Annals of Internal Medicine | Review

Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force

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Background: Vitamin and mineral supplements are commonly used to prevent chronic diseases.

Purpose: To systematically review evidence for the benefit and harms of vitamin and mineral supplements in community-dwelling, nutrient-sufficient adults for the primary prevention of cardiovascular disease (CVD) and cancer.

Data Sources: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects were searched from January 2005 to 29 January 2013, with manual searches of reference lists and gray literature.

Study Selection: Two investigators independently selected and reviewed fair- and good-quality trials for benefit and fair- and good-quality trials and observational studies for harms.

Data Extraction: Dual quality assessments and data abstraction.

Data Synthesis: Two large trials (n = 27 658) reported lower cancer incidence in men taking a multivitamin for more than 10 years (pooled unadjusted relative risk, 0.94 [95% CI, 0.89 to 1.00]). The study that included women showed no effect in them. High-quality studies (k = 24; n = 324,653) of single and paired nutrients (such as vitamins A, C, or D; folic acid; selenium; or calcium) were scant and heterogeneous and showed no clear evidence of benefit or harm. Neither vitamin E nor β-carotene prevented CVD or cancer, and β-carotene increased lung cancer risk in smokers.

Limitations: The analysis included only primary prevention studies in adults without known nutritional deficiencies. Studies were conducted in older individuals and included various supplements and doses under the set upper tolerable limits. Duration of most studies was less than 10 years.

Conclusion: Limited evidence supports any benefit from vitamin and mineral supplementation for the prevention of cancer or CVD. Two trials found a small, borderline-significant benefit from multivitamin supplements on cancer in men only and no effect on CVD.

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Vitamins and minerals are commonly used as dietary supplements to promote health and prevent chronic diseases (1). In the National Health and Nutrition Examination Survey III (1988–1994), nearly half of the U.S. population reported using a dietary supplement. A "multivitamin" was the most frequently used supplement (2). Americans spend an estimated $11.8 billion each year on vitamin and mineral supplements (3).

Cardiovascular disease (CVD) and cancer are the leading causes of illness and death in the United States (4). Cancer and CVD have several shared risk factors, including inflammation, oxidative stress, and methionine metabolism. The rationale for using these supplements is supported by many *in vitro* and animal studies showing they protect against these damaging cellular mechanisms.

In 2003, the U.S. Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to recommend for or against the use of vitamins A, C, and E; multivitamins with folic acid; or antioxidant combinations for the prevention of CVD or cancer (5). The USPSTF recommended against the use of β-carotene supplements, either alone or in combination, because they found good-quality evidence that these supplements not only carried no benefit but in fact caused harm among adults at an increased risk for lung cancer. To help the USPSTF update its recommendation, we identified and reviewed additional evidence on the benefits and harms of vitamin and mineral supplementation to prevent CVD and cancer in the general adult population.

Methods

We developed an analytic framework (**Appendix Figure 1** of the **Supplement**, available at www.annals.org) with 4 key questions that we adapted from a 2006 review by Huang and colleagues (6). Our full report describes our methods in detail (7). We specifically sought studies of the following vitamins and minerals: vitamins A, B_1, B_2, B_6, B_{12}, C, D, and E; calcium; iron; zinc; magnesium; niacin; folic acid; β-carotene; and selenium. We included studies that evaluated single, paired, and combinations of three or more vitamins and minerals; we use the term "multivitamin" to refer to these combinations of vitamins and minerals.

See also:

Web-Only
Supplement
CME quiz

Table. **Multivitamin Evidence Summary**

Study (Reference)	Quality	Study Design	Maximum Follow-up, *y*	Supplement*	Treatment Duration, *y*	Participants, *n*
SU.VI.MAX, (19, 47–53)	Good	RCT	13	3 vitamins, 2 minerals	7.5 (median)	13 017
PHS-II (21, 54, 55)	Good	2 × 2 × 2 × 2 factorial RCT	11.2	13 vitamins, 17 minerals	11.2 (median)	14 641
REACT (20)	Good	RCT	3	3 vitamins	3	297
Graat et al. (22)	Good	2 × 2 RCT	1.3	14 vitamins, 12 minerals (alone or combined with vitamin E, 200 mg)	1.3	652
NHS (23)	Good	Prospective cohort	18	MVI (ingredients not described)	NR	72 337

CRC = colorectal cancer; CVD = cardiovascular disease; MI = myocardial infarction; MVI = multivitamin; NA = not applicable; NHS = National Health Service; PHS-II = Physicians' Health Study II; RCT = randomized, controlled trial; REACT = Roche European American Cataract Trial; SU.VI.MAX = SUpplementation in VItamins and Mineral AntioXidants Study; ↑ = statistically significant increase in risk for outcome from supplementation; ↔ = no statistically significant difference between intervention groups; ↓ = statistically significant decrease in risk for outcome from supplementation.
* For a complete list of ingredients, see the full report (7).
† Statistically significant protective effect for any cancer in men, but not women.
‡ Decreased risk fatal MI ($P = 0.048$).

Data Sources and Searches

We reviewed all included studies from 3 USPSTF reviews published in 2003 (8–10) and the review conducted by Huang and colleagues (6). We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects from January 2005 through January 29, 2013, to identify articles published since the review conducted by Huang and colleagues (6). We also searched the bibliographies of relevant reviews and meta-analyses, as well as the Web sites of government agencies and professional organizations, for any relevant research published outside of peer-reviewed journals. We obtained additional references from outside experts.

Study Selection

Two investigators independently reviewed each study's abstract against prespecified inclusion criteria. We included fair- and good-quality randomized, controlled trials that assessed the effectiveness or safety of supplements in the primary prevention of CVD, cancer, or all-cause mortality in the general adult population without a history of CVD or cancer. We included fair- and good-quality secondary prevention trials if they hypothesized effects on outcomes included in this review and not present at baseline in the study (for example, a trial of secondary skin cancer prevention that also reported on other cancers). We included only studies that were conducted among community-dwelling, nutrient-sufficient adults who had no chronic disease and were performed in countries with a Human Development Index of "very high" (11). We also required supplement doses to be lower than the upper tolerable limit set by the U.S. Food and Nutrition Board (12). We included both fair- and good-quality trials and observational studies, without limitations on study sample size or duration, to assess potential harms in order to increase our likelihood of detecting serious harms that are rare or that develop only after long time periods (13). Serious harms included paradoxical increases in CVD, cancer, or mortality and events defined as "serious" by study investigators. We also considered adverse events in trials that reported less serious harms if they were common (that is, occurred in >5% of persons and were statistically significantly higher among those receiving supplements).

