JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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

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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.

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Cardiovascular disease and cancer are the 2 leading causes of death in the US.[1] 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.[2-4] Further, observational evidence has suggested associations between higher plasma levels of various vitamins and minerals and lower rates of cardiovascular disease and cancer.[5,6] 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.[7]

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.[8] 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.[10] Methodological details and findings for the B and C vitamins, folic acid, magnesium, selenium, and zinc are available in the full evidence report.[11]

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]).[12] All studies in the prior review were also evaluated,[12] 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.[13] 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).[9] 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.

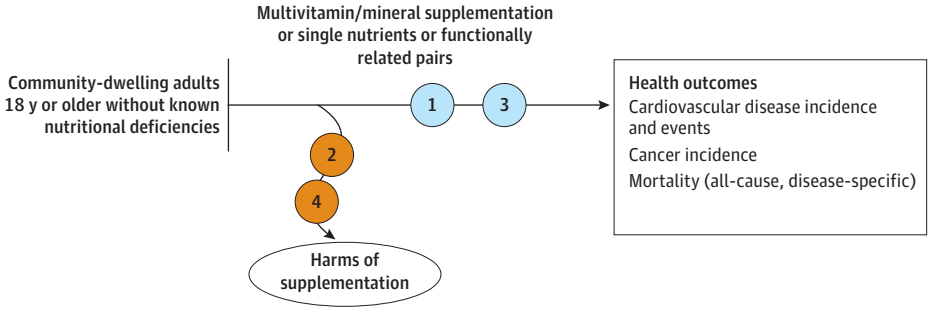
Peto odds ratios (ORs) with a restricted maximum likelihood (REML) model were used when events occurred in less than 5% of the sample for most studies in the analysis. When events typically occurred in 5% to 10% of the sample, a fixed-effects Mantel-Haenszel model was used as the primary analysis. When 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.[14,15] Because absolute event rates were highly variable for most analyses, sensitivity analyses using alternative pooling methods were conducted (see full report[11]). 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)[16-93] and 6 cohort studies (n = 390 689),[71,94-99] 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.[12] The included studies addressed multivitamins; vitamins A, B_3, B_6, B_{12}, 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



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]

zinc was low, insufficient, or absent for all outcomes. Results for these supplements can be found in the full evidence report.[11]

The mean age across all included studies was 61.0 years. An estimated 65.1% of all participants were women. Most participants were White in studies conducted in the US (with data from 22 of 36 studies). An estimated 19.6% of participants were Black, among studies reporting race and ethnicity. The vitamin D trials had, on average, greater representation of Black participants. Other racial and ethnic groups had minimal representation for all supplements.

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?

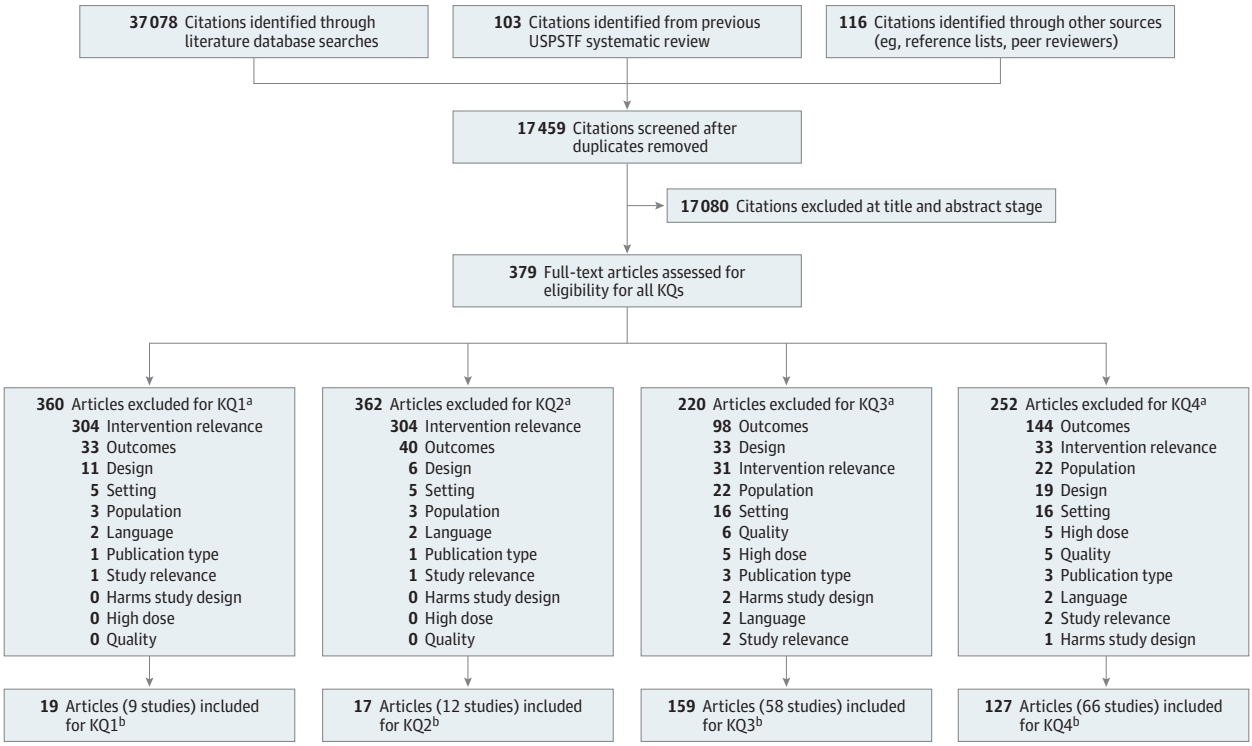
Nine RCTs addressed KQ1 (n = 51 945) (eTable 4 in the Supplement).[16,26,31,43,54,70,72,81,93] Three large studies had primary aims of cardiovascular disease and cancer prevention, were all rated as good quality, and comprised most of the evidence for this KQ.[16,26,93] These were the Supplementation 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 [n = 14 641]), which examined a broad-spectrum supplement among male physicians 50 years or older[26]; and the Cocoa Supplement and Multivitamin Outcomes Study (COSMOS [n = 21 442]), which examined a broad-spectrum supplement among adults aged 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]; I^2 = 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]; I^2 = 28.9%) and cancer incidence (OR, 0.93 [95% CI, 0.87-0.99]; 4 RCTs [n = 48 859]; I^2 = 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])[100]; effects were slightly larger in SU.VI.MAX (RR, 0.90 [95% CI, 0.76-1.06] after 7.5 years) and PHS-II (HR, 0.92 [95% CI, 0.86-1.00] after 11.2 years). The pooled effect 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]; I^2 = 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)[16,26,31,48,54,70,72,81] and 3 cohort studies (n = 188 027).[94,96,99] Among the 4 trials reporting any adverse effects,[54,81] 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%

