

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

Stephen P. Fortmann, MD; Brittany U. Burda, MPH; Caitlyn A. Senger, MPH; Jennifer S. Lin, MD, MCR; and Evelyn P. Whitlock, MD, MPH

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, 0.93 [95% CI, 0.87 to 0.99]). The study that included women showed no effect in that group. 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.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2013;159:824-834.

www.annals.org

For author affiliations, see end of text.

This article was published online first at www.annals.org on 12 November 2013.

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 that 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 they 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, B₁, B₂, B₆, B₁₂, 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 3 or

See also:

Print

Related articles 797, 806
Editorial comment 850

Web-Only

Supplement
CME quiz

more vitamins and minerals; we use the term “multivitamin” to refer to those combinations.

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 29 January 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 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 1 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.

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**). Four trials (19–22) and 1 cohort study (23) examined the benefits and harms of multivitamin supplementation (**Supplement**). Twenty-two trials and 2 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

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; NR = not reported; 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 for fatal MI (*P* = 0.048).

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 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 (Figure 2 and Appendix Table 1, available at www.annals.org). PHS-II found a borderline statistically significant benefit for fatal myocardial infarction (adjusted hazard 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 [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) (Figure 3). 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 [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 (unadjusted pooled relative risk, 0.93 [CI, 0.87 to 0.99]).

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 Supplement). For most nutrients, however, we found 3 or fewer studies. Trials often varied

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 (↑)

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 and cancer incidence 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).

Six 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, 46), 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 (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).

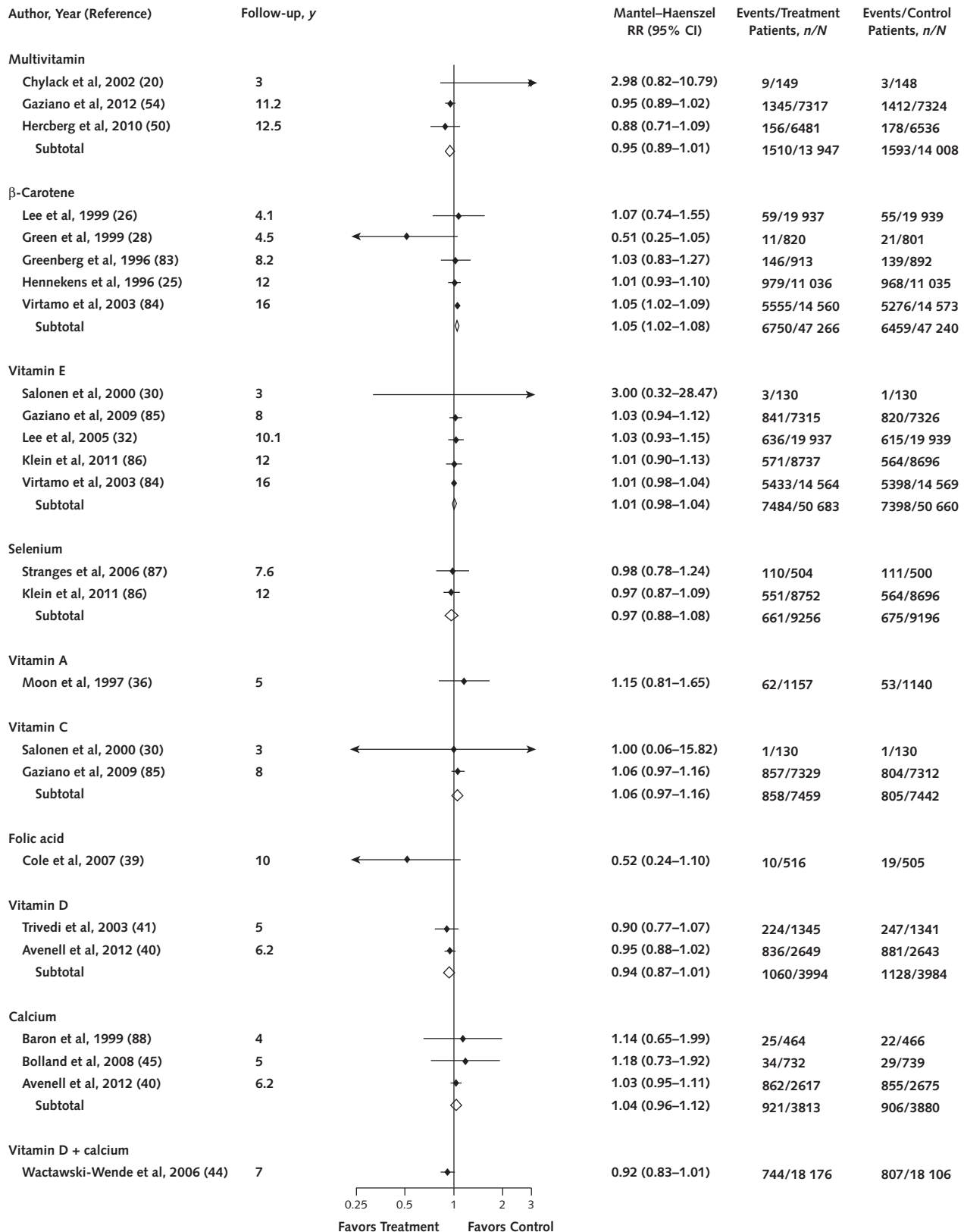
We found little consistent evidence of harm across studies. Although vitamin A use in 1 trial was associated

