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

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Structured Abstract

Objective: To review the benefits and harms of vitamin and mineral supplementation in healthy adults to prevent cardiovascular disease (CVD) and cancer.

Data Sources: MEDLINE, PubMed (publisher-supplied records only), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and Embase, between January 2013 and August 28, 2020. Additionally, we evaluated all studies included in the prior USPSTF review for inclusion in the current review. We conducted ongoing surveillance for relevant literature through January 22, 2021.

Study Selection: We reviewed 14,180 unique citations and 351 full-text articles against a priori inclusion criteria. We included English-language randomized clinical trials (RCTs) of vitamin or mineral use among persons without CVD or cancer reporting all-cause mortality, CVD, cancer, or adverse outcomes as well as observational cohort studies examining serious harms of supplement use. Critical appraisal was completed independently by two investigators. Data were extracted from studies by one reviewer and checked by a second.

Data Analysis: We conducted quantitative pooling when at least three studies of the same supplement reported the same outcome. Because most outcomes occurred in less than 10 percent of the study sample, we typically used methods appropriate for rare events, including a fixed effects Mantel-Haenszel model or a random effects restricted maximum likelihood model using Peto odds ratio. Stratified or subgroup analyses and meta-regression were used to explore effect modification for trials of vitamin D, which had the largest body of evidence.

Results: A total of 78 studies (n=694,084) were included. Vitamin D (with or without calcium) was associated with a statistically non-significant lower risk of all-cause mortality (OR, 0.94 [95% CI, 0.89 to 1.00]; 22 RCTs [n=90,038]; I^2=0%) and a lower risk of cancer mortality (OR, 0.88 [95% CI, 0.79 to 0.97]; 5 RCTs [n=72,622]; I^2=0%), compared to placebo. In one of the largest studies, 1.2 percent of participants taking vitamin D and calcium had died of cancer, compared with 1.4 percent taking placebo.

Beta-carotene, with or without vitamin A, was associated with an increased risk of cardiovascular mortality (OR 1.10 [95% CI, 1.02 to 1.19]; 5 RCTs [n=94,506]; I^2=0%), and lung cancer (OR 1.20 [95% CI, 1.01 to 1.42]; 4 RCTs [n=94,830]; I^2=38.8%). In one of the largest trials, which was limited to people at high risk of lung cancer, 3.3 percent of participants taking beta-carotene developed lung cancer, compared with 2.8 percent who were not taking beta-carotene after 6.1 years (RR, 1.18 [95% CI, 1.03 to 1.36]; n=29,133). In addition, we found less robust evidence that folic acid was associated with an increased risk of cancer incidence.

We found clear evidence that vitamin E (with or without vitamin C or selenium) offers no benefit for all-cause mortality (OR, 1.02 [95% CI, 0.97 to 1.07]; 9 RCTs [n=107,772]; I^2=0%), CVD events (OR, 0.96 [95% CI, 0.90 to 1.04]; 4 RCTs [n=62,136]; I^2=0%), and cancer (OR, 1.02 [95% CI, 0.98 to 1.08]; 5 RCTs [n=76,777]; I^2=0%), and more equivocal evidence that multivitamins (antioxidant-focused or broad spectrum), vitamin A (without beta-carotene),

vitamin C, calcium (without vitamin D), and selenium also had no impact on all-cause mortality, CVD, and cancer.

There was also weak evidence that supplements increased the risk of some other serious harms, such as hip fracture (vitamin A), hemorrhagic stroke (vitamin E), and kidney stones (vitamin C, calcium). Several supplements were associated with an increased risk of some minor and reversible adverse outcomes, such as skin yellowing (beta-carotene) and gastrointestinal symptoms (calcium).

Limitations: Some studies lacked full outcome ascertainment or had insufficient followup or power for the main review outcomes; varied background interventions (primarily due to factorial designs) may cloud supplement effects; people of color were minimally represented. Most supplements had too few studies to explore effect modification.

Conclusions: Vitamin and mineral supplementation provides little to no benefit in preventing cancer, CVD, and death, with the exception of a benefit for cancer-related mortality and a possible small benefit for all-cause mortality with vitamin D use. Beta-carotene increases the risk of lung cancer and other harmful outcomes in persons at high risk of lung cancer. Data were absent or insufficient to draw conclusions for any of the B vitamins, iron, zinc, or magnesium.