Figure 2. Literature Search Flow Diagram: Vitamin and Mineral Supplements for Primary Prevention of Cardiovascular Disease and Cancer



[a] Reasons for exclusion: Intervention relevance: Study used an excluded intervention. Outcomes: Study did not report relevant outcomes. Design: Study did not use an included design. Setting: Study not conducted in a country relevant to US practice. Population: Study not conducted in community-dwelling adults without chronic disease and without nutritional deficiencies. Language: Not available in English. Publication type: Conference abstract. Study relevance: Study aim not relevant. Harms study design: Short-term nonserious harms reported, but lack of evidence of benefit. High dose: Supplement dose greater than the tolerable upper intake level as determined by the National Academies of Sciences, Engineering, and Medicine Food and Nutrition Board. Quality: Study did not meet criteria for fair or good quality.

[b] Studies could be included for more than 1 key question (KQ).

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 cataracts[94,99] and hip fractures[94] 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?

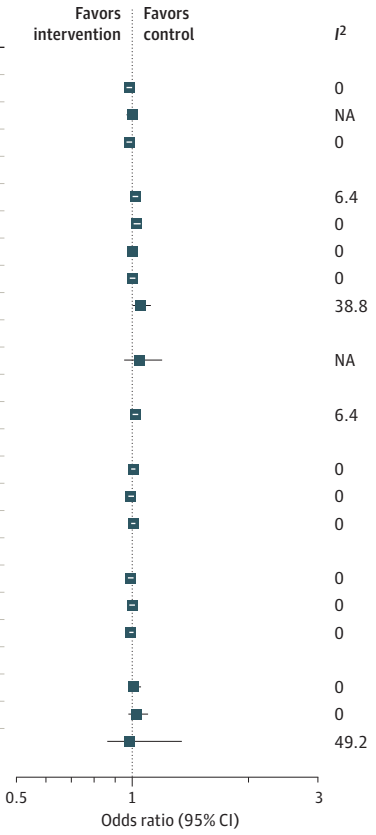
Beta Carotene and Vitamin A

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.[19] 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 men[20] 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) trial[21] 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 primary[17] or secondary[32] 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]; I^2 = 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]; I^2 = 0%).

Figure 3. Summary of Meta-analysis Results or Best Evidence for Primary Key Question 1 and Key Question 3 Outcomes