Data Extraction and Quality Assessment

One investigator abstracted study design information, baseline population characteristics, intervention details, disease incidence, mortality, and harms data from all included studies into a standardized evidence table. A second investigator checked these data for accuracy. Two investigators independently assessed each study's quality as "good," "fair," or "poor" by using predefined quality criteria based on USPSTF methods (14). We excluded all poor-quality randomized, controlled trials and observational studies. In general, a good-quality study met all prespecified criteria. A fair-quality study did not meet at least one criterion but also did not have a known limitation that could invalidate its results. A poor-quality study had a fatal flaw or multiple important limitations. We supplemented the USPSTF criteria with criteria from the National Institute for Health and Clinical Excellence for the quality assessment of observational studies (15). We resolved any disagreements through discussion.

Table—Continued

Mean Age, *y*	Women, %	CVD Incidence	Cancer Incidence	Mortality	Harms	Comments
49	59	Any: ↔ MI: NR Stroke: NR	Any: ↔† Lung: ↔ CRC: ↔ Prostate: ↔ Breast: ↔ Other: ↔	↔	↔	Protective effect against cancer in men (↓) but not women (↔)
64	0	Any: ↔ MI: ↔‡ Stroke: ↔	Any: ↓ Lung: ↔ CRC: ↔ Prostate: ↔ Breast: NA Other: ↔	↔	↔	Minor adverse effects (↔), rashes (↑), and bleeding (↑)
66	59	NA	NA	↔	↔	
73	50	NA	NA	NA	↔	Acute respiratory infections (↔)
58	100	NA	NA	NA	↑	Hip fractures among current and former MVI users (↑)

Data Synthesis and Analysis

We qualitatively described and summarized the evidence. We stratified results by supplement and synthesized the results of included studies by examining estimates of effects. We conducted meta-analyses to estimate the effect size of supplementation on CVD incidence, cancer incidence, and all-cause mortality at the longest follow-up time point by using the metan procedure of Stata software, version 11.2 (Stata Corp., College Station, Texas) (16). For all cases, we analyzed unadjusted relative risks based on the number of events and nonevents. We used the fixed-effects Mantel–Haenszel method because few trials could be combined and to help avoid bias associated with rare events (1% to 10% of participants in most trials) (17, 18).

Role of Funding Source

The Agency for Healthcare Research and Quality funded this review under a contract to support the work of the USPSTF. Members of the USPSTF and an AHRQ medical officer assisted in defining this review's scope. Although approval from AHRQ was required before the manuscript could be submitted for publication, the authors are solely responsible for its content and the decision to submit it for publication.

Results

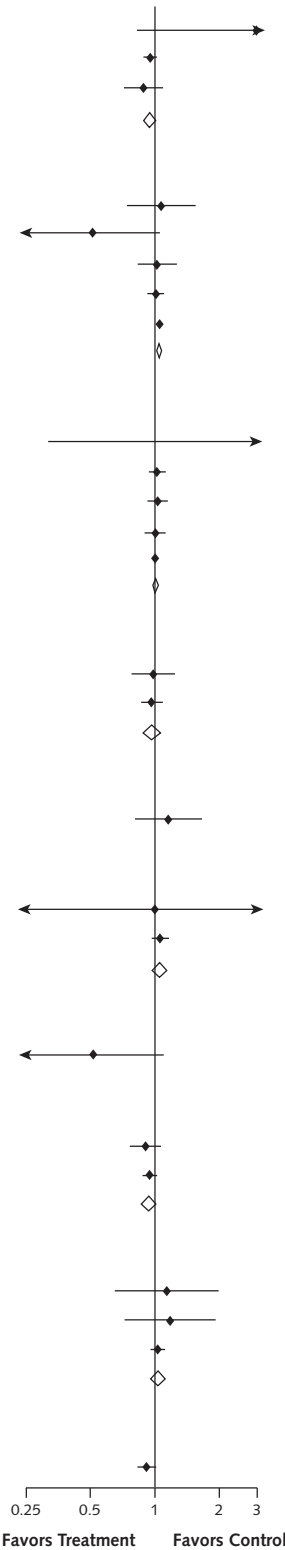
We screened 12 766 abstracts, reviewed 277 full-text articles, and included 103 articles (26 studies) (**Appendix Figure 2** of the **Supplement**, available at www.annals.org). Four trials (19–22) and 1 cohort study (23) examined the benefits and harms of multivitamin supplementation (**Supplement**, available at www.annals.org). Eighteen trials and 5 cohort studies examined the benefits and harms of individual or paired supplements (**Supplement**): 6 studies of β-carotene (24–29), 6 studies of vitamin E (22, 24, 30–33), 3 studies of selenium (33–35), 5 studies of vitamin A (23, 29, 36–38), 2 studies of vitamin C (30, 31), 1 study of folic acid (39), 3 studies of vitamin D (40–42), 2 studies of vitamin D in combination with calcium (43, 44), and 4 studies of calcium (40, 43, 45, 46). The study sizes ranged from 128 to 72 337 individuals with average ages ranging from 22 to 77 years, although in most studies the mean age was older than 50 years (**Supplement**). Six studies were conducted among women only, 5 were conducted among men only, and the remaining studies were in mixed populations (24.2% to 84.7% women). The effects of the supplements were examined between 6 months and 16 years; most studies provided less than a decade of follow-up.

Multivitamin Studies

We identified 4 good-quality trials ($n = 28\,607$) (19–22) and 1 good-quality cohort study ($n = 72\,337$) (23) that evaluated a multivitamin's effect on cardiovascular, cancer, and mortality outcomes or harms (**Table** and the **Supplement**) (47–55). Two of the 4 multivitamin trials were large ($n = 27\,658$): SUpplementation in VItamins and Mineral AntioXidants Study (SU.VI.MAX) and the Physicians' Health Study II (PHS-II). SU.VI.MAX was conducted among 13 017 men and women living in France and examined a 5-ingredient multivitamin (19). PHS-II tested the efficacy of a 30-ingredient commercial multivitamin among 14 641 U.S. male physicians (21). Neither SU.VI.MAX nor PHS-II reported that supplements affected all-cause mortality after 7.5 and 11.2 years of follow-up, respectively (**Figure 1**). A third trial, the Roche European American Cataract Trial (REACT), reported more deaths in the intervention group ($n = 9$) than in the control group ($n = 3$) after 3 years, but this difference was not statistically significant ($P = 0.07$) (20). We found no effect on all-cause mortality when we pooled the results of these trials (**Figure 1**).

