease (eg, composite cardiovascular disease event outcome: OR, 1.00 [95% CI, 0.95-1.05]; 7 RCTs [n = 74,925]; I² = 0%), or cancer outcomes (eg, any cancer incidence: OR, 0.98 [95% CI, 0.92-1.03]; 19 RCTs [n = 86,899]; I² = 0%) (Figure 3). No clear effect modifiers were identified in sensitivity analyses or meta-regression (eTable 9 in the Supplement). For example, point estimates for all-cause mortality did not differ for vitamin D without calcium (OR, 0.968 [95% CI, 0.92-1.05]; 20 RCTs [n = 74,398]; I² = 0%) and vitamin D administered with calcium (OR, 0.93 [95% CI, 0.85-1.01]; 8 RCTs [n = 45,322]; I² = 0%). Similarly, findings were almost identical to the overall findings when limited to trials that reported robust outcome ascertainment methods (OR, 0.96 [95% CI, 0.91-1.02]; 12 RCTs [n = 103,457]; I² = 0%), rather than trials that assessed outcomes incidentally or through adverse events reporting or not reporting the source of these outcomes. In addition, there was no clear association between effect size and vitamin D dose or the use of bolus dosing (eg, 100,000 IU monthly) vs daily doses (interaction P = .12).

Calcium (Without Vitamin D)

Seven RCTs addressed KQ3 for calcium (n = 11,884, eTable 10 in the Supplement).27, 28, 30, 35, 38, 52, 53 The most common doses were 1000 and 1200 mg/d, and duration of use ranged from 6 months to 5 years. Follow-up time ranged from 6 months to 12 years. The largest study was the RECORD trial (n = 5292), which examined the effects of 1000 mg/d of calcium, with or without 800 IU/d of vitamin D, on cardiovascular disease and cancer outcomes among older adults with fragility fractures.35

Most of the evidence indicated that calcium had no benefit for mortality, cardiovascular disease, or cancer. Pooled effects uniformly indicated no group differences, and very few individual study findings demonstrated an effect of calcium supplementation on cancer, cardiovascular disease, or mortality. For example, pooled estimates for all-cause mortality (OR, 1.05 [95% CI, 0.92-1.21]; 6 RCTs [n = 83,941]; I² = 0%), cardiovascular disease events (OR, 1.11 [95% CI, 0.90-1.36]; 4 RCTs [n = 40,76]; F = 0%), and any incidence of cancer (OR, 0.94 [95% CI, 0.41-2.14]; 3 RCTs [n = 50,51]; F = 49.2%) all showed no statistically significant association with calcium use (Figure 3).

Harms of Single-Nutrient Supplementation

Key Question 4. What are the harms of supplementation with single nutrients in the general adult population?

Beta Carotene and Vitamin A

Six RCTs17-21, 32 and 1 cohort study94 reported on the harms of beta carotene supplementation, with or without the use of other supplements (eTable 5 in the Supplement). The most prominent harms were the paradoxical harms of increased all-cause mortality, cardiovascular disease mortality, and lung cancer described under KQ3. Other than these outcomes, there was a consistent and statistically significant increased risk of hypercarotenodermia with beta carotene use in the 4 trials reporting this adverse event at 2 to 12 years of follow-up.18, 20, 21, 32 The only other harm for which there was a statistically significant increased risk from beta carotene in an RCT was gastrointestinal symptoms in PHS-I.70 One cohort study limited to women found no statistically significant association between hip fractures and beta carotene (adjusted risk ratio [RR], 0.91 [95% CI, 0.57-1.44]).94 In addition to the trial of vitamin A alone reporting an increase in any adverse effects (OR, 1.77 [95% CI, 1.49-2.09]; n = 2264),33 2 cohort studies explored harms of vitamin A (eTable 6 in the Supplement).94, 95 A higher but not statistically significant risk of hip fracture with vitamin A use was suggested by both the Nurses’ Health Study (NHS-I) (adjusted RR, 1.50 [95% CI, 0.99-1.99])94 and the Iowa Women’s Health Study (RR, 1.18 [95% CI, 0.99-1.41]).95 The Iowa Women’s Health Study found no statistically significant association between vitamin A use and overall fracture risk (adjusted RR, 1.00 [95% CI, 0.95-1.05]).95 The NHS-I indicated no clear association between vitamin A use and cataract extraction.