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Chapter 1. Introduction

Scope and Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2014 recommendations on vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer.[1]

Background

Vitamins and Minerals

Vitamins (e.g., vitamin A, C, D, E, K, and the B vitamins) are groups of chemically diverse organic compounds that are essential or conditionally essential to maintaining normal metabolism.[2] Minerals are inorganic substances that humans also need to maintain function (e.g., calcium, iron, zinc).[3] Vitamins and minerals are primarily obtained from nutrient-dense foods and beverages, but are also available in the form of supplements.[4] Vitamins and minerals can be combined, with or without other substances, in multivitamin or multimineral supplements. In the United States, there is no standardized or regulatory definition for multivitamins or multiminerals with respect to required components or doses, thus these terms can refer to a wide variety of products available on the market.[5] For the purposes of this review, we use the term multivitamin to refer to any three or more vitamins or minerals, with minimal added herbs, hormones, enzymes, or drugs, each at a dose less than the tolerable upper intake level, as determined by the Food and Nutrition Board.[6] Upper intake levels are the maximum daily intake unlikely to cause adverse health effects.[7, 8] While supplements can be taken to combat various vitamin or mineral deficiencies, this report specifically evaluates vitamin and mineral supplementation in populations without known chronic disease or known nutritional deficiencies.

Use of Vitamin and Mineral Supplements in the United States

Dietary supplementation is a $30 billion industry in the United States, with over 90,000 products on the market.[9] In the United States, the regulation of dietary supplements is less stringent than for over-the-counter or prescription drugs. According to the Food and Drug Administration (FDA), supplements—unlike drugs—are not intended to treat, diagnose, prevent, or cure diseases.[10] The FDA requires that manufacturers submit safety data only for ingredients introduced in the US as a dietary supplement after 1993, but otherwise does not review dietary supplements for safety and effectiveness prior to marketing.[11] Additionally, studies have found that the content of vitamins and minerals may not be accurate to the package labeling.[12]

According to 2011–2014 National Health and Nutrition Examination Survey (NHANES) data, over half (52%) of surveyed US adults (n=11,024) reported using at least one dietary supplement in the past 30 days with 31 percent reported using a multivitamin-mineral supplement.[13] Dietary supplement use varies by age, gender, race, and ethnicity, as well as socioeconomic

characteristics, such as educational attainment and income (**Table 1**). The prevalence of dietary supplement use increases with age, with 36 percent of adults aged 19–30 years, 45 percent of adults age 31–50 years, 63 percent of adults aged 51–70 years, and 75 percent of adults aged 71 years or older reporting supplement use in the past 30 days. Women are more likely to report using dietary supplements than men (59% vs. 45%, respectively), and White people are more likely to report using dietary supplements than people of other racial and ethnic background (58%, vs. 40% of Black, 35% of Hispanic, and 54% of Asian American persons). Dietary supplement use increases with education and income (**Table 1**).[9] Older data (2007-2011) from a trade group report that the reasons most often cited for supplement use were for overall health and wellness (58%) and to fill nutrient gaps in the diet (42%).[14]

Prevalence and Burden of CVD and Cancer in the United States

Cardiovascular disease and cancer are the two leading causes of death[15] and combined account for approximately half of deaths in the US annually.[16] Between 2013 and 2016, 24.3 million Americans had some form of cardiovascular disease. Cardiovascular disease accounted for 793,840 deaths in the U.S. in 2017, approximately one of every three deaths.[16] The prevalence of and mortality from cardiovascular disease (CVD) varies substantially by age, race/ethnicity, and socioeconomic factors.[17] As shown in **Table 2**, heart disease and stroke are most common among older adults, males, and low socioeconomic status groups. The prevalence rates of CVD, and notably stroke, are particularly high among Black Americans and American Indian/Alaska Native compared to other races and ethnicities.[16-18] Similar to CVD morbidity, mortality from CVD is more common in men than women (age-adjusted mortality rate of 264.1 vs. 180.1 per 100,000 population, respectively), and varies by race, with the highest mortality rate among Black Americans (285.5), followed by White (220.1), Native North American (199.6), Hispanic (158.2), and Asian and Pacific Islander Americans (combined, 127.7).[16]

In 2018, an estimated 1.7 million individuals were diagnosed with cancer in the United States.[19] The annual age-adjusted incidence rate for any cancer was 447.9 per 100,000 individuals. Cancer is the second leading cause of death in the United States, accounting for 21.3 percent of all deaths in 2017.[16] The overall age-adjusted mortality rate for any cancer was 158.2 per 100,000 individuals, with a median age at death of 72 years in 2013–2017.[20] Black men have the highest rates of cancer incidence in any gender and racial/ethnic group (547.6 per 100,000 population) (**Table 3**).[21] Rates of cancer incidence are lowest in Asian American and Pacific Islander men and women (combined, 296.5 and 295.7 per 100,000 population, respectively).[21] The leading incident cancers in men are prostate (108.1 per 100,000), lung (69.5 per 100,000), and colorectal (45.1 per 100,000) and in women are breast (126.8 per 100,000), lung (51.8 per 100,000), and colorectal (34.4 per 100,000).[21] Similarly, cancer mortality rates differ by gender, with men being more likely to die from cancer than women.[16] Black men and women have the highest total cancer mortality and the highest mortality rates for most major cancer sites.[21]