Multivitamins had no effect on fatal and nonfatal CVD events overall (**Appendix Table 1**, available at www.annals.org). PHS-II found a borderline statistically significant benefit for fatal myocardial infarction (adjusted haz-

Figure 1. **Unadjusted relative risk for all-cause mortality at longest follow-up only, by supplement.**



Author, Year (Reference)	Follow-up, *y*	Mantel–Haenszel RR (95% CI)	Events/Treatment Patients, *n/N*	Events/Control Patients, *n/N*
Multivitamin				
Chylack et al, 2002 (20)	3	2.98 (0.82–10.79)	9/149	3/148
Gaziano et al, 2012 (54)	11.2	0.95 (0.89–1.02)	1345/7317	1412/7324
Hercberg et al, 2010 (50)	12.5	0.88 (0.71–1.09)	156/6481	178/6536
Subtotal		0.95 (0.89–1.01)	1510/13 947	1593/14 008
β-carotene				
Lee et al, 1999 (26)	4.1	1.07 (0.74–1.55)	59/19 937	55/19 939
Green et al, 1999 (28)	4.5	0.51 (0.25–1.05)	11/820	21/801
Greenberg et al, 1996 (83)	8.2	1.03 (0.83–1.27)	146/913	139/892
Hennekens et al, 1996 (25)	12	1.01 (0.93–1.10)	979/11 036	968/11 035
Virtamo et al, 2003 (84)	16	1.05 (1.02–1.09)	5555/14 560	5276/14 573
Subtotal		1.05 (1.02–1.08)	6750/47 266	6459/47 240
Vitamin E				
Salonen et al, 2000 (30)	3	3.00 (0.32–28.47)	3/130	1/130
Gaziano et al, 2009 (85)	8	1.03 (0.94–1.12)	841/7315	820/7326
Lee et al, 2005 (32)	10.1	1.03 (0.93–1.15)	636/19 937	615/19 939
Klein et al, 2011 (86)	12	1.01 (0.90–1.13)	571/8737	564/8696
Virtamo et al, 2003 (84)	16	1.01 (0.98–1.04)	5433/14 564	5398/14 569
Subtotal		1.01 (0.98–1.04)	7484/50 683	7398/50 660
Selenium				
Stranges et al, 2006 (87)	7.6	0.98 (0.78–1.24)	110/504	111/500
Klein et al, 2011 (86)	12	0.97 (0.87–1.09)	551/8752	564/8696
Subtotal		0.97 (0.88–1.08)	661/9256	675/9196
Vitamin A				
Moon et al, 1997 (36)	5	1.15 (0.81–1.65)	62/1157	53/1140
Vitamin C				
Salonen et al, 2000 (30)	3	1.00 (0.06–15.82)	1/130	1/130
Gaziano et al, 2009 (85)	8	1.06 (0.97–1.16)	857/7329	804/7312
Subtotal		1.06 (0.97–1.16)	858/7459	805/7442
Folic Acid				
Cole et al, 2007 (39)	10	0.52 (0.24–1.10)	10/516	19/505
Vitamin D				
Trivedi et al, 2003 (41)	5	0.90 (0.77–1.07)	224/1345	247/1341
Avenell et al, 2012 (40)	6.2	0.95 (0.88–1.02)	836/2649	881/2643
Subtotal		0.94 (0.87–1.01)	1060/3994	1128/3984
Calcium				
Baron et al, 1999 (88)	4	1.14 (0.65–1.99)	25/464	22/466
Bolland et al, 2008 (45)	5	1.18 (0.73–1.92)	34/732	29/739
Avenell et al, 2012 (40)	6.2	1.03 (0.95–1.11)	862/2617	855/2675
Subtotal		1.04 (0.96–1.12)	921/3813	906/3880
Vitamin D + calcium				
Wactawski-Wende et al, 2006 (44)	7	0.92 (0.83–1.01)	744/18 176	807/18 106

RR = relative risk.

ard ratio, 0.61 [95% CI, 0.38 to 0.995]; $P = 0.048$) (which could be a type I error due to multiple testing) and no effect for combined fatal and nonfatal myocardial infarction (adjusted hazard ratio, 0.93 [95% CI, 0.80 to 1.09]; $P = 0.39$]).

PHS-II found that multivitamins reduced overall cancer incidence after 11.2 years of follow-up (**Appendix Table 1**) (54). SU.VI.MAX did not find that multivitamins affected total cancer incidence after an initial follow-up of 7.5 years or during posttreatment follow-up for an additional 5 years (51). This study stratified randomization by sex and tested for a sex–by–treatment group interaction, which was statistically significant ($P = 0.02$). The sex-specific subgroup analysis showed a protective effect among men (adjusted relative risk, 0.69 [95% CI, 0.53 to 0.91]) but not women. When SU.VI.MAX's findings in men were pooled with the PHS-II results, the unadjusted relative risk for all cancer incidence was reduced over 10 years of follow-up (data not shown).

Our 5 included studies showed no consistent pattern of harms from nutritional dosages of multivitamins (19, 20, 22, 23, 54). Some individual studies or subgroup analyses, however, did find possible harms. For example, there was an increase in melanomas among women enrolled in SU.VI.MAX, and the Nurse's Health Study found higher hip fracture rates (23). The fifth study, by Graat and colleagues, examined only effects on respiratory illness in the elderly and reported no harms (22).

Single and Paired Vitamins and Minerals

We identified 24 studies ($n = 324\,653$) of single and paired nutrients. Overall, we found little consistent evidence to support or refute a health effect on all-cause mortality or the incidence of CVD or cancer for supplementation with vitamins A, C, or D; folic acid; selenium; or calcium (**Appendix Table 2**, available at www.annals.org; **Figures 1 to 3**; and the **Supplement**). For most nutrients, however, we found 3 or fewer studies. Trials often varied considerably in principal aims, study design, and recruitment criteria. Such a small body of evidence makes a type II error more likely. In addition, for some supplements the evidence of no benefit was inconsistent. In 1 of 2 studies of selenium, for example, cancer risk decreased (33, 34). Likewise, 1 of 2 studies of calcium plus vitamin D supplementation in women found a decreased cancer risk (43, 44).