Vitamin E

Harms of vitamin E were reported in 7 RCTs18, 21, 22, 25, 26, 51, 77 (n = 115,576) and 2 cohort studies34, 96 (n = 149,043) (eTable 7 in the Supplement). The 3 trials that reported the total number of adverse events,57, 77 serious adverse events,77 or withdrawals due to adverse events22, 77 found no group differences. Trial evidence also supported no group differences in hospitalization from pneumonia,21 gastrointestinal disease,31 several bleeding outcomes,26, 51 fatigue,25 nail changes,25 halitosis,25 easy bruising,26 and noncataract ophthalmic events.77 However, some of these results were based on a very small or unknown number of events. Two21, 26 of 4 trials that reported an increased risk of hemorrhagic stroke or hemorrhagic shock mortality are discussed above in KQ3.

PHS-II found no increase in the incidence of cataracts with vitamin E use at 8 years of follow-up (HR, 0.99 [95% CI, 0.89-1.11]).26 Similarly, a large cohort study of women (NHS-III) (n = 1,217,000) with supplement use assessed biannually found no association with cataracts.94 However, a smaller cohort study (n = 27,343) of Swedish men found a higher incidence of cataracts among men who reported any vitamin E use compared with no use on a 1-time survey at 8.4 years of follow-up (HR, 1.57 [95% CI, 1.10-2.22]).95
Vitamin D With or Without Calcium
KO4 outcomes for vitamin D were reported in 31 RCTs24-28,34-36,38-42, 47,50,55,58,61,63-67,71-73,75,76,82,83,86,88-90 (n = 117 100) and 3 cohort studies (n = 289 659) (eTable B in the Supplement).94,97,98 Among RCTs reporting the percent of participants experiencing any adverse events,36,39,61,63,65,76,87,90 any serious adverse events,28,40,50,83,86,90 or withdrawal due to adverse events,40,42,50,67,71,75,83,86,90 only 1 found an increase in withdrawals due to adverse events in a trial that administered 10 000 IU/wk of vitamin D plus 1000 mg/d of calcium to postmenopausal women.75

While most trials that reported data on kidney stones had very few events, 2 of the 3 largest trials indicated a small increased risk.28,38-41,58,78 In WHI, 2.5% of participants who were taking 400 IU of vitamin D and 1000 mg of calcium daily developed kidney stones after 7 years, compared with 2.1% in the placebo group (HR, 1.17 [95% CI, 1.02-1.34]). VITAL found a similar effect size, although it was not statistically significant (HR, 1.12 [95% CI, 0.99-1.28]). After 5.3 years, 3.7% of those who were taking 2000 IU/d of vitamin D developed kidney stones vs 3.3% of those in the placebo group. However, there was no significant association found in the D-Health study (incidence rate ratio, 1.03 [95% CI, 0.82-1.28]); 1.5% in the vitamin D group vs 1.4% in the placebo group). Two of the cohort studies97,98 found an increased risk of kidney stones with use of 1000 IU/d or more of vitamin D after 20 to 26 years, compared with no vitamin D use, but only 1 of these findings was statistically significant.97 There was no suggestion of increased risk with lower doses in either of these studies. The third cohort study, NHS-I,94 found no association between any dose of vitamin D and kidney stones. No statistically significant group differences were identified among a wide array of non-serious harms.

Calcium (Without Vitamin D)
Harms of calcium were reported in 8 RCTs27,28,30,35,52,53,61 (n = 12 961), and 1 cohort study (n = 121 700) (eTable 10 in the Supplement).94 Studies that reported the occurrence of any adverse events,94 any serious adverse events,28 and withdrawals due to adverse events30,53 identified very few events and found no group differences. Constipation and gastrointestinal symptoms were generally increased with calcium use, but findings were statistically significant in only 3 studies.27,35,52 Evidence from 5 trials suggested no increased risk of fractures.27,35,52 The cohort study, NHS-I, included only women and reported an increased incidence of kidney stones for any calcium use compared with no calcium use, but no dose-response trend was identified.94 Evidence on kidney stones from the trials was inconclusive due to the small numbers of events.

Discussion
This updated evidence review examined the use of vitamins and minerals for primary prevention of cardiovascular disease and cancer; the evidence is summarized in the Table. The findings from 84 RCTs and 6 cohort studies suggest that most vitamin and mineral supplements provide no clinically important protective effects for cardiovascular disease, cancer, or all-cause mortality in healthy adults without known nutritional deficiencies. One exception was a slightly lower risk of cancer incidence with multivitamin use. However, the evidence for multivitamins had important limitations, including only 3 adequately powered trials, 1 with a median of only 3.6 years of multivitamin use and another that was limited to antioxidants.