Role of Vitamins and Minerals in the Prevention of CVD and Cancer

Despite the differences in their clinical manifestations, CVD and cancer share several risk and etiologic factors, including age, alcohol use, smoking status, poor nutrition, sedentary behavior, and obesity.[22] Inflammation and oxidative stress, both prime targets of vitamin and mineral

supplements, appear to account for at least part of this overlap in risk factors between diseases.[23] Another possible common pathway for CVD and cancer etiology is impaired regulation of methionine metabolism and methylation of a variety of biochemical targets.[24-28] Several dietary supplements are known to have antioxidant and anti-inflammatory effects or influence methionine metabolism. This has served as the rationale for proposing dietary supplements as an effective means to prevent both CVD and cancer.

Vitamins and minerals might protect against oxidative damage by neutralizing free radicals and other reactive species and thus reduce both CVD and cancer risk. Fat-soluble antioxidant vitamins such as vitamin E circulate principally in lipoproteins, especially LDL. Oxidized LDL is highly atherogenic and vitamin E protects against this oxidation.[29] To maintain vitamin E in its antioxidant or reduced state, however, circulating, water-soluble antioxidants such as vitamin C are required. Natural, enzymatic antioxidants catalyze the reactions that suppress free radicals and peroxide, and contain copper, zinc, and manganese as integral parts of their structure, providing a rationale for supplementing with minerals. Low levels of vitamin B12 and folate that participate in DNA synthesis may result in deficiency of methionine and contribute to aberrant DNA synthesis and carcinogenesis.[30-32] Also, it has been demonstrated that increased levels of homocysteine, an amino acid formed by demethylation of methionine, is associated with increased risk of coronary heart disease events.[33] Vitamin E (alpha-tocopherol), zinc, and vitamin A are supplements that are thought to inhibit inflammation. Beta-carotene is a precursor vitamin, or provitamin, that the body converts into vitamin A. While vitamin A has an upper limit due to the risk of toxicity at high doses, beta-carotene has not been shown to cause toxicity and therefore does not have a defined upper limit.[7]

Regular human exposure to vitamins and minerals is through diet,[4] which includes a vast array of micronutrients that interact in complex ways with each other and with macronutrients such as fiber and fatty acids.[34-36] The existence of such interactions, their mechanisms, and effects are often unknown or understudied.[32] In addition, variability in individuals' absorption and metabolization of food may influence the effects of these nutrients. As such, multivitamins cannot mimic the content of a healthful diet that includes a wide variety of unprocessed foods. Additionally, the chemical structure of single vitamin supplements may vary substantially from what is found in whole foods, which could alter biological impacts.[37, 38] The importance of a supplement's chemical form and potential vitamin-vitamin interactions can be exponentially expanded when we consider a supplement's potential interactions with other nutrients, supplements, and medications.

Current Clinical Practice in the United States and Recommendations of Other Organizations

The 2015–2020 US Dietary Guidelines recommend that nutrient needs be met primarily from nutrient-dense foods because, in addition to vitamins and minerals, they contain fiber and other naturally occurring substances with beneficial health effects.[4] Similarly, other organizations including the Academy of Nutrition and Dietetics (2018);[39] World Cancer Research Fund and American Institute for Cancer Research (2018);[40] National Osteoporosis Foundation and American Society for Preventive Cardiology (2017);[41] and the American Heart Association (2014)[42] have guidelines or positions recommending that healthy adults meet their nutrient needs

primarily through a healthy diet, and that vitamins should not be used for CVD or cancer prevention (**Table 4**). Varying slightly, the Canadian Cancer Society (2018) recommends that nutritional needs be met by a healthy diet with the exception of vitamin D, for which individuals should discuss supplementation during the fall and winter months with their physician, noting a possible role of vitamin D in cancer prevention.[43]

Contemporary and independently collected data on the prevalence with which health care professionals recommend vitamins and minerals for CVD and cancer prevention are sparse. Older data collected by a trade group suggest that it is common for a variety of health care providers to recommend vitamin and mineral supplements to their patients. A 2007 survey found that 72 percent of surveyed physicians (n=900), 82 percent of nurses (n=277), and 97 percent of registered dietitians (n=300) reported recommending supplemental vitamins and minerals to patients.[44, 45] The most common reason physicians and nurses reported recommending supplements was for overall health and wellness (41% of physicians and 62% of nurses).[45] Supplements were also recommended for reasons related to bone health (41% of physicians and 58% of nurses, respectively), joint health (37% and 36%), flu or colds (24% and 39%), heart health (33% and 26%), immune health (19% and 36%), musculoskeletal pain (26% for both), and energy (19% and 25%).[43]

Previous and Related USPSTF Recommendations

In 2014, the USPSTF concluded that there was insufficient evidence to assess the balance of benefits and harms associated with the use of multivitamins (**I statement**[46]) and many single- or paired-nutrient supplements for the prevention of CVD or cancer (**I statement**).[1] The USPSTF recommended against supplementation with beta-carotene or vitamin E for the prevention of cardiovascular disease or cancer (**Grade D recommendation**).[1] The USPSTF found that there was adequate evidence that beta-carotene and vitamin E do not reduce the risk of cancer or CVD in healthy populations without known nutritional deficiencies, and that beta-carotene increases the risk of lung cancer and persons at increased risk for this condition.