We found consistent null results for CVD incidence, cancer incidence, and all-cause mortality across 6 trials of β-carotene (**Figures 1** and **3**) (24–29). We found a probable increase in lung cancer incidence in high-risk subgroups (smokers and asbestos workers). We found 5 trials for vitamin E supplementation that showed no effect on the 3 outcomes (**Figures 1 to 3**) (24, 30–33).

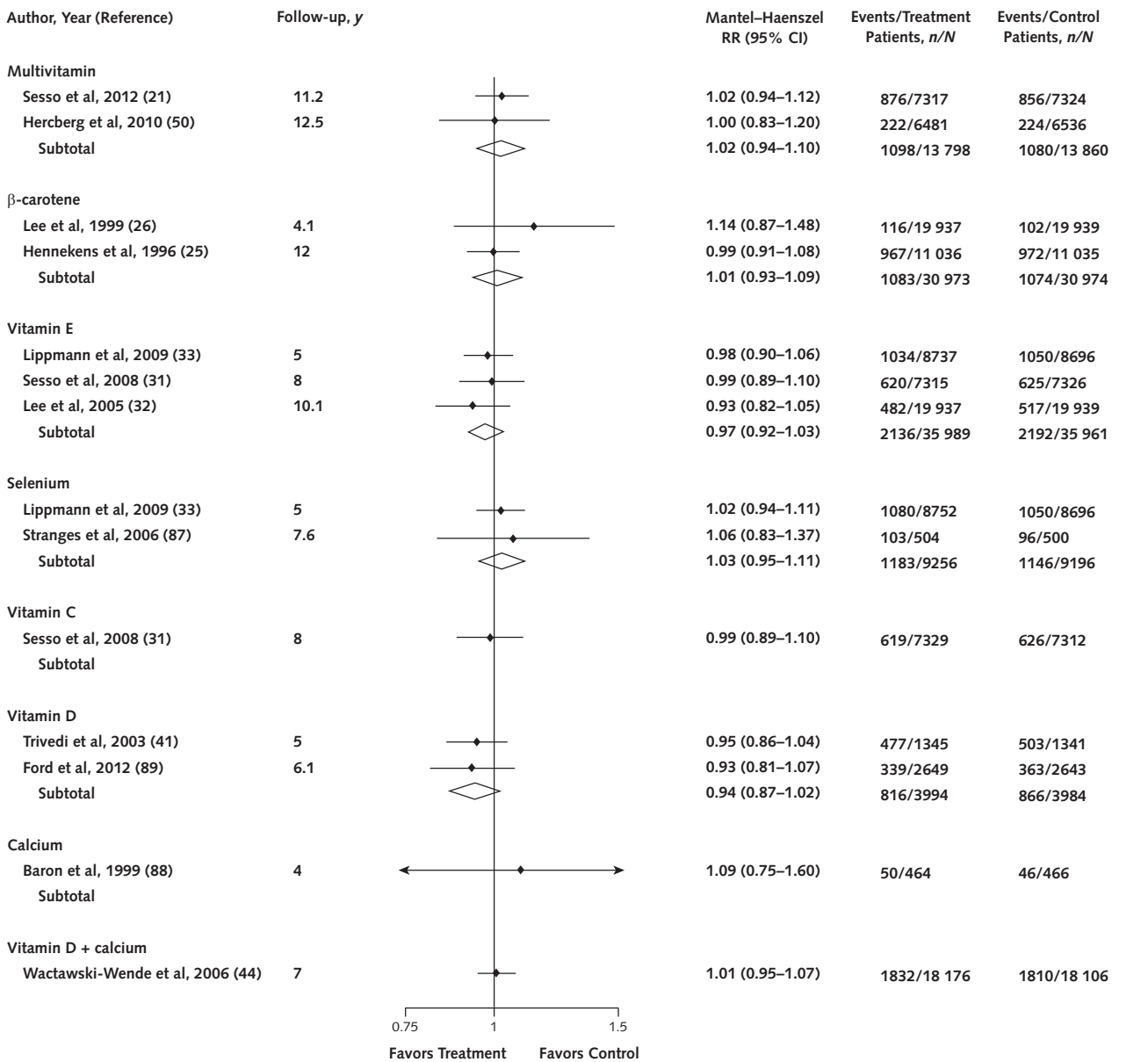
Five trials evaluated the effects of vitamin D and calcium supplementation on CVD and cancer incidence when used alone or in combination. Four of these trials provided data on calcium supplementation without vitamin D (40, 43, 45, 46) and reported no statistically significant effect on CVD or cancer incidence or on all-cause mortality (**Figures 1 to 3**). Although the overall cancer rate reported for calcium supplementation was lower than the rate in the placebo group in 2 trials (43), the opposite was observed in another trial (40); neither difference was statistically significant (**Figure 3**). Vitamin D plus calcium supplementation was specifically studied in 2 trials (43, 44), 1 of which examined CVD incidence and found no effect (44). Both of these trials reported cancer outcomes, and while the smaller trial found a statistically significant decrease in overall cancer incidence over 4 years (43), the larger trial did not (44). The pooled unadjusted relative risk was 0.98 (95% CI, 0.91 to 1.04). Another trial examined vitamin D and calcium supplementation under a 2×2 factorial design and also found no main effect for either supplement (40).

We found little consistent evidence of harm across studies. Although vitamin A use in 1 trial was associated with increased risk for lung cancer, it was combined with β-carotene (29). Two cohort studies also implicated vitamin A use for increased risk for hip fracture (23, 38), although total fracture rate was not higher in the study that reported this outcome (38). One study assessed folic acid supplementation in patients with prior colorectal adenomas and found that folic acid supplementation was associated with an increase in prostate cancer incidence (39). Incidence of colorectal cancer in the calcium group was increased in a pooled analysis of 2 trials of calcium supplementation, but this was a post hoc subgroup analysis (40, 43). The large trial of vitamin D and calcium supplementation found a small increase in kidney stones in the supplement group (44).