Outcome	No. of studies	No. analyzed	% with event		Odds ratio (95% CI)	I^2
			Intervention	Control		
Multivitamin						
All-cause mortality[a]	9	51 550	7.3	7.7	0.94 (0.87-1.01)	0
CVD event[b]	1	21 442	4	4.1	0.98 (0.86-1.12)	NA
Any cancer[a]	4	48 859	8.5	9	0.93 (0.87-0.99)	0
Beta carotene						
All-cause mortality	6	112 820	5.4	5.1	1.06 (1.00-1.12)	6.4
CVD mortality	5	94 506	2.8	2.6	1.10 (1.02-1.19)	0
CVD events	2	61 947	3.5	3.5	1.01 (0.92-1.10)	0
Any cancer	2	61 947	5.3	5.4	0.99 (0.92-1.07)	0
Lung cancer[c]	4	94 830	1.2	1	1.20 (1.01-1.42)	38.8
Vitamin A						
All-cause mortality[d]	1	2297	5.4	4.6	1.16 (0.80-1.69)	NA
Beta carotene or vitamin A						
All-cause mortality	7	115 117	5.4	5.1	1.06 (1.01-1.12)	6.4
Vitamin E						
All-cause mortality	9	107 772	6.9	6.8	1.02 (0.97-1.07)	0
CVD events	4	62 136	5.1	5.2	0.96 (0.90-1.04)	0
Any cancer	5	76 777	8.8	8.6	1.02 (0.98-1.08)	0
Vitamin D						
All-cause mortality	27	117 082	5	5.7	0.96 (0.91-1.02)	0
CVD events	7	74 925	8.1	8.2	1.00 (0.95-1.05)	0
Any cancer	19	86 899	6.7	6.8	0.98 (0.92-1.03)	0
Calcium						
All-cause mortality	6	8394	13.1	12.7	1.05 (0.92-1.21)	0
CVD events	4	4076	10.7	9.7	1.11 (0.90-1.36)	0
Any cancer[a]	3	5051	8.7	8.9	0.94 (0.41-2.14)	49.2



Mantel-Haenszel fixed-effects model used unless otherwise specified. Percent with an event is calculated as the weighted mean percent with an event across the studies included in the analysis, weighted by the number of participants analyzed in the relevant group for each study. Results do not correspond directly to pooled odds ratios (ORs) because weighting in meta-analysis models differs from this approach.

[a] Restricted maximum likelihood model with the Knapp-Hartung (REML-KH) correction used.

[b] Evidence shown is a hazard ratio from a single study, PHS-II. PHS-II provided the number of cardiovascular disease (CVD) events rather than the number of persons experiencing a CVD event, so the percentage of participants with an event was not calculable.

[c] The Peto OR was used with REML-KH correction.

[d] Evidence shown is from a single study, SKICAP (Skin Cancer Prevention).

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]; I^2 = 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.[22,51,74] 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]; I^2 = 0%) or the composite outcome of any cardiovascular disease event (OR, 0.96 [95% CI, 0.90-1.04]; 4 RCTs [n = 62 136]; I^2 = 0%) or incidence of any cancer (OR, 1.02 [95% CI, 0.98-1.08]; 5 RCTs [n = 76 777]; I^2 = 0%) (Figure 3). Effect sizes were very similar when vitamin E was used with or without selenium.[25] Additionally, 2[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 8 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),[41] 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.[90] 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 cosupplementation showed no significant reduction in all-cause mortality (OR, 0.96 [95% CI, 0.91-1.02]; 27 RCTs [n = 117 082]; I^2 = 0%), cardiovascular disease (eg, composite cardiovascular disease event outcome: OR, 1.00 [95% CI, 0.95-1.05]; 7 RCTs [n = 74 925]; I^2 = 0%), or cancer outcomes (eg, any cancer incidence: OR, 0.98 [95% CI, 0.92-1.03]; 19 RCTs [n = 86 899]; I^2 = 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]; I^2 = 0%) and vitamin D administered with calcium (OR, 0.93 [95% CI, 0.85-1.01]; 8 RCTs [n = 45 322]; I^2 = 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]; I^2 = 0%), rather than trials that assessed outcomes incidentally 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 = 8394]; I^2 = 0%), cardiovascular disease events (OR, 1.11 [95% CI, 0.90-1.36]; 4 RCTs [n = 4076]; I^2 = 0%), and any incidence of cancer (OR, 0.94 [95% CI, 0.41-2.14]; 3 RCTs [n = 5051]; I^2 = 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 RCTs[17-21,32] and 1 cohort study[94] 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.[20] 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 RCTs[18,21,22,25,26,51,77] (n = 115 576) and 2 cohort studies[94,96] (n = 149 043) (eTable 7 in the Supplement). The 3 trials that reported the total number of adverse events,[51,77] serious adverse events,[77] or withdrawals due to adverse events[22,77] found no group differences. Trial evidence also supported no group differences in hospitalization from pneumonia,[21] gastrointestinal disease,[51] 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. Two[21,26] of 4 trials that reported an increased risk of hemorrhagic stroke or hemorrhagic stroke 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, 0.88-1.11]).[26] Similarly, a large cohort study of women (NHS-I) (n = 121 700) 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]).[96]

Vitamin D With or Without Calcium

KQ4 outcomes for vitamin D were reported in 31 RCTs[24,28,34-36,38-42,47,50,55,58,61,63-67,71-73,75,76,82,83,86,88-90] (n = 117 100) and 3 cohort studies (n = 289 659) (eTable 8 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.[28,38-41,58,73] 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 studies[97,98] 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 nonserious harms.