The USPSTF has published other recommendations related to supplements for aims other than cancer or CVD prevention. Taken together, these are statements of evidence insufficiency or recommendations against supplementation with vitamin D. Specifically, the USPSTF conclusions include:

- For the prevention of fractures:[47]
    - Insufficient evidence to recommend the use of any level of vitamin D and calcium for men and premenopausal women (**I statement**)
    - Insufficient evidence to recommend daily supplementation at doses greater than 400 IU for vitamin D and 1000 mg for calcium for postmenopausal women (**I statement**).
    - Adequate evidence that daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium is not effective for the primary prevention of fractures in postmenopausal women (**Grade D recommendation**).[47]

- For the prevention of falls:[48] Adequate evidence that vitamin D supplementation in community-dwelling adults age 65 and older is not effective in preventing falls (**Grade D recommendation**).
- Screening of vitamin D deficiency in asymptomatic adults:[49] Insufficient evidence to recommend for or against screening for vitamin D deficiency in asymptomatic adults (**I statement**).
- For the prevention of cognitive decline in people with mild to moderate dementia or mild cognitive impairment:[50] The systematic review supporting the 2020 recommendation for screening for cognitive impairment concluded that vitamin supplements did not improve global cognition or physical function in persons with mild to moderate dementia or mild cognitive impairment, with no clear increase in harms.

For the prevention of neural tube defects: The USPSTF found convincing evidence that folic acid supplementation in the periconceptional period provides substantial benefits in reducing the risk of neural tube defects in the developing fetus and recommends that women who are planning or capable of pregnancy take a daily supplement of 0.4 to 0.8 mg of folic acid daily for the prevention of congenital neural tube defects (**Grade A recommendation**).[51]

Chapter 2. Methods

Scope and Purpose

This review is an update of the systematic review[52] that supported the 2014 USPSTF recommendations on vitamin supplementation to prevent cancer and CVD.[1] The approach for the current review was very similar to the previous review with 3 main differences: the current review addressed harms for all supplements (rather than selected supplements), included secondary prevention trials in persons with a history of adenomas or non-melanoma skin cancers, and included trials of supplements designed to prevent diseases other than CVD or cancer that reported all-cause mortality or adverse events.

Analytic Framework and Key Questions

With input from the USPSTF, we developed an Analytic Framework (**Figure 1**) and four Key Questions (KQs) to guide the literature search and selection of studies, data abstraction, and evidence synthesis.

KQs

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

Data Sources and Searches

We conducted a search to identify literature published since the previous review for the USPSTF covering January 1, 2013 through August 28, 2020. We worked with a research librarian to develop our search strategy, which included the following databases: MEDLINE, PubMed (publisher-supplied records only), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and Embase (**Appendix A**).

Additionally, we evaluated all previously included studies from the prior review for the USPSTF and reviewed reference lists of other systematic reviews for inclusion in the current review.[53-60] We also reviewed table-of-contents alerts such as those produced by the USPSTF Scientific Resource Center LitWatch activity to identify additional studies not identified in our literature searches. We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for relevant ongoing trials. Active surveillance was conducted after our

searches through January 22, 2021 via article alerts and targeted journal searches to identify major studies that might affect the conclusions or understanding of the evidence. We managed all literature search results using EndNote™ version 7.3.1 (Thomson Reuters, New York, NY).

Study Selection

Detailed inclusion and exclusion criteria were developed to guide study selection (**Appendix A Table 1**). One investigator independently prescreened titles and abstracts of a subset of studies with electronically identified keywords pertaining to an excluded setting, population, or condition in the title, abstract, or keyword fields of EndNote (**Appendix A Table 2**). Abstracts deemed potentially relevant during single review were advanced for dual review. Of the 14,180 total citations screened, 5,929 were prescreened by a single reviewer based on keywords highly probable for exclusion in the title or abstract; of these, six were identified as potentially relevant and moved forward for dual review, along with the 8,251 assigned to dual review from the beginning. Two investigators independently reviewed 351 full-text articles. We used DistillerSR (Evidence Partners, Ottawa, Canada) to conduct abstract and full-text review.