Discussion

This review included 26 studies (24 randomized, controlled trials and 2 cohort studies) that examined the benefits and harms of using vitamin and mineral supplements for primary prevention of CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies. We found no consistent evidence that the included supplements affected CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies. Other systematic reviews have arrived at this same conclusion (56–66). The certainty of this result is tempered, however, by the fact that few fair- or good-quality studies are available for all supplements except vitamin E and β-carotene. For vitamin E, we identified 6 fair- to good-quality trials that produced clearly null effects on these end points. This result is consistent with the conclusions of other systematic reviews and meta-analyses of vitamin E (67–71). Our review also confirmed the established harm of β-carotene supplementation on lung cancer incidence and death for individuals at high risk for lung cancer (24, 29, 72). Further, we identified 5 trials that

Figure 2. **Unadjusted relative risk for cardiovascular disease incidence at longest follow-up only, by supplement.**



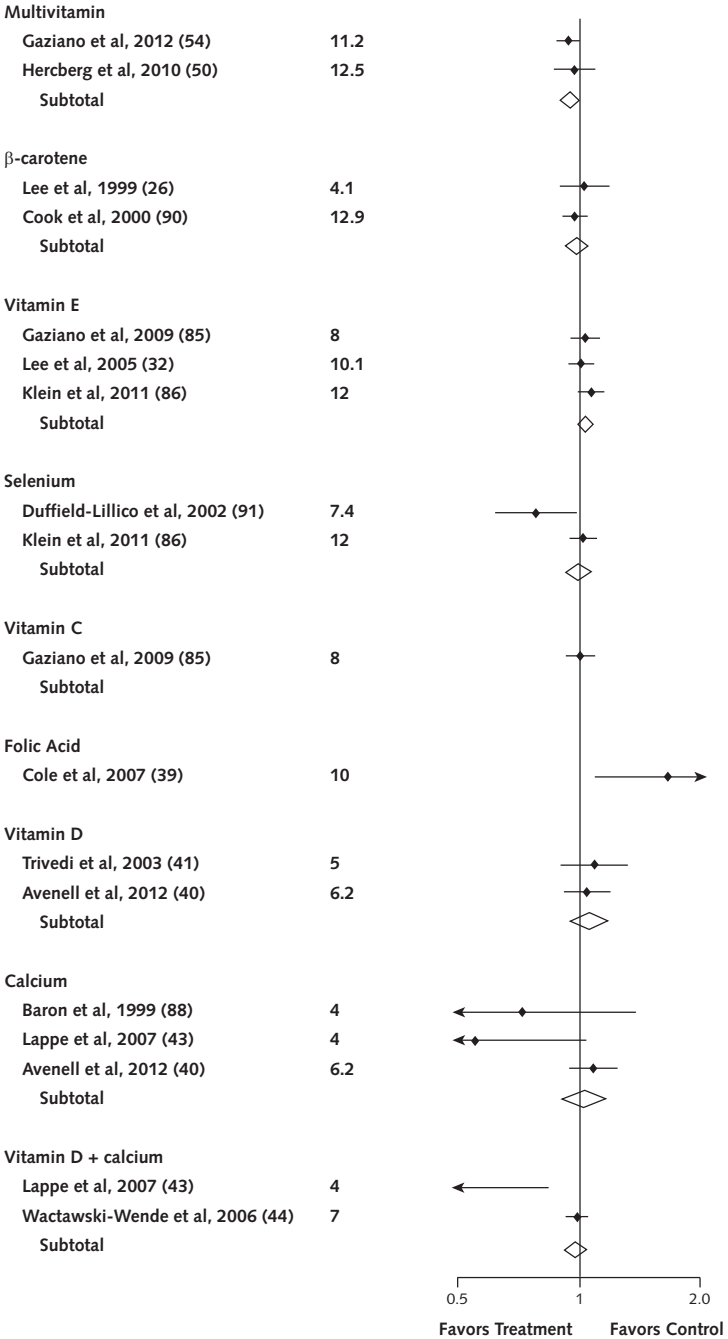
RR = relative risk.

failed to detect any benefit from β-carotene supplementation for any individuals.

The results of vitamin supplementation trials have been disappointing at best, despite having a solid mechanistic basis (73). One explanation for this result could be that the physiologic systems affected by vitamins and other antioxidant supplements are so complex that the effects of supplementing with only 1 or 2 components is generally ineffective or actually does harm (74). This hypothesis is compatible with our finding that the best support for benefit of supplementation came from 2 multivitamin trials that used physiologic doses of a wider variety of agents.

Two good-quality trials of multivitamin supplementation found lower cancer incidence in men (19, 54). The SU.VI.MAX trial included women and did not find an effect in this subgroup (19). We found a statistically significant protective effect from multivitamin supplementation when we pooled data for men in these 2 trials. The borderline significance level in both studies and the lack of an effect in women in SU.VI.MAX suggest we should not try to overgeneralize these results. The SU.VI.MAX investigators speculate that the observed sex difference in multivitamin effects on cancer incidence in their trial may have been due to lower baseline antioxidant status in men than

Figure 3. **Unadjusted relative risk for cancer incidence at longest follow-up only, by supplement.**