Other than the new finding related to multivitamin use and lower cancer incidence, these conclusions are generally consistent with those of the previous review for the USPSTF on this topic.12 Vitamin E had the strongest body of evidence demonstrating no benefit for outcomes relevant to this review. These updated review findings also confirm the previous review’s finding that beta carotene supplementation, especially with concomitant vitamin A use, likely increases the risk of lung cancer incidence, particularly in those at high risk for lung cancer. New evidence in this update was predominately for vitamin D supplementation. Despite the new inclusion of 32 RCTs and 2 cohort studies, pooled estimates for all-cause mortality were similar to that in the prior review with confidence intervals only slightly crossing 1 and point estimates suggesting at most a very small benefit.

This review found minimal other recent synthesized evidence on the effect of multivitamin use, but another review concluded that observational studies suggest a possible lower breast cancer recurrence among breast cancer survivors using multivitamins.101 The findings for vitamin D in the current review are generally consistent with those from other reviews, for example, pooled estimates in the range of 0.93 to 0.97 that may not be statistically significant for all-cause mortality.102-104 In general, the statistical significance of an all-cause mortality benefit in pooled analyses is unstable, being sensitive to the number of included studies and which study aims are considered. For vitamin E, another review of primary prevention in adults concluded that vitamin E may reduce the risk of cardiovascular disease mortality.105 The pooled analysis for cardiovascular disease mortality was not statistically significant in the current review, although the point estimate was in the direction of benefit (OR, 0.88 [95% CI, 0.74-1.04]). The point estimate in the other review was the same but was statistically significant (RR, 0.88 [95% CI, 0.80-0.96]).105 The other review included studies of multivitamins that contained vitamin E in addition to vitamin E alone, in contrast to the meta-analysis in the current review, which was limited to intervention groups examining vitamin E alone. While this might indicate a relatively small effect that is detectable in only very large pooled analyses, the lack of association with all-cause mortality and cardiovascular disease events and the lack of statistical significance in the current review led to the conclusion that vitamin E most likely has little to no effect on cardiovascular disease mortality, although some uncertainty remains.

A general limitation of literature included in this review is that the effects of individual micronutrients on human health are very difficult to detect in generally healthy populations with adequate nutrition. Supplement exposure is complicated by exposure to nutrients through dietary intake, and some studies reported fairly high levels of independent use of supplements among their study populations. There is variability in how individuals absorb and metabolize nutrients, and interactions among nutrients and between nutrients and myriad enzymes and hormones in the human body complicate the ability to detect their effects.

There is a lack of information about whether broad-spectrum multivitamins (rather than antioxidant-focused formulations) prevent cardiovascular disease and cancer in general populations including both men and women. Other limitations of this evidence include insufficient information on the effect of vitamins and minerals
Table. Summary of Evidence