Population and Setting

For all KQs, we excluded studies limited to adults with known chronic disease, including but not limited to CVD, type 2 diabetes, cancer, or known nutritional or vitamin deficiencies. We excluded studies in which more than 50 percent of participants had vitamin deficiency, or a mean serum level in the deficient range across all participants. Consistent with the previous review, populations with risk factors for CVD or cancer, such as those with high blood pressure, smokers, or previous removal of colorectal adenoma were eligible for inclusion. Populations with a history of non-melanoma skin cancer were considered for non-skin cancer outcomes. We only included studies that were conducted in countries classified as "very high" on the 2017 Human Development Index to avoid the possibility of higher prevalence of nutritional deficiencies in other countries.[61]

Intervention and Comparator

For KQs 1 and 2, we included studies evaluating supplementation with multivitamins/minerals, defined as three or more vitamins, minerals, or combinations of both without extensive added herbs, hormones, or drugs. For KQs 3 and 4, we included studies evaluating supplementation with single nutrients and functionally-related pairs (i.e., calcium; folic acid; vitamins B1, B2, B6, B12, D, E, C, and A; iron; zinc; magnesium; niacin; calcium/vitamin D; calcium/magnesium; folic acid/vitamin B12; selenium; beta-carotene; beta-carotene/vitamin A, and folic acid/vitamin B6)**.** We only included studies that tested supplements at doses lower than their tolerable upper intake level, with the exception of three studies: two that included higher than recommended levels of vitamin A[62, 63] and one that included higher doses of vitamin D.[64] These were included for consistency with the previous review. The decision to focus on supplementation at or below the upper limit reflects a focus on preventive vitamin and mineral supplementation, as opposed to therapeutic supplementation. **Appendix A Table 3** lists the recommended dietary allowance

(RDA) and upper intake levels for the micronutrients we included in the review. We excluded supplementation with other types of dietary supplements (e.g., herbal supplements, omega-3 fatty acids, amino acids, enzymes, proprietary products, fiber, garlic, or turmeric), vitamin-derived agents with dermatologic indication (i.e., tretinoin, isotretinoin) and interventions to increase dietary (rather than supplemental) intake of nutrients.

Outcomes

For KQs 1 and 3, outcomes of interest were cancer (any cancer or site-specific), CVD incidence (including coronary heart, peripheral artery, and cerebrovascular disease), CVD events (myocardial infarction and ischemic and hemorrhagic stroke), heart failure, or mortality (all-cause, CVD–related, or cancer-related). A minimum of 1 year of followup was required for all-cause mortality, but other outcomes had no minimum followup requirement. For KQs 2 and 4, outcomes of interest were paradoxical effects on CVD, cancer, and mortality outcomes, serious adverse events (as defined by the study, or those likely requiring medical attention, such as kidney stones, sarcoidosis, and hip fracture), withdrawals due to adverse events, and nonserious adverse events (based on self-report or objective measurements and reported by at least 5% of the study sample taking the supplement). Studies that reported on a serious harms but no cancer, CVD, or mortality outcomes were included in this review.

Precancerous lesions (e.g., cervical intraepithelial neoplasia) and intermediate cardiovascular risk measure (blood pressure, lipid levels, glucose levels) were not systematically reviewed. These outcomes are addressed contextually in the **Appendix D**.

Study Design

For KQs 1 and 3, only randomized controlled trials were included. Eligible comparator groups could be allocated to placebo, no intervention, or usual diet. For KQs 2 and 4, we additionally allowed large ($n \geq 1{,}000$) comparative observational studies (cohort or case-control) or post-market surveillance data for outcomes of serious harm. However, we did not include cohort studies reporting on KQ1 and KQ3 outcomes; only randomized controlled trials were considered for studies showing paradoxical harmful effects on mortality, cancer, and CVD.

Quality Assessment and Data Abstraction

Two reviewers independently rated the studies' methodological quality using USPSTF design-specific criteria (**Appendix A Table 4**).[46] Studies were rated as "good," "fair," or "poor," and discrepancies between raters were resolved by discussion or consultation with the larger review team. Good-quality studies were those that met nearly all of the specified quality criteria (e.g., comparable groups were assembled initially and maintained throughout the study and followup was approximately 90% or higher), whereas fair-quality studies did not meet these criteria but did not have serious threats to their internal validity related to their design, execution, or reporting. Poor-quality studies had several important limitations, including at least one of the following risks of bias: very high attrition (generally >40%), differential attrition between

intervention arms (generally >20%); substantial lack of baseline comparability between groups without adjustment; or issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting, inappropriate exclusion of participants from analyses, questionable validity of randomization and allocation concealment procedures, or data for relevant outcomes not collected systematically). Studies rated as "poor" quality were excluded from the review. For trials that had been included in the previous review on this topic, we did not repeat critical appraisal of the original studies. However, we did downgrade cohort studies that had been previously rated as "good" to "fair." We felt that reliance on self-reported supplement use to determine the impact of supplement use along with the non-randomized nature of the studies qualified as "fair" quality data, even if methods were good otherwise. Cohort studies are only included for harms (KQs 2 and 4).