Author, Year (Reference)	Follow-up, *y*	Mantel–Haenszel RR (95% CI)	Events/Treatment Patients, *n/N*	Events/Control Patients, *n/N*
Multivitamin				
Gaziano et al, 2012 (54)	11.2	0.94 (0.87–1.00)	1290/7317	1379/7324
Hercberg et al, 2010 (50)	12.5	0.97 (0.86–1.09)	490/6481	511/6536
Subtotal		0.94 (0.89–1.00)	1780/13 798	1890/13 860
β-carotene				
Lee et al, 1999 (26)	4.1	1.02 (0.89–1.18)	378/19 937	369/19 939
Cook et al, 2000 (90)	12.9	0.97 (0.90–1.04)	1314/11 036	1353/11 035
Subtotal		0.98 (0.92–1.05)	1692/30 973	1722/30 974
Vitamin E				
Gaziano et al, 2009 (85)	8	1.03 (0.95–1.12)	984/7315	959/7326
Lee et al, 2005 (32)	10.1	1.01 (0.94–1.08)	1437/19 937	1428/19 939
Klein et al, 2011 (86)	12	1.07 (0.99–1.15)	1190/8737	1108/8696
Subtotal		1.03 (0.99–1.08)	3611/35 989	3495/35 961
Selenium				
Duffield-Lillico et al, 2002 (91)	7.4	0.78 (0.62–0.98)	105/621	137/629
Klein et al, 2011 (86)	12	1.02 (0.94–1.10)	1132/8752	1108/8696
Subtotal		0.99 (0.92–1.06)	1237/9373	1245/9325
Vitamin C				
Gaziano et al, 2009 (85)	8	1.00 (0.92–1.09)	973/7329	970/7312
Subtotal				
Folic Acid				
Cole et al, 2007 (39)	10	1.65 (1.09–2.51)	54/516	32/505
Vitamin D				
Trivedi et al, 2003 (41)	5	1.08 (0.89–1.31)	188/1345	173/1341
Avenell et al, 2012 (40)	6.2	1.04 (0.91–1.19)	369/2649	354/2643
Subtotal		1.05 (0.94–1.18)	557/3994	527/3984
Calcium				
Baron et al, 1999 (88)	4	0.72 (0.37–1.37)	15/464	21/466
Lappe et al, 2007 (43)	4	0.55 (0.29–1.03)	17/445	20/288
Avenell et al, 2012 (40)	6.2	1.08 (0.94–1.23)	371/2617	352/2675
Subtotal		1.03 (0.90–1.17)	403/3526	393/3429
Vitamin D + calcium				
Lappe et al, 2007 (43)	4	0.42 (0.21–0.83)	13/446	20/288
Wactawski-Wende et al, 2006 (44)	7	0.98 (0.92–1.05)	1634/18 176	1655/18 106
Subtotal		0.98 (0.91–1.04)	1647/18 622	1675/18 394

RR = relative risk.

women (19). A baseline difference in blood levels, however, was found only for β-carotene and not for vitamins E and C, selenium, or zinc (19), although blood levels may not fully reflect nutritional status. Although it is possible that other behavioral or biological factors might modify the effects of antioxidant supplements on men and women, with only 1 study available it would be better to reconfirm the sex difference before speculating on its cause.

The simplest way to interpret the vitamin D and calcium results is that these vitamins have no effect on CVD or cancer. A systematic review by Wang and colleagues came to a similar conclusion (59). Our data do suggest,

however, that the effects of calcium on these end points may differ from the effects of vitamin D. When we pooled the 2 vitamin D trials (40, 41), for example, we found a lower mortality in the supplement groups (unadjusted relative risk, 0.94 [95% CI, 0.87 to 1.01]). In contrast, the point estimates for calcium were all greater than 1, although albeit CIs for all estimates were wide. These findings support the idea that future research should include separate studies of calcium and vitamin D.

Recently, several investigators have posited that calcium intake or supplementation have harmful effects on CVD outcomes (75–80). Much of this speculation, however, derives from 2 meta-analyses that used different sets of trials (75, 76) and were heavily influenced by data from a reanalysis of the Women's Health Initiative (WHI) trial (77). The WHI reanalysis identified harms only in the subgroup of women *not* taking calcium or vitamin D at baseline. Such post hoc subgroup analyses, however, can be misleading (81). Indeed, the WHI investigators found no evidence of harm for CVD or cancer in their own reanalysis of their trial results, even when results were stratified by baseline supplement use and the results of their large observational study were added (78). Two other recent studies included only observational data. These studies did not show consistent findings across studies, between sexes, or between dietary and supplemental calcium use (79, 80). Although available studies are insufficiently consistent to permit the conclusion that calcium supplementation is harmful, future controlled trials should address this question.

Our analysis has some limitations. We considered only primary prevention interventions in generally healthy people and excluded secondary and tertiary prevention trials and treatment studies. Thus, our results do not apply to the targeted use of nutrients in deficient or higher-risk individuals. Only 2 trials of multivitamin supplements were included for efficacy, even though we broadly defined a multivitamin as 3 or more ingredients. Those 2 trials studied very different supplements (19, 21). Because the only multivitamin trial to include women used a supplement with 5 ingredients (19), it could be argued that there are no data on a "true" multivitamin in women. Most of the included vitamin trials provided less than a decade of follow-up, and vitamin effects on CVD and cancer may take longer to manifest. The small number of studies in each pooled analysis made it difficult to evaluate between-study heterogeneity. We limited our examination of harms to fair- and good-quality trials and observational studies and thus may have underestimated harms. In addition, we did not assess harms from higher doses of vitamins and minerals than the upper tolerable limit set by the U.S. Food and Nutrition Board.

This is a review of trials, a study design used primarily to evaluate drug therapy. This design might not be ideally suited to evaluating nutrients (82). The control group in a placebo-controlled trial of medications is not exposed to the medication. In a nutrient supplementation study, however, the control group is exposed to some level of the nutrient because it is designed to answer a different question: Does exposure to an optimal level of the nutrient produce better health outcomes than exposure to the usual level? To conduct this type of study, one must know both the usual and optimal level of exposure. In practice, however, exposure to the nutrient in the control group may change during the course of a trial as societal norms change, complicating interpretation of the trial results. Women in the WHI control group, for example, had twice the average calcium intake of that anticipated when the trial was designed, and the vitamin D dose was lower than many now think is necessary to achieve optimal blood levels.

Few studies have evaluated the effectiveness of vitamin and mineral supplements in the primary prevention of CVD and cancer in nutrient-sufficient adults. Published studies have used a wide variety of supplements, in different doses, with different study objectives and populations, and usually for short duration (5 years). Although 2 relatively large trials examined the efficacy of a multivitamin in the primary prevention of CVD and cancer in a general population, population selection and potential sex-specific findings limit the applicability of their results. Future studies of multivitamin supplements should recruit from a general population with representation of multiple minority groups and both sexes, use a multivitamin that is reasonably similar to the popular brands in the current market, continue for at least a decade, and include enough participants to provide adequate power to detect benefits and harms within important subgroups, including men and women. This is a tall order, and any such study would also face other difficulties, including agreement on the content of the multivitamin, so the results of the trial might be dismissed by observers who felt that an important ingredient was omitted. The wide availability of multivitamins could result in substantial crossover, and the large number of participants and long follow-up needed would result in an expensive trial. Still, the U.S. public is devoting major financial resources to multivitamins, so such a trial could have a large public health impact, whatever the outcome.