<table>
<thead>
<tr>
<th>Studies</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Other limitations</th>
<th>Strength of evidence</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ1: Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivitamin: 9 RCTs (n = 51 945 observations)</td>
<td>Evidence suggested a possible small benefit for cancer but small to no benefit for all-cause mortality or CVD</td>
<td>All-cause, CVD, and cancer-specific mortality, cancer incidence: reasonably consistent, reasonably precise</td>
<td>Specific formulations differed widely and included both broad-spectrum and antioxidant-focused supplements</td>
<td>All-cause mortality: low for small to no benefit</td>
<td>Most studies were conducted outside the US, including 1 of the 3 main trials; the other main trial was limited to male physicians</td>
</tr>
<tr>
<td></td>
<td>Pooled results reflected the findings of 3 large good-quality trials with CVD and cancer aims that provided most of the evidence</td>
<td>Other CVD outcomes: reasonably consistent or NA, reasonably precise</td>
<td>Two of the main trials had background interventions in factorial study designs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled results included:</td>
<td>Site-specific cancers: reasonably consistent, inconsistent, or NA; imprecise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All-cause mortality: OR, 0.94 (95% CI, 0.87-1.01); 9 RCTs (n = 51 550)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVD mortality: OR, 0.94 (95% CI, 0.83-1.06); 4 RCTs (n = 37 400)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any cancer incidence: OR, 0.93 (95% CI, 0.87-0.99); 4 RCTs (n = 48 859)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung cancer incidence: OR, 0.75 (95% CI, 0.58-0.95); 2 RCTs (n = 36 052)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>KQ2: Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivitamin: 9 RCTs (n = 51 614 observations)</td>
<td>No evidence of increased risk of serious adverse events, but few events</td>
<td>Cataracts: consistent, imprecise</td>
<td>Cataracts, hip fractures: evidence limited to observational studies, supplement use self-reported</td>
<td>Low for increased risk of rash, epistaxis, insufficient for other harms</td>
<td>Most studies were conducted outside the US, including 1 of the 3 main trials; the other main trial was limited to male physicians</td>
</tr>
<tr>
<td></td>
<td>Small increases in cataracts reported by cohort studies were not statistically significant and were not examined in any of the trials</td>
<td>Other serious adverse events: consistency NA, imprecise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A large trial found small increased risk of rash and epistaxis</td>
<td>Rash and epistaxis: consistency NA, reasonably precise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KQ3: Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta carotene: 6 RCTs (n = 112 820 observations)</td>
<td>Pooled estimates for several outcomes showed statistically significant paradoxical harm associated with beta carotene use, for example:</td>
<td>All-cause mortality: reasonably consistent, precise for increased risk for beta carotene with or without vitamin A</td>
<td>Variation in study dose and duration</td>
<td>All-cause mortality: moderate for small increased risk for beta carotene with or without vitamin A</td>
<td>Most studies of beta carotene and vitamin A conducted in the US, but participants were primarily White</td>
</tr>
<tr>
<td>Vitamin A: 2 RCTs (n = 20 611 observations)</td>
<td>All-cause mortality: OR, 1.06 (95% CI, 1.00-1.12); 6 RCTs (n = 112 820)</td>
<td>CVD mortality: reasonably consistent, precise for increased risk for beta carotene</td>
<td>Combined supplement use in CARET and varied background interventions in almost all other trials</td>
<td>Low for no increased risk with vitamin A alone</td>
<td>Included general risk samples as well as those limited to persons at increased risk for lung cancer due to smoking status or asbestos exposure</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality, including vitamin A study (Skin Cancer Prevention [SKICAP]): OR, 1.06 (95% CI, 1.01-1.12); 7 RCTs (n = 115 117)</td>
<td>Lung cancer: reasonably consistent, precise for increased risk</td>
<td>Multiple comparisons and outcomes examined in a body of literature with different primary aims</td>
<td>CVD mortality: moderate for a small increased risk for beta carotene</td>
<td>Vitamin A doses above the current upper limit in all trials evaluating vitamin A</td>
</tr>
<tr>
<td></td>
<td>CVD mortality: OR, 1.10 (95% CI, 1.02-1.19); 5 RCTs (n = 95 506); range in ARD, −0.8% to 0.8%</td>
<td>Any cancers and other site-specific cancers: consistent and imprecise for no difference</td>
<td>CVD events: low for no association for beta carotene</td>
<td>Any cancer and other site-specific cancers: low for no difference for beta carotene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung cancer: OR, 1.20 (95% CI, 1.01-1.42); 4 RCTs (n = 94 830); range in ARD, −0.1% to 0.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled estimates for all cancer mortality, any cancer incidence, colorectal, breast, and prostate cancer showed no statistically significant differences in risk associated with beta carotene use; there were no differences in composite CVD events in 2 reporting trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| | Vitamin A had no significant association with all-cause mortality | | | | (continued)
<table>
<thead>
<tr>
<th>Studies</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Other limitations</th>
<th>Strength of evidence</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E:</td>
<td>Most evidence indicated that vitamin E had no benefit for mortality, CVD, or cancer; example, pooled ORs included:</td>
<td>All-cause mortality: reasonably consistent, precise</td>
<td>Few studies for most outcomes other than all-cause mortality, several studies underpowered for the main outcomes of this review (but all main outcomes for the review also include some studies powered for CVD, cancer outcomes, or both)</td>
<td>All-cause mortality: high for no benefit; CVD: other than hemorrhagic stroke: moderate for small to no benefit; Hemorrhagic stroke: low for increased risk; Cancer: low for small to no benefit for prostate; moderate for small to no benefit for other cancer outcomes</td>
<td>Most included participants were White American or European adults 45 y or older; Included general-risk samples as well as those limited to persons at increased risk for cancer or CVD due to smoking or CVD risk factors</td>
</tr>
<tr>
<td>9 RCTs (n = 116468 observations)</td>
<td>- All-cause mortality: 1.02 (95% CI, 0.97-1.07); 9 RCTs (n = 107772) CVD events: 0.96 (95% CI, 0.90-1.04); 4 RCTs (n = 62136) Any cancer: 1.02 (95% CI, 0.98-1.08); 5 RCTs (n = 76777)</td>
<td>CVD: consistent, imprecise for prostate cancer; consistent, imprecise for other cancer outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D (with or without calcium):</td>