For all of the included studies, one reviewer extracted key data into standardized abstraction forms in DistillerSR (Evidence Partners, Ottawa, Canada). A second reviewer checked the data for accuracy. For each study, we abstracted general characteristics (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race/ethnicity, CVD and cancer risk factors, vitamin use, serum vitamin levels, setting, country), intervention details (e.g., supplement, dose, duration of use), and results (see Outcomes section).

We did not abstract unexpected or paradoxical negative findings for studies with primary aims other than CVD or cancer. We did this because studies reporting paradoxical findings for their main outcome are a skewed subset of the evidence for that outcome. For example, there is a large, separate body of literature on vitamin and mineral supplementation to prevent fractures.[65] In our review, fractures were not abstracted as a benefit or harm from studies with the primary aim of evaluating supplements for fractures. Selective inclusion of fracture outcomes only when findings demonstrated a harm would result in a small, unrepresentative subset of studies being included here. Inclusion of all studies of supplement use to prevent fractures is beyond the scope of this review, since most did not report mortality, CVD, or cancer. Other relevant outcomes that were reported (i.e., mortality, CVD, cancer, other harms) were abstracted from studies designed for fracture prevention. Fractures were abstracted from studies with other aims when reported as harms.

For multifactorial trials with additional randomization to other (non-vitamin or mineral) agents or placebo, we abstracted results for combined groups that compared all participants who received the relevant intervention with all those who did not, ignoring the assignments to the other intervention in the two groups.

During abstraction we noted whether cancer, CVD, or all-cause mortality outcomes had full outcome ascertainment, defined as comprehensive use of a study exam, medical records (with or without independent adjudication), or a health plan database for full capture of the outcome. Outcomes that were taken from participant flow reporting (e.g., CONSORT diagrams) or self-reported in response to open-ended querying of adverse events were not considered to have full outcome ascertainment. Outcome ascertainment status was subsequently used in sensitivity analyses, described further below.

Data Synthesis and Analysis

We created summary tables for all KQs showing study, population, intervention characteristics, and outcomes for qualitative synthesis of the evidence. Analyses were stratified by supplement where multivitamins were addressed in KQs 1 and 2 and single nutrients or functionally related nutrient pairs were addressed in KQs 3 and 4. With regard to our use of terms to describe populations defined by sex or gender, none of the included studies explicitly distinguished between sex and gender, but most referred to "sex" when exploring subpopulations, presumably on the assumption that differences in effects may be related to biologically defined sex (e.g., due to differing impact of hormones or other biochemical differences). Despite this, we assume that sex/gender was collected through participant self-report and thus reflects the participants' gender. Therefore, we use the nouns gender, man, and woman rather than sex, male, and female when referring to participant characteristics.

We conducted quantitative pooling where at least three studies of the same supplement reported the same outcome, however we de-emphasized pooled results when there were few studies and concerning levels of statistical heterogeneity (e.g., more than approximately 30% when combining very few studies, or more than approximately 70% when 10 or more studies were combined). We selected a single effect per study to include in each meta-analysis, preferentially selecting the timepoint corresponding with the end of supplement use and the intervention arm most consistent with the related studies in terms of dose and comparison group (preferring a straightforward comparison of the substance vs. a placebo, rather than a factorial approach comparing use vs. non-use of the supplement). Results for other followup times and groups are available in appendix tables, and in the results text we note the rare cases where longer followup findings differed substantially from the end-of-intervention findings.

For pooling, most outcomes occurred in less than 10 percent of the study sample, so we used methods appropriate for rare events. Consistent with AHRQ's EPC program guidance,[66] when events typically occurred in less than 3 to 4 percent of the sample, study groups were balanced, and effects were in the range of OR=0.2 to 5.0, we used the Peto Odds ratios with a Restricted Maximum Likelihood (REML) model. When events typically occurred in 5 to 10 percent of the sample, we used a fixed effects Mantel-Haenszel model as the primary analysis. When events were typically more common, we pooled standard ORs using a REML model, adding the Knapp-Hartung correction for pooling a small number of studies.[67, 68] Because event rates were usually wide-ranging, we generally performed at least two analyses and report one or more as sensitivity analyses. In tables of pooled results, we list results using multiple approaches; the first effect listed for each outcome is the one judged most appropriate by the study team, and others are considered sensitivity analyses. However, if we judged the most appropriate analysis to be the fixed effects Mantel-Haenszel model, in the text and summary figures we provide I^2 values from the parallel random effects model. We did this in order to provide a sense for statistical heterogeneity in the studies, since fixed effects models assume no statistical heterogeneity and do not calculate I^2.