Despite its limitations, the current literature on single or paired vitamins and minerals is sufficient to discourage additional studies of β-carotene or vitamins A, C, and E in general populations not deficient in the nutrients. Future studies of selenium should clearly separate individuals with adequate and low baseline selenium levels. Future studies of vitamin D should be done separately from studies of calcium. Vitamin D and calcium studies should include the full range of hypothesized benefits, including fracture prevention, to allow a comprehensive comparison of overall benefits and harms.

In conclusion, we found no evidence of an effect of nutritional doses on CVD, cancer, or mortality in healthy individuals without known nutritional deficiencies for

most supplements we examined. In most cases there are insufficient data to draw any conclusion, although for vitamin E and β-carotene a lack of benefit is consistent across several trials. We identified 2 multivitamin trials that both found lower overall cancer incidence in men (19, 21). Both these trials were both methodologically sound, but the lack of an effect for women (albeit in 1 trial), the borderline significance in men in both trials, and the lack of any effect on CVD in either study makes it difficult to conclude that multivitamin supplementation is beneficial.

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Appendix Table 1. Cardiovascular Disease and Cancer Incidence and Mortality Among Multivitamin Studies

Outcome	Study (Reference)	Comparison	Mean Follow-up, *y*	Intervention: Participants With Event, *n/N* (%)	Comparator: Participants With Event, *n/N* (%)	Adjusted RR or HR (95% CI)	*P* Value
Ischemic CVD incidence*	SU.VI.MAX (19, 50)	MVI vs. placebo	7.5	134/6481 (2.1)	137/6536 (2.1)	0.97† (0.77–1.20)	0.80
			12.5	222/6481 (3)	224/6539 (4)	0.97† (0.80–1.17)	0.73
Any CVD incidence‡	PHS-II (21)	MVI vs. no MVI	11.2	876/7317 (12)	856/7324 (11.7)	1.01§ (0.91–1.10)	0.91
Any CVD death	PHS-II (21)	MVI vs. no MVI	11.2	408/7317 (5.6)	421/7324 (5.7)	0.95§ (0.83–1.09)	0.47
All cancer sites, incidence	SU.VI.MAX (19, 50, 53)	MVI vs. placebo	7.5	267/6481 (4.1)	295/6536 (4.5)	0.90† (0.76–1.06)	0.19
			12.5	490/6481 (7.5)	511/6536 (7.8)	0.93† (0.82–1.05)	0.27
	PHS-II (54)	MVI vs. no MVI	11.2	1290/7317 (17.6)	1379/7324 (18.8)	0.92§ (0.86–0.998)	0.04
Any cancer death	PHS-II (54)	MVI vs. no MVI	11.2	403/7317 (5.5)	456/7324 (6.2)	0.88§ (0.77–1.01)	0.07
All-cause mortality	SU.VI.MAX (19, 50)	MVI vs. placebo	7.5	76/6481 (1.2)	98/6536 (1.5)	0.77† (0.57–1.00)	0.09
			12.5	156/6481 (2.4)	178/6536 (2.7)	0.87† (0.70–1.04)	0.19
	PHS-II (54)	MVI vs. no MVI	11.2	1345/7317 (18.4)	1412/7324 (19.3)	0.94§ (0.88–1.02)	0.13
	REACT (20)	MVI vs. placebo	3	9/149 (6)	3/148 (2)	NR	0.07

CVD = cardiovascular disease; HR = hazard ratio; MVI = multivitamin; NR = not reported; PHS-II = Physicians' Health Study II; REACT = Roche European American Cataract Trial; RR = relative risk; SU.VI.MAX = SUpplementation in VItamins and Mineral AntioXidants Study.
* Includes fatal and nonfatal ischemic CVD events.
† RR adjusted by age and sex.
‡ Includes nonfatal myocardial infarction, nonfatal stroke, and CVD death.
§ Hazard ratios adjusted by age, PHS cohort, β-carotene assignment, vitamin E assignment, and vitamin C assignment and stratified on CVD at baseline.

Appendix Table 2. **Summary of Evidence of Included Studies**

Supplement	Study Design (κ Value)	Participants Randomly Assigned, *n**	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
Key question 1 (efficacy)							
MVI	RCT (κ = 3)	27 955	Only 2 studies examining the efficacy of MVI on cancer and CVD (19, 54); generalizability may be an issue because protective effect seen only in men among healthy subjects; only 1 study included women	Consistent	Moderate-to-high: Healthy adult volunteers in France; healthy U.S. male physicians; primary care adult patients in the United States and United Kingdom with cataracts	Good	2 RCTs examining efficacy of MVI on cancer and CVD incidence and mortality (19, 54) showed minor protective effect against cancer in men but not women; similar pattern for all-cause mortality; small number of deaths reported in third RCT, which is probably unreliable (20)
Key question 2 (harms)							
MVI	RCT (κ = 4) Prospective cohort study (κ = 1)	100 944		Consistent	Moderate-to-high: Healthy adult volunteers from France, male physicians and female nurses from the United States; primary care adult patients in the United States and United Kingdom with cataracts; Dutch elderly patients	Good	Increased risk for hip fractures among MVI users compared with nonusers in 1 study (may be due to vitamin A) (23); 4 RCTs reported no difference between groups in the number of hypercarotenemia cases, other adverse effects, and intercurrent illnesses and respiratory tract infections (19, 20, 22, 54); mixed results for bleeding (54)
Key question 3 (efficacy)							
β-carotene	RCT (κ = 6)	112 820	1 trial discontinued early because of increased risk for lung cancer and related deaths (29); another discontinued because of reported harms from other trials (26)	Consistent	Moderate-to-high: Increased risk for lung cancer (smokers and/or asbestos-exposed workers), healthy male physicians or female nurses from the United States; participants with a previous history of BCC and/or SCC	Good	Increased risk for lung cancer incidence and mortality and all-cause mortality among participants at high risk for lung cancer at baseline (i.e., smokers and/or asbestos-exposed workers) (24, 29)
Vitamin E	RCT (κ = 5)	120 335		Consistent	Moderate-to-high: Healthy men (general population or physicians) and female nurses; individuals with hypercholesterolemia; male smokers in the United States	Good	No effect on CVD, cancer, or all-cause mortality.
Selenium	RCT (κ = 2)	36 845	1 trial discontinued early because of no treatment effect; other study used secondary analyses of CVD and cancer outcomes	Inconsistent	Moderate-to-high: Healthy men and men with a previous SCC or BCC from the United States	Good	No effect on CVD or all-cause mortality; however, mixed results for effects on any cancer and site-specific cancers, with 1 small trial finding statistically significant reduced risks (34) and the other finding no significant difference between selenium alone or when combined with vitamin E (33)