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 the 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

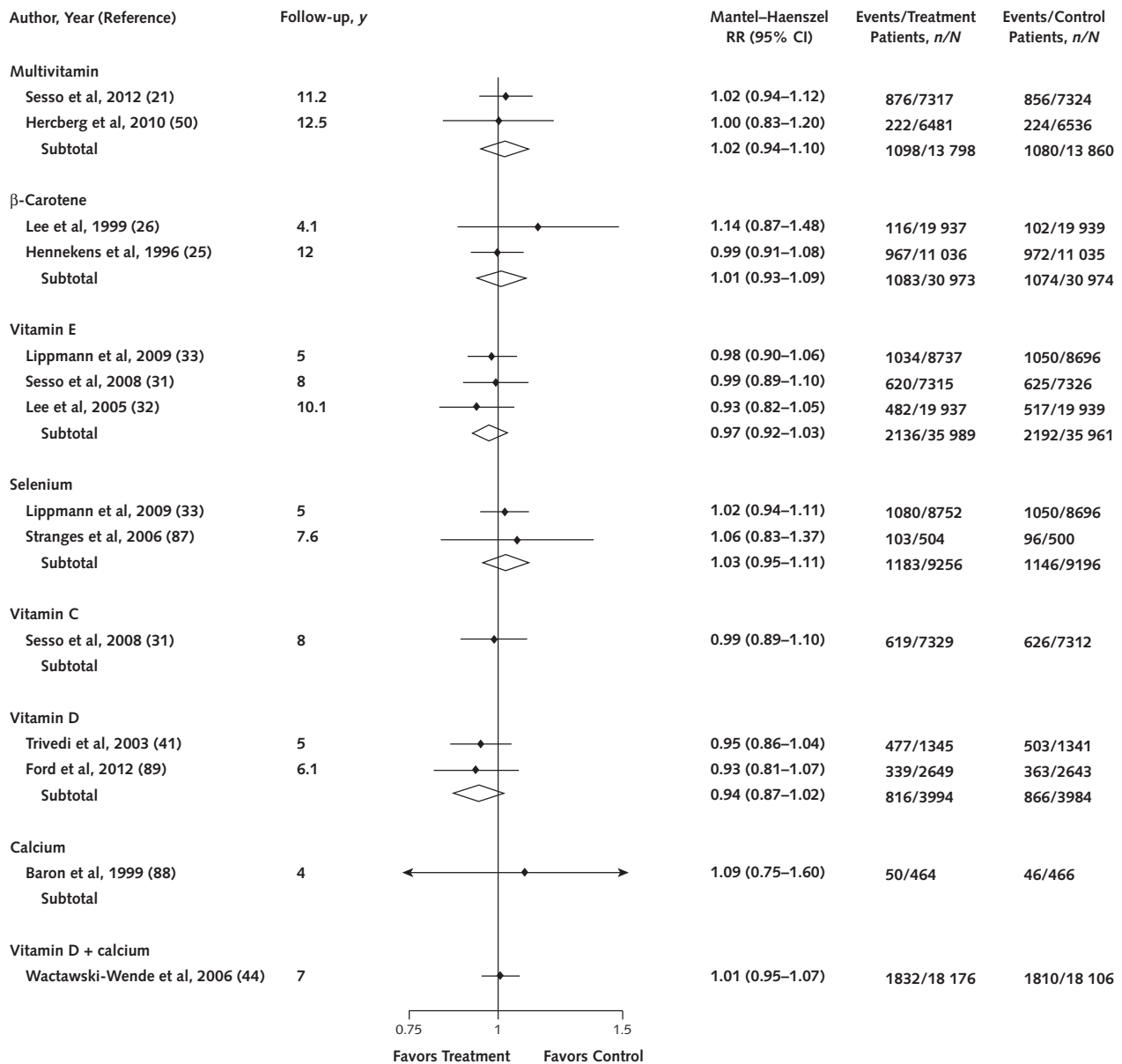
This review included 26 studies (24 randomized, controlled trials and 2 cohort studies) that examined the benefits and harms of using vitamin and mineral supplements for primary prevention of CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies. We found no 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, because 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 6 trials that failed to detect