Calcium (Without Vitamin D)

Harms of calcium were reported in 8 RCTs[27,28,30,35,38,52,53,61] (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,[61] any serious adverse events,[28] and withdrawals due to adverse events[30,53] 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.[27,35,38,52,53] 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

Studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits					
Multivitamin: 9 RCTs (n = 51 945 observations)	Evidence suggested a possible small benefit for cancer but small to no benefit for all-cause mortality or CVD Pooled results reflected the findings of 3 large good-quality trials with CVD and cancer aims that provided most of the evidence Pooled results included: All-cause mortality: OR, 0.94 (95% CI, 0.87-1.01); 9 RCTs (n = 51 550) CVD mortality: OR, 0.94 (95% CI, 0.83-1.06); 4 RCTs (n = 37 400) Any cancer incidence: OR, 0.93 (95% CI, 0.87-0.99); 4 RCTs (n = 48 859) Lung cancer incidence: OR, 0.75 (95% CI, 0.58-0.95); 2 RCTs (n = 36 052)	All-cause, CVD, and cancer-specific mortality, cancer incidence: reasonably consistent, reasonably precise Other CVD outcomes: reasonably consistent or NA, reasonably precise Site-specific cancers: reasonably consistent, inconsistent, or NA; imprecise	Specific formulations differed widely and included both broad-spectrum and antioxidant-focused supplements Two of the main trials had background interventions in factorial study designs	All-cause mortality: low for small to no benefit CVD: low for no benefit Cancer incidence: low for small benefit	Most studies were conducted outside the US, including 1 of the 3 main trials; the other main trial was limited to male physicians
KQ2: Harms					
Multivitamin: 9 RCTs (n = 51 614 observations) 3 Prospective cohort studies (n = 188 027 observations)	No evidence of increased risk of serious adverse events, but few events Small increases in cataracts reported by cohort studies were not statistically significant and were not examined in any of the trials A large trial found small increased risk of rash and epistaxis	Cataracts: consistent, imprecise Other serious adverse events: consistency NA, imprecise Rash and epistaxis: consistency NA, reasonably precise	Cataracts, hip fractures: evidence limited to observational studies, supplement use was self-reported	Low for increased risk of rash, epistaxis, insufficient for other harms	Most studies were conducted outside the US, including 1 of the 3 main trials; the other main trial was limited to male physicians
KQ3: Benefits					
Beta carotene: 6 RCTs (n = 112 820 observations) Vitamin A: 2 RCTs (n = 20 611 observations)	Pooled estimates for several outcomes showed statistically significant paradoxical harm associated with beta carotene use, for example: All-cause mortality: OR, 1.06 (95% CI, 1.00-1.12); 6 RCTs (n = 112 820) 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) CVD mortality: OR, 1.10 (95% CI, 1.02-1.19); 5 RCTs (n = 95 506); range in ARD, −0.8% to 0.8% Lung cancer: OR, 1.20 (95% CI, 1.01-1.42); 4 RCTs (n = 94 830); range in ARD, −0.1% to 0.6% 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 Vitamin A had no significant association with all-cause mortality	All-cause mortality: reasonably consistent, precise for increased risk for beta carotene with or without vitamin A CVD mortality: reasonably consistent, precise for increased risk for beta carotene Lung cancer: reasonably consistent, precise for increased risk Any cancers and other site-specific cancers: consistent and imprecise for no difference	Variation in study dose and duration Combined supplement use in CARET and varied background interventions in almost all other trials Multiple comparisons and outcomes examined in a body of literature with different primary aims	All-cause mortality: moderate for small increased risk for beta carotene with or without vitamin A Low for no increased risk with vitamin A alone CVD mortality: moderate for a small increased risk for beta carotene CVD events: low for no association for beta carotene Lung cancer: moderate for an increased risk for beta carotene Any cancer and other site-specific cancers: low for no difference for beta carotene	Most studies of beta carotene and vitamin A conducted in the US, but participants were primarily White Included general risk samples as well as those limited to persons at increased risk for lung cancer due to smoking status or asbestos exposure Vitamin A doses above the current upper limit in all trials evaluating vitamin A

(continued)

Table. Summary of Evidence (continued)

Studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Vitamin E: 9 RCTs (n = 116 468 observations)	Most evidence indicated that vitamin E had no benefit for mortality, CVD, or cancer; for example, pooled ORs included: All-cause mortality: 1.02 (95% CI, 0.97-1.07); 9 RCTs (n = 107 772) CVD events: 0.96 (95% CI, 0.90-1.04); 4 RCTs (n = 62 136) Any cancer: 1.02 (95% CI, 0.98-1.08); 5 RCTs (n = 76 777)	All-cause mortality: reasonably consistent, precise CVD: consistent, imprecise Cancer: inconsistent, imprecise for prostate cancer; consistent, imprecise for other cancer outcomes	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)	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	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
Vitamin D (with or without calcium): 32 RCTs (n = 123 140 observations)	Evidence suggested no benefit for all primary outcomes of this review; for example, pooled ORs included: All-cause mortality: 0.96 (95% CI, 0.91-1.02); 27 RCTs (n = 117 082) CVD events: 1.00 (95% CI, 0.95-1.05); 7 RCTs (n = 74 925) Any cancer: 0.98 (95% CI, 0.92-1.03); 19 RCTs (n = 86 899) Findings were consistent across different pooling methods, robustness of outcome ascertainment, and whether vitamin D was taken alone or with calcium	All-cause mortality, CVD mortality, any cancer incidence: reasonably consistent, precise CVD events: consistent, precise Cancer mortality: inconsistent, reasonably precise Site-specific cancers: reasonably consistent, imprecise	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	All-cause mortality: moderate for no benefit CVD: high for no benefit Cancer: low for no benefit	Primarily White older adults
Calcium: 7 RCTs (n = 11 884 observations)	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 Pooled ORs for other outcomes include: 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])	All-cause mortality: reasonably consistent, reasonably precise CVD: inconsistent, imprecise Cancer: inconsistent or NA (for site-specific cancers), imprecise	Primary outcomes were often underpowered, since half of studies had primary aims irrelevant to this review	All-cause mortality: moderate for no benefit CVD: low for no benefit Cancer: low for no benefit	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