In some included studies, all cause-mortality, CVD events, and cancer outcomes were only identified through participant flow diagrams or adverse events reporting, or ascertainment was not described, rather than reporting attempts to fully capture these outcomes through means such

as medical record review or death certificates. This was typically the cases when the aim of the study was not related to CVD or cancer. For outcomes with a substantial number of such studies that did not report full ascertainment methods, we conducted sensitivity analyses restricted to studies with full outcome ascertainment for these outcomes. We defined full ascertainment as an attempt to identify these outcomes for all participants with followup assessment, such as through medical records or similar databases or direct examination. Additionally, for vitamin D, which had the largest body of literature, we conducted stratified analyses to explore whether the effect size was associated with the presence of calcium in combination with vitamin D and whether they used large bolus dosing vs. daily or weekly doses. We also conducted meta-regressions to examine the association of dose and effect size, and whether the effect sizes were similar for the previously included and newly added studies. For other supplements, data were generally insufficient to statistically test the impact of dose, however study-level forest plots are sorted by dose, to allow visual inspection of the impact on dose. We detected no pattern of association between dose and effect size for any supplement and do not comment further on dose as an effect modifier.

We used Stata 16.1 (StataCorp LLC, College Station, TX). All significance testing was 2-sided, and results were considered statistically significant if the p-value was 0.05 or less.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each key question. We adapted the Evidence-based Practice Center approach,[69] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[70] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth domain—directness—as it is implied in the structure of the key questions (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

The domain of consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). The domain of precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body-of-evidence limitations field highlights important restrictions in answering the overall key question (e.g., evidence of reporting bias, lack of replication of interventions, nonreporting of outcomes important to patients).

At least two independent reviewers rated the overall strength of evidence for each intervention type. We resolved discrepancies through consensus discussion with the full review team, consulting with outside reviewers as needed. We graded the overall strength of evidence as high, moderate, low, or insufficient. “High” indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of

effects. “Moderate” indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. “Low” indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and to change the estimate. A grade of “insufficient” indicates that evidence is either unavailable or does not permit an estimate of an effect.

Expert Review and Public Comment

The draft Research Plan was posted from May 23, 2019 to June 19, 2019. Comments addressed the inclusion of outcomes and suggestions to examine the influence of patient, supplement, and study characteristics on effect size. Additional specificity was added regarding cancer outcomes and clarifying text was added to note that populations with obesity are included. Metabolic syndrome, atrial fibrillation, and renal disease were added as outcomes that would be reviewed contextually. Comments regarding characteristics that might influence effect sizes were incorporated in our analysis plan. The draft version of this report was reviewed by five invited experts and 3 individuals at USPSTF Federal Partner agencies. Experts were selected based on their expertise with both methodologic and content aspects of the review and were selected to obtain diverse informed perspectives. All expert comments were considered, and the report was updated to improve clarity, ensure accuracy, and address scientifically relevant concerns. All comments were shared with members of the USPSTF and the Agency for Healthcare Research and Quality (AHRQ).

USPSTF Involvement

This systematic review was funded by AHRQ under contract to support the USPSTF. We consulted with USPSTF liaisons at key points in the review regarding the development of the research plan (i.e., KQs, analytic framework, and inclusion and exclusion criteria) and the finalization of the systematic review. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the review, and assisted with public comment on the research plan and draft review. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the systematic review.

Chapter 3. Results

Description of Included Studies

A total of 78 studies (n=694,084) were included, comprising 72 RCTs (n= 303,395)[62-64, 71-139] and six cohort studies (n=390,689),[123, 140-145] which are listed in **Appendix B.** Throughout this report, we will be citing the primary publication from these included studies; ancillary publications that were also considered are listed in **Appendix B**. These studies addressed multivitamins, vitamins A, B3, B6, B12, C, D, E, beta-carotene, folic acid, calcium, selenium, zinc, and magnesium. Fifteen of the studies were included only for harms (KQs 2 and 4), including all of the cohort studies. Overall, 54 studies were newly identified and not included in the previous review. Many of the newly-included studies became eligible due to our more inclusive approach to studies reporting harms or all-cause mortality without CVD or cancer outcomes, but 19 were newly published since the previous review. Most of the new studies since the previous recommendation evaluated vitamin D with or without calcium (35 studies) or multivitamins (8 studies). We found no eligible studies addressing benefits or harms of iron, niacin, or vitamins B1 or B2.

The weighted average age across all included studies was 60.2 years. An estimated 65.9 percent of all participants were women. Among the 33 studies conducted in the United States, 20 provided any information on participants' race or ethnicity. Most participants were non-Hispanic White in studies conducted in the US; in the 14 studies reporting the percent of Black participants, an estimated 21.2 percent were Black. Representation of other racial and ethnic groups was even lower. Studies conducted outside of the US were in Canada, European countries, Australia, and New Zealand. Additional detailed participant characteristics are reported within sections addressing specific supplements.