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



RR = relative risk.

Figure 2. Unadjusted RR for cardiovascular disease at longest follow-up only, by supplement.



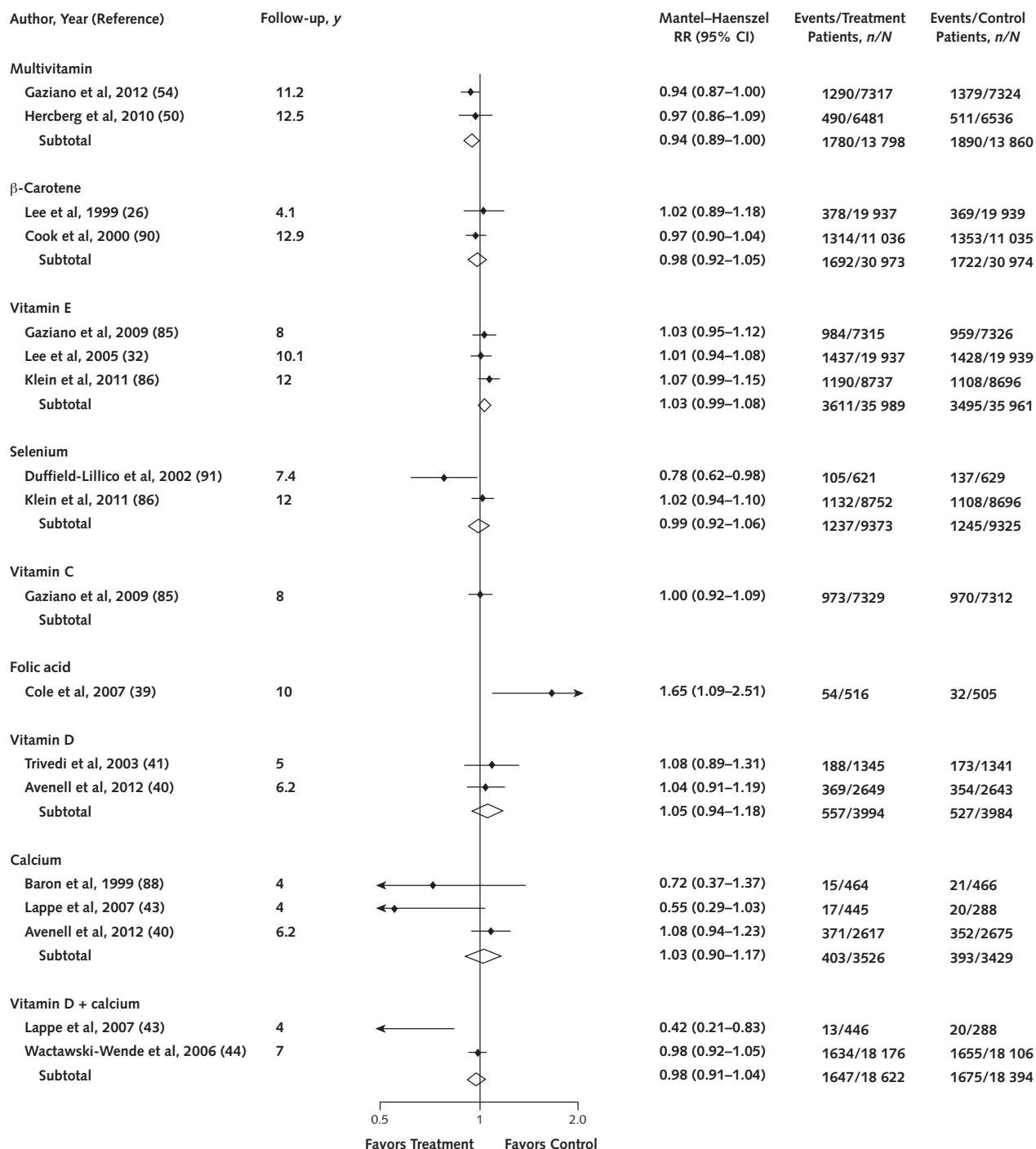
RR = relative risk.