(continued)

Table. Summary of Evidence (continued)

Studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ4: Harms					
Beta carotene: 6 RCTs (n = 112 820 observations) 1 Prospective cohort study (n = 121 700 observations) Vitamin A: 2 RCTs (n = 20 611 observations) 2 Prospective cohort studies (n = 156 403 observations)	The most substantial serious harms are the paradoxical harms of increased all-cause mortality, CVD mortality, and lung cancer (see KQ3) Trials generally showed no statistically significant findings for other adverse events other than hypercarotenodermia (4 trials, ORs ranging from 1.10 to 24.75) and GI symptoms in the 1 trial reporting this outcome Two cohort studies in women found an elevated but not statistically significantly increased risk of hip fracture associated with vitamin A supplementation	Excluding increased all-cause mortality, CVD mortality, and lung cancer: consistent, precise for beta carotene and increased risk of hypercarotenodermia Consistent and imprecise for vitamin A and increased risk of hip fracture Consistent and imprecise for other nonserious harms for beta carotene and vitamin A	Variation in study dose and duration Combined supplement use in CARET and varied background interventions in almost all other trials Supplement use in cohort study was self-reported	Excluding increased all-cause mortality, CVD mortality, and lung cancer: Hypercarotenodermia: moderate for increased risk with beta carotene Hip fractures: low for increased risk for vitamin A Cataracts: low for no increased risk for vitamin A	Most studies of beta carotene and vitamin A conducted in the US, but participants were primarily White 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 Vitamin A doses were above the current upper limit in all trials evaluating vitamin A Data suggesting a possible increased hip fracture risk with vitamin A are from cohort studies of primarily White women
Vitamin E: 7 RCTs (n = 115 576 observations) 2 Prospective cohort studies (n = 149 043 observations)	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	Inconsistent, imprecise	Supplement use in cohort studies was self-reported	Other than paradoxical harm for hemorrhagic stroke: Cataracts, hospitalization from pneumonia, other nonserious: low for no increased risk	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
Vitamin D (with or without calcium): 31 RCTs (n = 117 100 observations) 3 Prospective cohort studies (n = 289 659 observations)	Both trial and cohort evidence suggested an increased risk of kidney stones with 1000 IU/d or more of vitamin D over ≥7 y Most evidence supported no increased risk of GI-related symptoms Other nonserious symptoms also generally found no group differences, and other serious harms had too few events to draw conclusions	Kidney stones: inconsistent, imprecise GI symptoms: consistent, precise Other adverse events: inconsistent, imprecise	Most studies had primary aims related to bone density, fractures, or falls Supplement use in cohort studies was self-reported	Kidney stones: low for small increased risk GI: moderate for no increased risk Other adverse events: low for no increased risk	Primarily White older adults
Calcium: 8 RCTs (n = 11 930) 1 Prospective cohort study (n = 121 700 observations)	Findings suggested an increased risk of constipation and GI symptoms and possibly kidney stones	GI symptoms: consistent, reasonably precise Kidney stones: reasonably consistent and imprecise	Reporting of any adverse effects, any serious adverse effects, and withdrawal due to adverse effects sparely reported; kidney stone evidence primarily limited to observational data in women only, in whom supplement use was measured by self-report	GI-related symptoms: moderate for increased risk Kidney stones: low for increased risk	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

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.[106] 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.[107] 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.

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Concept and design: O'Connor, Evans, Ivlev, Rushkin, Lin.
Acquisition, analysis, or interpretation of data: O'Connor, Evans, Ivlev, Rushkin, Thomas, Martin.
Drafting of the manuscript: O'Connor, Evans, Ivlev.
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REFERENCES

1. 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.

2. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104-1114. doi:10.1161/CIRCULATIONAHA.115.020406

3. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002;288(16):2015-2022. doi:10.1001/jama.288.16.2015

4. Zhang D, Wen X, Wu W, Guo Y, Cui W. Elevated homocysteine level and folate deficiency associated with increased overall risk of carcinogenesis: meta-analysis of 83 case-control studies involving 35,758 individuals. *PLoS One*. 2015;10(5):e0123423 doi:10.1371/journal.pone.0123423

5. Danik JS, Manson JE. Vitamin D and cardiovascular disease. *Curr Treat Options Cardiovasc Med*. 2012;14(4):414-424. doi:10.1007/s11936-012-0183-8

6. Huang J, Weinstein SJ, Yu K, Männistö S, Albanes D. Relationship between serum alpha-tocopherol and overall and cause-specific mortality. *Circ Res*. 2019;125(1):29-40. doi:10.1161/CIRCRESAHA.119.314944

7. 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):E1114. doi:10.3390/nu10081114

8. 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

9. US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Published May 2021. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual

10. US Preventive Services Task Force. Final research plan: vitamin, mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer. Published 2019. Accessed May 9, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/document/final-research-plan/vitamin-supplementation-to-prevent-cvd-and-cancer-preventive-medication

11. O'Connor EA, Evans CV, Ivlev 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.

12. Fortmann SP, Burda BU, Senger CA, 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*. Agency for Healthcare Research and Quality; 2013.

13. United Nations Development Programme. *Human Development Report 2016: Human Development for Everyone*. United Nations Development Programme; 2016.

14. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889. doi:10.1002/sim.1009

15. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28(2):105-114. doi:10.1016/j.cct.2006.04.004

16. 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

17. Green A, Williams G, Neale R, et al. Daily sunscreen application and beta carotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*. 1999;354(9180):723-729. doi:10.1016/S0140-6736(98)12168-2

18. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294(1):56-65. doi:10.1001/jama.294.1.56

19. 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

20. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334(18):1145-1149. doi:10.1056/NEJM199605023341801

21. 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

22. 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

23. Clark LC, Combs GF Jr, Turnbull BW, et al; Nutritional Prevention of Cancer Study Group. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA*. 1996;276(24):1957-1963. doi:10.1001/jama.1996.03540240035027

24. Wactawski-Wende J, Kotchen JM, Anderson GL, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696. doi:10.1056/NEJMoa055222

25. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39-51. doi:10.1001/jama.2008.864

26. 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

27. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336(7638):262-266. doi:10.1136/bmj.39440.525752.BE

28. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85(6):1586-1591. doi:10.1093/ajcn/85.6.1586

29. 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

30. Baron JA, Beach M, Wallace K, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):586-589. doi:10.1158/1055-9965.EPI-04-0319

31. Chylack LT Jr, Brown NP, Bron A, et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. *Ophthalmic Epidemiol*. 2002;9(1):49-80. doi:10.1076/opep.9.1.49.1717

32. Greenberg ER, Baron JA, Stukel TA, et al; Skin Cancer Prevention Study Group. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. *N Engl J Med*. 1990;323(12):789-795. doi:10.1056/NEJM199009203231204

33. 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.

34. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469. doi:10.1136/bmj.326.7387.469

35. Avenell A, MacLennan GS, Jenkinson DJ, et al; RECORD Trial Group. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab*. 2012;97(2):614-622. doi:10.1210/jc.2011-1309

36. Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults—a randomised controlled trial. *PLoS One*. 2011;6(11):e25966. doi:10.1371/journal.pone.0025966

37. Rayman MP, Blundell-Pound G, Pastor-Barriuso R, Guallar E, Steinbrenner H, Stranges S. A randomized trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin. *PLoS One*. 2012;7(9):e45269. doi:10.1371/journal.pone.0045269

38. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*. 2015;373(16):1519-1530. doi:10.1056/NEJMoa1500409

39. Scragg R, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the Vitamin D Assessment Study : a randomized clinical trial. *JAMA Cardiol*. 2017;2(6):608-616. doi:10.1001/jamacardio.2017.0175

40. Lappe J, Watson P, Travers-Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. *JAMA*. 2017;317(12):1234-1243. doi:10.1001/jama.2017.2115

41. 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

42. Brisson J, Bérubé S, Diorio C, et al. A randomized double-blind placebo-controlled trial of the effect of vitamin D_3 supplementation on breast density in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2017;26(8):1233-1241. doi:10.1158/1055-9965.EPI-17-0249

43. Bonelli L, Puntoni M, Gatteschi B, et al. Antioxidant supplement and long-term reduction of recurrent adenomas of the large bowel: a double-blind randomized trial. *J Gastroenterol*. 2013;48(6):698-705. doi:10.1007/s00535-012-0691-z

44. 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

45. Rayman MP, Winther KH, Pastor-Barriuso R, et al. Effect of long-term selenium supplementation on mortality: results from a multiple-dose, randomised controlled trial. *Free Radic Biol Med*. 2018;127:46-54. doi:10.1016/j.freeradbiomed.2018.02.015

46. Thompson PA, Ashbeck EL, Roe DJ, et al. Selenium supplementation for prevention of colorectal adenomas and risk of associated type 2 diabetes. *J Natl Cancer Inst*. 2016;108(12):djw152. doi:10.1093/jnci/djw152

47. Witham MD, Ireland S, Houston JG, et al. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. *Hypertension*. 2014;63(4):706-712. doi:10.1161/HYPERTENSIONAHA.113.02177

48. Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial.