<td>Evidence suggested no benefit for all primary outcomes of this review; for example, pooled ORs included:</td>
<td>All-cause mortality, CVD mortality, any cancer incidence: reasonably consistent, precise</td>
<td>Most studies had primary aims related to bone density, fractures, or falls (however, there were 2 very large good-quality trials plus additional smaller trials with cancer and CVD as primary aims); Few large studies reported most site-specific cancers</td>
<td>All-cause mortality: moderate for no benefit; CVD: high for no benefit; Cancer: low for no benefit</td>
<td>Primarily White older adults</td>
</tr>
<tr>
<td>32 RCTs (n = 123140 observations)</td>
<td>- All-cause mortality: 0.96 (95% CI, 0.91-1.02); 27 RCTs (n = 117082) CVD events: 1.00 (95% CI, 0.95-1.05); 7 RCTs (n = 74925) Any cancer: 0.98 (95% CI, 0.92-1.03); 19 RCTs (n = 86899)</td>
<td>CVD events: consistent, precise Cancer mortality: inconsistent, reasonably precise Site-specific cancers: reasonably consistent, imprecise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium:</td>
<td>Most evidence indicated no benefit for mortality, CVD, or cancer after up to 6 y of calcium use; however, 1 smaller study suggested a possible reduction in prostate cancer among persons with a recent adenoma</td>
<td>All-cause mortality: reasonably consistent, reasonably precise</td>
<td>Primary outcomes were often underpowered, since half of studies had primary aims irrelevant to this review</td>
<td>All-cause mortality: moderate for no benefit; CVD: low for no benefit; Cancer: low for no benefit</td>
<td>Best evidence limited to White adults 70 y or older with fragility fractures; Other studies also primarily in adults 40 y or older, White, and mostly female</td>
</tr>
<tr>
<td>7 RCTs (n = 11884 observations)</td>
<td>Pooled ORs for other outcomes include:</td>
<td>Cancer: inconsistent or NA (for site-specific cancers, imprecise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality: 1.05 (95% CI, 0.92-1.21; 6 RCTs [n = 8394]) CVD events: 1.11 (95% CI, 0.90-1.36; 4 RCTs [n = 4076]) Any cancer: 0.94 (95% CI, 0.41-2.14; 3 RCTs [n = 5051])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>Summary of findings</td>
<td>Consistency and precision</td>
<td>Other limitations</td>
<td>Strength of evidence</td>
<td>Applicability</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>KQ4: Harms</td>
<td>The most substantial serious harms are the paradoxical harms of increased all-cause mortality, CVD mortality, and lung cancer (see KQ3)</td>
<td>Excluding increased all-cause mortality, CVD mortality, and lung cancer: consistent, precise for beta carotene and increased risk of hypercarotenodermia</td>
<td>Variation in study dose and duration</td>
<td>Excluding increased all-cause mortality, CVD mortality, and lung cancer: Consistent and imprecise for vitamin A and increased risk of hip fracture</td>
<td>Most studies of beta carotene and vitamin A conducted in the US, but participants were primarily White</td>
</tr>
<tr>
<td>Beta carotene:</td>
<td>6 RCTs (n = 112 820 observations) 1 Prospective cohort study (n = 121 700 observations) Vitamin A:</td>
<td>Two cohort studies in women found an elevated but not statistically significantly increased risk of hip fracture associated with vitamin A supplementation</td>
<td></td>
<td></td>
<td>Evidence included general-risk samples as well as those limited to persons at increased risk for lung cancer due to smoking status or asbestos exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variations in study dose and duration</td>
<td></td>
<td></td>
<td>Vitamin A doses were above the current upper limit in all trials evaluating vitamin A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combined supplement use in CARET and varied background interventions in almost all other trials</td>
<td></td>
<td></td>
<td>Data suggesting a possible increased hip fracture risk with vitamin A are from cohort studies of primarily White women</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E:</td>
<td>Although data on specific outcomes were sparse, no clear increased risk of serious harm was identified, but effects were wide-ranging and included findings in the direction of benefit and harm across all review outcomes, including 2 trials with increased risk of hemorrhagic stroke; 1 cohort study with a single assessment of vitamin E use found an increased risk of cataracts, but a higher-quality cohort study with biennial reporting of vitamin E use showed no increased risk of cataracts</td>
<td>Inconsistent, imprecise</td>
<td>Supplement use in cohort studies was self-reported</td>
<td>Other than paradoxical harm for hemorrhagic stroke: Cataracts, hospitalization from pneumonia, other nonserious: low for no increased risk</td>
<td>Most included participants were White American or European adults 45 y or older</td>
</tr>
<tr>
<td></td>
<td>7 RCTs (n = 115 576 observations) 2 Prospective cohort studies (n = 149 043 observations)</td>
<td></td>
<td></td>
<td></td>
<td>Included general risk samples as well as those limited to persons at increased risk for cancer or CVD due to smoking or CVD risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D (with or without calcium):</td>
<td>Both trial and cohort evidence suggested an increased risk of kidney stones with 1000 IU/d or more of vitamin D over ≥7 y</td>
<td>Kidney stones: inconsistent, imprecise</td>
<td>Most studies had primary aims related to bone density, fractures, or falls</td>
<td>Kidney stones: low for small increased risk</td>
<td>Primarily White older adults</td>
</tr>
<tr>
<td></td>
<td>31 RCTs (n = 117 100 observations) 3 Prospective cohort studies (n = 289 659 observations)</td>
<td>GI symptoms: consistent, precise</td>
<td>GI-related symptoms: moderate for increased risk</td>
<td>GI-related symptoms: moderate for increased risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other adverse events: inconsistent, imprecise</td>
<td>Other adverse events: low for no increased risk</td>
<td>Other adverse events: low for no increased risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium:</td>
<td>Findings suggested an increased risk of constipation and GI symptoms and possibly kidney stones</td>
<td>GI symptoms: consistent, reasonably precise</td>
<td>Reporting of any adverse effects, any serious adverse effects, and withdrawal due to adverse effects sparsely reported; kidney stone evidence primarily limited to observational data in women only, in whom supplement use was measured by self-report</td>
<td>GI-related symptoms: moderate for increased risk</td>
<td>Best evidence limited to White adults 70 y or older with fragility fractures</td>
</tr>
<tr>
<td></td>
<td>8 RCTs (n = 11 930) 1 Prospective cohort study (n = 121 700 observations)</td>
<td>Kidney stones: reasonably consistent and imprecise</td>
<td>Kidney stones: low for increased risk</td>
<td>Kidney stones: low for increased risk</td>
<td>Other studies also primarily in adults 40 y or older, White, and mostly female</td>
</tr>
</tbody>
</table>