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 RR for cancer at longest follow-up only, by supplement.



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. Other behavioral or biological factors might modify the effects of antioxidant supplements on men and women; however 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 lower mortality in the supplement groups (unadjusted relative risk, 0.94 [CI, 0.87 to 1.01]). In contrast, the point estimates for calcium were all greater than 1, although 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 has 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. The 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. 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 of vitamins or minerals on CVD, cancer, or mortality in healthy individuals without known nutri-

tional deficiencies for most supplements we examined. In most cases data are insufficient 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 trials were 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.

From Kaiser Permanente Center for Health Research, Portland, Oregon.

Disclaimer: This review was conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to AHRQ. AHRQ staff provided oversight for the project and assisted in the external review of the companion draft evidence synthesis.

Acknowledgment: The authors thank the following individuals for their contributions to this project: AHRQ staff; the USPSTF; JoAnn Manson, MD, DrPH, MPH, Thomas Trikalinos, MD, PhD, and Janelle Peralez-Gunn, MPH, for providing expert review of the report; and Kevin Lutz, MFA, Daphne A. Plaut, MLS, Carin M. Olson, MD, Elizabeth O'Connor, PhD, Tracy L. Beil, MS, at the Kaiser Permanente Center for Health Research.

Grant Support: By contract HHS-290-2007-10057-I from AHRQ.

Potential Conflicts of Interest: Dr. Fortmann: *Grant:* AHRQ. Ms. Burda: *Grant:* AHRQ. Dr. Lin: *Grant:* AHRQ. Dr. O'Connor: *Grant:* AHRQ. Ms. Senger: *Grant:* AHRQ. All other authors have no disclosures. Disclosures can also be viewed at www.acponline.org/icmj/author/ConflictOfInterestForms.do?msNum=M13-1702.

Requests for Single Reprints: Reprints are available from the AHRQ Web site (www.ahrq.gov).

Current author addresses and author contributions are available at www.annals.org.