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Appendix Table 2—**Continued**

Supplement	Study Design (κ Value)	Participants Randomly Assigned, *n**	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
Vitamin A	RCT (κ = 2)	20 611	Participants withdrawn form study during years 4 and 5 because of funding issues in 1 trial; the other trial discontinued early because of increased risk for lung cancer and related deaths associated with β-carotene supplementation	Consistent	Moderate: Participants with a history of actinic keratosis; heavy smokers or asbestos-exposed workers in the United States	Good	Vitamin A appears to have no effect on CVD, cancer, or mortality; increased risk for lung cancer incidence and mortality and all-cause mortality among participants at high risk for lung cancer at baseline (i.e., smokers and/or asbestos-exposed workers) attributed to β-carotene component of vitamin A and β-carotene combination supplement (29)
Vitamin C	RCT (κ = 2)	15 161	1 study did not report results using its 2 × 2 factorial design, which may have limited the study's power (30)	Consistent	Moderate: Healthy U.S. male physicians and patients with hypercholesterolemia in Denmark	Fair	No effect on CVD, cancer, or mortality (30, 31)
Folic acid	RCT (κ = 1)	1021	Secondary analysis of CVD and cancer in a study examining colorectal adenomas	NA	Low: Recruited participants with a recent history of colorectal adenomas	Fair	Secondary analysis showed more noncolorectal cancer incident cases in folic acid group than placebo (P = 0.02), attributed to more prostate cancer cases in intervention group; no significant difference between groups on CVD outcomes (39)
Vitamin D	RCT (κ = 2)	7978	Includes a 2 × 2 factorial study of vitamin D and calcium	Consistent	High: Older adults from United States and United Kingdom	Fair	No effect on CVD, cancer, or mortality
Calcium	RCT (κ = 4)	8873	Includes a 2 × 2 factorial study of vitamin D and calcium	Consistent	Moderate: Older women from United States, United Kingdom, and New Zealand; results may not apply to men or younger age groups	Fair	No effect on CVD, cancer, or mortality; when pooled, 2 trials showed negative effect on colorectal cancer incidence (40, 43)
Vitamin D + calcium	RCT (κ = 2)	37 462	Women only	Inconsistent	Moderate: Older women from the United States; results may not apply to men or younger age groups	Fair/good	1 trial (43) showed statistically significant decreased risk for developing any cancer while the other trial did not (44); no effect on CVD or mortality
Key question 4 (harms)							
β-carotene	RCT (κ = 6)	112 820	1 trial discontinued early because of increased risk for lung cancer and related deaths	Consistent	Moderate-to-high: Increased risk for lung cancer (smokers and/or asbestos-exposed workers), healthy male physicians or females from the United States; participants with a history of BCC and/or SCC	Good	Aside from paradoxical increase in lung cancer and related deaths among participants at high risk for lung cancer at baseline, no apparent serious harms from β-carotene supplementation; yellowing of skin frequently reported

Appendix Table 2—**Continued**

Supplement	Study Design (κ Value)	Participants Randomly Assigned, *n**	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
Vitamin E	RCT (κ = 6)	120 355		Consistent	Moderate-to-high: Healthy men and women (general population or health care providers); individuals with hypercholesterolemia; male smokers in the United States'	Good	Paradoxical effect on hemorrhagic stroke in 1 trial (31); mixed bleeding outcomes reported in other trials; no other apparent serious harms from vitamin E supplementation
Selenium	RCT (κ = 3)	37 346	1 study discontinued early because of no treatment effects	Inconsistent	Moderate-to-high: Healthy men and men with a previous SCC or BCC from the United States; elderly volunteers from the United Kingdom	Good	Mixed dermatologic results; 1 study (34) found no dermatologic signs of toxicity while the other study (33) found an increased risk for alopecia and mild dermatitis ($P < 0.01$) with selenium supplementation; third trial found no serious harms (35)
Vitamin A	RCT (κ = 3) Prospective cohort study (κ = 2)	127 998	1 trial discontinued early because of increased risk for lung cancer and related deaths	Consistent	Moderate-to-high: All studies conducted in the United States; 2 in all women, 2 in patients with a previous skin condition; 1 in heavy smokers or asbestos-exposed workers	Fair/good	2 studies in women reported negative effect on bone mass (i.e., increased risk for fractures); no other serious adverse events reported; paradoxical effect for lung cancer and related death among participants at high risk for lung cancer at baseline (29)
Folic acid	RCT (κ = 1)	1021	Secondary analysis of prostate cancer cases in a study examining colorectal adenomas	NA	Low: Recruited participants with a recent history of colorectal adenomas	Fair	Paradoxical effects on prostate cancer incidence; AFPPS did not report on other harms (39)
Vitamin D	RCT (κ = 2)	5420	Includes a 2 × 2 factorial study of vitamin D and calcium	Consistent	Moderate: 1 study in older adults from the United Kingdom; other study in healthy young adults from Australia	Fair	No harms clearly associated with vitamin D supplementation; most attributed to calcium supplementation
Calcium	RCT (κ = 4)	8873	Includes a 2 × 2 factorial study of vitamin D and calcium	Consistent	Moderate: Older women from United States, United Kingdom, and New Zealand; results may not apply to men or younger age groups	Fair	Constipation and other digestive symptoms more frequently reported in calcium groups, as did renal events; increased risk for hip fractures in calcium group (P = 0.013) but not other sites (45)
Vitamin D + calcium	RCT (κ = 2)	37 462	Women only	Consistent	Moderate: Older women from the United States; results may not apply to men or younger age groups	Fair/good	Increase risk for kidney stones reported in 1 trial (44); no significant difference between combination and placebo group on other harms
Iron							No evidence identified

AFPPS = Aspirin/Folate Poly Prevent Study; BCC = basal cell carcinoma; CVD = cardiovascular disease; MVI = multivitamin; NA = not applicable; RCT = randomized, controlled trial; SCC = squamous cell carcinoma.
* Number of participants randomly assigned is reported for entire study population.
† No evidence identified for vitamin B_1, vitamin B_2, vitamin B_6, iron, zinc, magnesium, niacin, calcium + magnesium, folic acid + vitamin B_{12}, or folic acid + vitamin B_6.