Br J Psychiatry. 2014;204:306-315. doi:10.1192/bjp.bp.113.132126

49. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2015;373(17):1618-1626. doi:10.1056/NEJMoa1506197

50. Aloia J, Fazzari M, Islam S, et al. Vitamin D supplementation in elderly black women does not prevent bone loss: a randomized controlled trial. *J Bone Miner Res*. 2018;33(11):1916-1922. doi:10.1002/jbmr.3521

51. de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet*. 2001;357(9250):89-95. doi:10.1016/S0140-6736(00)03539-X

52. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. *J Bone Miner Res*. 2011;26(1):35-41. doi:10.1002/jbmr.176

53. Reid IR, Ames R, Mason B, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med*. 2008;168(20):2276-2282. doi:10.1001/archinte.168.20.2276

54. Avenell A, Campbell MK, Cook JA, et al. Effect of multivitamin and multimineral supplements on morbidity from infections in older people (MAVIS trial): pragmatic, randomised, double blind, placebo controlled trial. *BMJ*. 2005;331(7512):324-329. doi:10.1136/bmj.331.7512.324

55. Toss G, Magnusson P. Is a daily supplementation with 40 microgram vitamin D_3 sufficient? a randomised controlled trial. *Eur J Nutr*. 2012;51(8):939-945. doi:10.1007/s00394-011-0271-7

56. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR; ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology*. 2008;134(1):29-38. doi:10.1053/j.gastro.2007.10.014

57. 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

58. Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med*. 1991;115(7):505-512. doi:10.7326/0003-4819-115-7-505

59. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 1996;124(4):400-406. doi:10.7326/0003-4819-124-4-199602150-00003

60. Komulainen M, Kröger H, Tuppurainen MT, et al. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D_3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab*. 1999;84(2):546-552. doi:10.1210/jc.84.2.546

61. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. *Cancer Prev Res (Phila)*. 2009;2(3):213-223. doi:10.1158/1940-6207.CAPR-08-0157

62. Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr*. 2009;89(5):1321-1327. doi:10.3945/ajcn.2008.27004

63. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815-1822. doi:10.1001/jama.2010.594

64. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *J Bone Miner Res*. 2012;27(1):170-176. doi:10.1002/jbmr.524

65. Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. *J Am Geriatr Soc*. 2003;51(12):1762-1767. doi:10.1046/j.1532-5415.2003.51561.x

66. Murdoch DR, Slow S, Chambers ST, et al. Effect of vitamin D_3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA*. 2012;308(13):1333-1339. doi:10.1001/jama.2012.12505

67. Wood AD, Secombes KR, Thies F, et al. Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab*. 2012;97(10):3557-3568. doi:10.1210/jc.2012-2126

68. Uusi-Rasi K, Patil R, Karinkanta S, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med*. 2015;175(5):703-711. doi:10.1001/jamainternmed.2015.0225

69. Grady D, Halloran B, Cummings S, et al. 1,25-Dihydroxyvitamin D_3 and muscle strength in the elderly: a randomized controlled trial. *J Clin Endocrinol Metab*. 1991;73(5):1111-1117. doi:10.1210/jcem-73-5-1111

70. Pike J, Chandra RK. Effect of vitamin and trace element supplementation on immune indices in healthy elderly. *Int J Vitam Nutr Res*. 1995;65(2):117-121.

71. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337(10):670-676. doi:10.1056/NEJM199709043371003

72. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int*. 1998;8(3):255-260. doi:10.1007/s001980050062

73. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab*. 2001;86(8):3618-3628. doi:10.1210/jcem.86.8.7703

74. Hodis HN, Mack WJ, LaBree L, et al; VEAPS Research Group. Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: the Vitamin E Atherosclerosis Prevention Study (VEAPS). *Circulation*. 2002;106(12):1453-1459. doi:10.1161/01.CIR.0000029092.99946.08

75. Cooper L, Clifton-Bligh PB, Nery ML, et al. Vitamin D supplementation and bone mineral density in early postmenopausal women. *Am J Clin Nutr*. 2003;77(5):1324-1329. doi:10.1093/ajcn/77.5.1324

76. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. *J Am Geriatr Soc*. 2004;52(2):230-236. doi:10.1111/j.1532-5415.2004.52060.x

77. McNeil JJ, Robman L, Tikellis G, Sinclair MI, McCarty CA, Taylor HR. Vitamin E supplementation and cataract: randomized controlled trial. *Ophthalmology*. 2004;111(1):75-84. doi:10.1016/j.ophtha.2003.04.009

78. Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of vitamin D_3 supplementation in African American women. *Arch Intern Med*. 2005;165(14):1618-1623. doi:10.1001/archinte.165.14.1618

79. Magliano D, McNeil J, Branley P, et al. The Melbourne Atherosclerosis Vitamin E Trial (MAVET): a study of high dose vitamin E in smokers. *Eur J Cardiovasc Prev Rehabil*. 2006;13(3):341-347. doi:10.1097/00149831-200606000-00008

80. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet*. 2007;369(9557):208-216. doi:10.1016/S0140-6736(07)60109-3