References

1. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol*. 2004;160:339-49. [PMID: 15286019]
2. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, et al. Dietary supplement use among U.S. adults has increased since NHANES III (1988-1994). *NCHS Data Brief*. 2011;1-8. [PMID: 21592424]
3. Nutrition Business Journal. NBJ's Supplement Business Report: an analysis of markets, trends, competition and strategy in the U.S. dietary supplement industry. New York: Penton Media; 2011.
4. Centers for Disease Control and Prevention. Leading causes of death 2012. Accessed at www.cdc.gov/nchs/fastats/lcod.html on 20 March 2013.
5. U.S. Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med*. 2003;139:51-5. [PMID: 12834319]
6. Huang HY, Caballero B, Chang S, Alberg A, Semba R, Schneyer C, et al. Multivitamin/mineral supplements and prevention of chronic disease. *Evid Rep Technol Assess (Full Rep)*. 2006;1-117. [PMID: 17764205]
7. Fortmann SP, Burda BU, Senger CA, Lin JS, Beil TL, O'Connor E, et al. Vitamin, mineral and multivitamin supplements in the primary prevention of cardiovascular disease and cancer. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
8. Morris CD, Carson S. Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
9. Ritenbaugh C, Streit K, Helfand M. Routine vitamin supplementation to prevent cancer: a summary of evidence from randomized controlled trials for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
10. Atkins D, Shetty P. Routine vitamin supplementation to prevent cancer: update of the evidence from randomized controlled trials 199-2002. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
11. Human Development Report 2011. Sustainability and equity: a better future for all. New York: United Nations Development Programme; 2011.
12. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: National Academies Pr; 2006.
13. Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: Assessing harms when comparing medical interventions: AHRQ and the effective health-care program. *J Clin Epidemiol*. 2010;63:502-512. [PMID: 18823754]
14. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
15. National Institute for Health and Clinical Excellence. The Guidelines Manual. London: National Institute for Health and Clinical Excellence; 2006.
16. Bradburn MJ, Deeks JJ, Altman DG. Metan—a command for meta-analysis in Stata. In: Sterne JAC, ed. *Meta-analysis in Stata: An Updated Collection from the Stata Journal*. College Station, TX: Stata Press; 1998:3-28.
17. Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64:1187-97. [PMID: 21477993]
18. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. West Sussex: J Wiley; 2009.
19. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, 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;164:2335-42. [PMID: 15557412]
20. Chylack LT Jr, Brown NP, Bron A, Hurst M, Köpcke W, Thien U, 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;9:49-80. [PMID: 11815895]
21. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schwartz M, et al. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308:1751-60. [PMID: 23117775]
22. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA*. 2002;288:715-21. [PMID: 12169075]
23. Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. *JAMA*. 2002;287:47-54. [PMID: 11754708]
24. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med*. 1994;330:1029-35. [PMID: 8127329]
25. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, 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;334:1145-9. [PMID: 8602179]
26. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst*. 1999;91:2102-6. [PMID: 10601381]
27. Greenberg ER, Baron JA, Stukel TA, Stevens MM, Mandel JS, Spencer SK, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. *N Engl J Med*. 1990;323:789-95. [PMID: 2202901]
28. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-

- cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*. 1999;354:723-9. [PMID: 10475183]
29. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996;334:1150-5. [PMID: 8602180]
 30. Salonen JT, Nyyssönen K, Salonen R, Lakka HM, Kaikkonen J, Porkkala-Sarataho E, 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;248:377-86. [PMID: 11123502]
 31. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2008;300:2123-33. [PMID: 18997197]
 32. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294:56-65. [PMID: 15998891]
 33. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, 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;301:39-51. [PMID: 19066370]
 34. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276:1957-63. [PMID: 8971064]
 35. 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:e45269. [PMID: 23028897]
 36. Moon TE, Levine N, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev*. 1997;6:949-56. [PMID: 9367069]
 37. Levine N, Moon TE, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev*. 1997;6:957-61. [PMID: 9367070]
 38. 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;15:552-9. [PMID: 14760518]
 39. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, et al; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA*. 2007;297:2351-9. [PMID: 17551129]
 40. Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, 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;97:614-22. [PMID: 22112804]
 41. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326:469. [PMID: 12609940]
 42. Dean AJ, Bellgrove MA, Hall T, Phan WM, Eyles DW, Kvaskoff D, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults—a randomised controlled trial. *PLoS One*. 2011;6:e25966. [PMID: 22073146]
 43. 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;85:1586-91. [PMID: 17556697]
 44. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354:684-96. [PMID: 16481636]
 45. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336:262-6. [PMID: 18198394]
 46. Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol Biomarkers Prev*. 2005;14:586-9. [PMID: 15767334]
 47. Ezzedine K, Latreille J, Kesse-Guyot E, Galan P, Hercberg S, Guinot C, et al. Incidence of skin cancers during 5-year follow-up after stopping antioxidant vitamins and mineral supplementation. *Eur J Cancer*. 2010;46:3316-22. [PMID: 20605091]
 48. Hercberg S, Czernichow S, Galan P. Antioxidant vitamins and minerals in prevention of cancers: lessons from the SU.VI.MAX study. *Br J Nutr*. 2006;96 Suppl 1:S28-30. [PMID: 16923246]
 49. Hercberg S, Ezzedine K, Guinot C, Preziosi P, Galan P, Bertrais S, et al. Antioxidant supplementation increases the risk of skin cancers in women but not in men. *J Nutr*. 2007;137:2098-105. [PMID: 17709449]
 50. Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, et al. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. *Int J Cancer*. 2010;127:1875-81. [PMID: 20104528]
 51. Hercberg S, Galan P, Preziosi P, Roussel AM, Arnaud J, Richard MJ, et al. Background and rationale behind the SU.VI.MAX Study, a prevention trial using nutritional doses of a combination of antioxidant vitamins and minerals to reduce cardiovascular diseases and cancers. *Supplementation en Vitamines et Minéraux Antioxydants Study*. *Int J Vitam Nutr Res*. 1998;68:3-20. [PMID: 9503043]
 52. Hercberg S, Preziosi P, Briçon S, Galan P, Triol I, Malvy D, et al. A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study—design, methods, and participant characteristics. *Supplementation en Vitamines et Minéraux Antioxydants*. *Control Clin Trials*. 1998;19:336-51. [PMID: 9683310]
 53. Meyer F, Galan P, Douville P, Bairati I, Kegle P, Bertrais S, et al. Antioxidant vitamin and mineral supplementation and prostate cancer prevention in the SU.VI.MAX trial. *Int J Cancer*. 2005;116:182-6. [PMID: 15800922]
 54. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308:1871-80. [PMID: 23162860]
 55. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;10:125-34. [PMID: 10691066]
 56. Jeon YJ, Myung SK, Lee EH, Kim Y, Chang YJ, Ju W, et al. Effects of beta-carotene supplements on cancer prevention: meta-analysis of randomized controlled trials. *Nutr Cancer*. 2011;63:1196-207. [PMID: 21981610]
 57. Fritz H, Kennedy D, Fergusson D, Fernandes R, Cooley K, Seely A, et al. Selenium and lung cancer: a systematic review and meta analysis. *PLoS One*. 2011;6:e26259. [PMID: 22073154]
 58. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E. Selenium and coronary heart disease: a meta-analysis. *Am J Clin Nutr*. 2006;84:762-73. [PMID: 17023702]
 59. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med*. 2010;152:315-23. [PMID: 20194238]
 60. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007;167:1730-7. [PMID: 17846391]
 61. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Systematic review: primary and secondary prevention of gastrointestinal cancers with antioxidant supplements. *Aliment Pharmacol Ther*. 2008;28:689-703. [PMID: 19145725]
 62. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. *Cochrane Database Syst Rev*. 2008;CD004183. [PMID: 18677777]
 63. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev*. 2008;CD007176. [PMID: 18425980]
 64. Papaioannou D, Cooper KL, Carroll C, Hind D, Squires H, Tappenden P, et al. Antioxidants in the chemoprevention of colorectal cancer and colorectal adenomas in the general population: a systematic review and meta-analysis. *Colorectal Dis*. 2011;13:1085-99. [PMID: 20412095]