Abbreviations: ARD, absolute risk difference; CARET, Carotene and Retinol Efficacy Trial; CVD, cardiovascular disease; GI, gastrointestinal; KQ, key question; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial.
in Black and Native American populations, in whom the burden of cardiovascular disease and cancer is known to be high; limitations or uncertainty about the quality of cancer and cardiovascular disease outcome data in studies that were not designed for these outcomes; and likely insufficient follow-up in most studies, since cardiovascular disease and cancer may take a decade or more to manifest.

Limitations
This review has several limitations. First, there may be other benefits of some supplements that were not covered in this review owing to its focus on cardiovascular disease and cancer prevention. For example, folic acid use in women who are pregnant or soon to be pregnant is known to be valuable for prevention of neural tube defects in their offspring. Second, because of the focus on studies in predominantly healthy populations without known nutritional deficiencies, this review also did not cover therapeutic use of supplements in persons with physical symptoms, medical conditions, or nutritional deficits. Third, owing to the focus on serious harms, this review of nonserious harms is not comprehensive. The risks of high doses were not generally addressed here, but are comprehensively documented in an Institute of Medicine Report on dietary reference intakes that addresses setting tolerable upper limits. However, studies with vitamin A and vitamin D doses above the recommended upper limit were included for consistency with the previous review. Fourth, because of the large number of analyses, there is the potential for false-positive findings due to chance. Fifth, there may be other doses, formulations, or supplement combinations that could be beneficial or less harmful for which the review did not have the data to explore.

Conclusions
Vitamin and mineral supplementation was associated with little or no benefit in preventing cancer, cardiovascular disease, and death, with the exception of a small benefit for cancer incidence with multivitamin use. Beta carotene was associated with an increased risk of lung cancer and other harmful outcomes in persons at high risk of lung cancer.