81. Maraini G, Williams SL, Sperduto RD, et al; Clinical Trial of Nutritional Supplements and Age-Related Cataract Study Group. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities: clinical trial of nutritional supplements and age-related cataract report no. 3. *Ophthalmology*. 2008;115(4):599-607. doi:10.1016/j.ophtha.2008.01.005

82. Salovaara K, Tuppurainen M, Kärkkäinen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial—the OSTPRE-FPS. *J Bone Miner Res*. 2010;25(7):1487-1495. doi:10.1002/jbmr.48

83. Pittas AG, Dawson-Hughes B, Sheehan P, et al; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med*. 2019;381(6):520-530. doi:10.1056/NEJMoa1900906

84. Alonso A, Chen LY, Rudser KD, Norby FL, Rooney MR, Lutsey PL. Effect of magnesium supplementation on circulating biomarkers of cardiovascular disease. *Nutrients*. 2020;12(6):1697. doi:10.3390/nu12061697

85. Hemilä H, Haukka J, Alho M, Vahtera J, Kivimäki M. Zinc acetate lozenges for the treatment of the common cold: a randomised controlled trial. *BMJ Open*. 2020;10(1):e031662. doi:10.1136/bmjopen-2019-031662

86. Rake C, Gilham C, Bukasa L, et al. High-dose oral vitamin D supplementation and mortality in people aged 65-84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation. *Health Technol Assess*. 2020;24(10):1-54. doi:10.3310/hta24100

87. Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al; DO-HEALTH Research Group. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA*. 2020; 324(18):1855-1868. doi:10.1001/jama.2020.16909

88. Wood ME, Liu H, Storrick E, et al. The influence of vitamin D on mammographic density: results from CALGB 70806 (Alliance) a randomized clinical trial. *Cancer Prev Res (Phila)*. 2021;14(7):753-762. doi:10.1158/1940-6207.CAPR-20-0581

89. Virtanen JK, Nurmi T, Aro A, et al. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial—a randomized controlled trial. *Am J Clin Nutr*. Published online January 4, 2022. doi:10.1093/ajcn/nqab419

90. 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

91. Schutten JC, Joris PJ, Minović I, et al. Long-term magnesium supplementation improves glucocorticoid metabolism: a post-hoc analysis of an intervention trial. *Clin Endocrinol (Oxf)*. 2021;94 (2):150-157. doi:10.1111/cen.14350

92. Coelho C, Witt SA, Ji H, Hansen MR, Gantz B, Tyler R. Zinc to treat tinnitus in the elderly: a randomized placebo controlled crossover trial. *Otol Neurotol*. 2013;34(6):1146-1154. doi:10.1097/MAO.0b013e31827e609e

93. Sesso HD, Rist PM, Aragaki AK, et al; COSMOS Research Group. Multivitamins in the prevention of cancer and cardiovascular disease: The COSMOS randomized clinical trial. *Am J Clin Nutr*. 2022; nqac056. Published online March 16, 2022. doi:10.1093/ajcn/nqac056

94. 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

95. 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

96. Zheng Selin J, Rautiainen S, Lindblad BE, Morgenstern R, Wolk A. High-dose supplements of vitamins C and E, low-dose multivitamins, and the risk of age-related cataract: a population-based prospective cohort study of men. *Am J Epidemiol*. 2013;177(6):548-555. doi:10.1093/aje/kws279

97. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Vitamin D intake and the risk of incident kidney stones. *J Urol*. 2017;197(2):405-410. doi:10.1016/j.juro.2016.08.084

98. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol*. 2004;15(12):3225-3232. doi:10.1097/01.ASN.0000146012.44570.20

99. Rautiainen S, Lindblad BE, Morgenstern R, Wolk A. Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women. *Am J Clin Nutr*. 2010;91(2):487-493. doi:10.3945/ajcn.2009.28528

100. Agarwal A, Vishnu V, Sharma J, et al. Citicoline in acute ischemic stroke: a randomized controlled trial (CAISR). *Eur Stroke J*. 2021;6(1)(suppl):298.

101. Kanellopoulou A, Riza E, Samoli E, Benetou V. Dietary supplement use after cancer diagnosis in relation to total mortality, cancer mortality and recurrence: a systematic review and meta-analysis. *Nutr Cancer*. 2021;73(1):16-30. doi:10.1080/01635581.2020.1734215

102. Allan GM, Cranston L, Lindblad A, et al. Vitamin D: a narrative review examining the evidence for ten beliefs. *J Gen Intern Med*. 2016;31 (7):780-791. doi:10.1007/s11606-016-3645-y

103. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*. 2014;(1):CD007470. doi:10.1002/14651858.CD007470.pub3

104. Kahwati LC, LeBlanc E, Weber RP, et al. Screening for vitamin D deficiency in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;325(14):1443-1463.

105. Schwingshackl L, Boeing H, Stelmach-Mardas M, et al. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr*. 2017;8(1):27-39. doi:10.3945/an.116.013516

106. Viswanathan M, Treiman KA, Doto JK, Middleton JC, Coker-Schwimmer EJL, Nicholson WK. *Folic Acid Supplementation: An Evidence Review for the US Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2017.

107. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. National Academies Press; 2006.