65. Chang YJ, Myung SK, Chung ST, Kim Y, Lee EH, Jeon YJ, et al. Effects of vitamin treatment or supplements with purported antioxidant properties on skin cancer prevention: a meta-analysis of randomized controlled trials. *Dermatology*. 2011;223:36-44. [PMID: 21846961]
66. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S. Selenium supplementation for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;1:CD009671. [PMID: 23440843]
67. Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci*. 2011;4:158-70. [PMID: 21235492]
68. Alkhenizan A, Hafez K. The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials. *Ann Saudi Med*. 2007;27:409-14. [PMID: 18059122]
69. Shekelle P, Coulter I, Hardy M, Morton SC, Udani J, Spar M, et al. Effect of the supplemental use of antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
70. Shekelle PG, Morton SC, Jungvig LK, Udani J, Spar M, Tu W, et al. Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med*. 2004;19:380-9. [PMID: 15061748]
71. Bin Q, Hu X, Cao Y, Gao F. The role of vitamin E (tocopherol) supplementation in the prevention of stroke. A meta-analysis of 13 randomised controlled trials. *Thromb Haemost*. 2011;105:579-85. [PMID: 21264448]
72. Tanvetyanon T, Bepler G. Beta-carotene in multivitamins and the possible risk of lung cancer among smokers versus former smokers: a meta-analysis and evaluation of national brands. *Cancer*. 2008;113:150-7. [PMID: 18429004]
73. Byers T. Anticancer vitamins du Jour—the ABCED's so far [Editorial]. *Am J Epidemiol*. 2010;172:1-3. [PMID: 20562190]
74. Lichtenstein AH, Russell RM. Essential nutrients: food or supplements? Where should the emphasis be? *JAMA*. 2005;294:351-8. [PMID: 16030280]
75. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691. [PMID: 20671013]
76. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040. [PMID: 21505219]
77. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr*. 2011;94:1144-9. [PMID: 21880848]
78. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int*. 2013;24:567-80. [PMID: 23208074]
79. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. *JAMA Intern Med*. 2013;173:639-46. [PMID: 23381719]
80. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart*. 2012;98:920-5. [PMID: 22626900]
81. Moyé LA. Random research. *Circulation*. 2001;103:3150-3. [PMID: 11425783]
82. Lappe JM, Heaney RP. Why randomized controlled trials of calcium and vitamin D sometimes fail. *Dermatoendocrinol*. 2012;4:95-100. [PMID: 22928064]
83. Greenberg ER, Baron JA, Karagas MR, Stukel TA, Nierenberg DW, Stevens MM, et al. Mortality associated with low plasma concentration of beta carotene and the effect of oral supplementation. *JAMA*. 1996;275:699-703. [PMID: 8594267]
84. Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, et al; ATBC Study Group. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. *JAMA*. 2003;290:476-85. [PMID: 12876090]
85. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2009;301:52-62. [PMID: 19066368]
86. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306:1549-56. [PMID: 21990298]
87. Stranges S, Marshall JR, Trevisan M, Natarajan R, Donahue RP, Combs GF, et al. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. *Am J Epidemiol*. 2006;163:694-9. [PMID: 16495471]
88. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med*. 1999;340:101-7. [PMID: 9887161]
89. Ford JA, MacLennan G, Bolland MJ, Grey A, Avenell A. Vitamin D supplementation prevents cardiac failure: MRC record trial analysis, systematic review and meta-analysis [Abstract]. *Circulation*. 2012;126:A18397.
90. Cook NR, Le IM, Manson JE, Buring JE, Hennekens CH. Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). *Cancer Causes Control*. 2000;11:617-26. [PMID: 10977106]
91. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev*. 2002;11:630-9. [PMID: 12101110]

Current Author Addresses: Dr. Fortmann, Ms. Burda, Ms. Senger, and Drs. Lin and Whitlock: Kaiser Permanente Center for Health Research, 3800 North Interstate Avenue, Portland, OR 97227.

Author Contributions: Conception and design: B.U. Burda, C.A. Senger, J.S. Lin, E.P. Whitlock.

Analysis and interpretation of the data: S.P. Fortmann, B.U. Burda, C.A. Senger, J.S. Lin, E.P. Whitlock.

Drafting of the article: S.P. Fortmann, B.U. Burda, C.A. Senger.

Critical revision of the article for important intellectual content: S.P. Fortmann, B.U. Burda, C.A. Singer, J.S. Lin, E.P. Whitlock.

Final approval of the article: S.P. Fortmann, B.U. Burda, C.A. Senger, E.P. Whitlock.

Obtaining of funding: E.P. Whitlock.

Administrative, technical, or logistic support: B.U. Burda, C.A. Senger.

Collection and assembly of data: S.P. Fortmann, B.U. Burda, C.A. Senger.

Appendix Table 1. CVD 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
			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
			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.

§ HRs 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 ($\kappa = 3$)	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 participants; 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 ($\kappa = 4$) Prospective cohort study ($\kappa = 1$)	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 ($\kappa = 6$)	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 ($\kappa = 5$)	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 ($\kappa = 2$)	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 cancer, 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)

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 ($\kappa = 2$)	20 611	Participants withdrawn from 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 ($\kappa = 2$)	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 ($\kappa = 1$)	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 ($\kappa = 2$)	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 ($\kappa = 4$)	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 ($\kappa = 2$)	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 any cancer while the other trial did not (44); no effect on CVD or mortality
Key question 4 (harms) β -Carotene	RCT ($\kappa = 6$)	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

Continued on following page

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 ($\kappa = 6$)	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 ($\kappa = 3$)	37 346	1 study discontinued early because of no treatment effects	Inconsistent	Moderate-to-high: Healthy men and men with 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, whereas 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 ($\kappa = 3$) Prospective cohort study ($\kappa = 2$)	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 ($\kappa = 1$)	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 ($\kappa = 2$)	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 ($\kappa = 4$)	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 ($\kappa = 2$)	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 B₁, vitamin B₂, vitamin B₆, iron, zinc, magnesium, niacin, calcium + magnesium, folic acid + vitamin B₁₂, or folic acid + vitamin B₆.