Across the entire body of evidence, 24 studies (32.9%) had a stated aim of cancer or CVD prevention. The primary aims of the remaining studies were wide ranging. Primary aims in some of the other studies were related to cancer or CVD, such as prevention of colorectal adenomas or CVD risk factors, and other studies' aims were not, such as prevention of bone density loss and fractures, infections, cataracts, or improving mental health and cognitive function.

KQ1. What Is the Efficacy of Multivitamin Supplementation for Reducing Cardiovascular Disease, Cancer, and Mortality in the General Adult Population?

KQ2. What Are the Harms of Multivitamin Supplementation in the General Adult Population?

Summary of Results

Twelve studies of multivitamin use were included (n=218,610, **Table 5**), comprising nine RCTs (n=30,583)[71, 80, 85, 95, 100, 106, 122, 124, 133] and three cohort studies (n=188,027).[140, 142, 145] Most studies had study aims other than the prevention of CVD and cancer, two studies had primary aims of CVD and cancer prevention, both large good-quality trials with dual prevention aims of CVD and cancer. These were SUpplementation en VItamines et Minéraux AntioXydants (SU.VI.MAX, n=13,017),[71] which examined an antioxidant-focused supplement among adults age 35 to 60 years, and the Physicians' Health Study II (PHS-II, n=14,641), which examined a broad-spectrum supplement among male physicians age 50 and older.[80] Four of twelve studies were included in the previous review,[71, 80, 85, 140] including SU.VI.MAX and PHS-II, as well as the largest cohort study.[140] Three studies were conducted in the US.[80, 85, 140] The age ranges in the studies varied considerably, and the average age across all studies was 58.6 years. Among the RCTs, the specific formulations of micronutrients varied (**Table 6**). Followup times ranged from 8 weeks to 13 years.

Eight RCTs reported KQ1 outcomes (n=30,503)[71, 80, 85, 95, 106, 122, 124, 133] and KQ2 outcomes were reported in 8 RCTs (n=30,172)[71, 80, 85, 100, 106, 122, 124, 133] and 3 cohort studies (n=188,027).[140, 142, 145] The evidence suggested no benefits of multivitamin use for all-cause mortality, CVD, and cancer outcomes. The pooled OR for all-cause mortality was a statistically non-significant 0.94 (95% CI, 0.85 to 1.03; 8 RCTs [n=30,108]; I^2=0%, **Figure 2, Appendix E Figure 1**). The largest effect was seen in SU.VI.MAX, in which 1.2 percent of intervention participants had died after 7.5 years, compared with 1.5 percent taking a placebo (RR, 0.77 [0.57 to 1.00]). The pooled effect sizes were similar for cancer mortality (OR, 0.96 [95 % CI, 0.60 to 1.54]; 3 RCTs; n=15,958; I^2=28.0%) and cancer incidence (OR, 0.92 [95 % CI, 0.84 to 1.01]; 3 RCTs; n=27,417; I^2=0%). For cancer incidence, 4.2 percent of participants taking the antioxidant supplement had developed cancer in SU.VI.MAX, compared with 4.6 percent taking the placebo (RR, 0.90 [95% CI, 0.76 to 1.06]) after 7.5 years. Findings were broadly consistent between PHS-II and SU.VI.MAX, despite the differing nutrient formulations. There was no indication that multivitamin use increased the risk of serious harm, but evidence was minimal due to very few serious adverse events being reported. PHS-II found that skin rash and epistaxis were slightly more common with multivitamin use.

Detailed Study Characteristics

Twelve studies of multivitamin use were included (n=218,610, **Table 5**), comprising nine RCTs (n=30,583)[71, 80, 85, 95, 100, 106, 122, 124, 133] and three cohort studies (n=188,027).[140, 142, 145] The best

evidence comes from two large good-quality studies with primary aims of CVD and cancer prevention: SU.VI.MAX (n=13,017)[71] of adults age 35 to 60 years, and PHS-II (n=14,641) of male physicians age 50 and older.[80] Four of twelve studies were included in the previous review,[71, 80, 85, 140] including SU.VI.MAX and PHS-II, as well as the largest cohort study.[140]

The studies were conducted in the U.S., Canada, New Zealand, and European countries. Across all studies, the average age was 58.7 years, and 77.8 percent of participants were women. Race and ethnicity were typically not reported, and ranged from 80 to 100 percent White in the few trials that provided these data.[100, 122, 124]

The specific supplement combinations in the RCTs varied and included both broad-spectrum formulations and those that focused on antioxidants. Followup times among the RCTs ranged from 8 weeks to 13 years. The RCT with 8-week followup was only included for harms.[100] PHS-II (n=14,641),[80] conducted in the U.S., examined the effects of a broad-spectrum multivitamin (Centrum® Silver®) that included 31 different specific nutrients, taken daily for a median of 11.2 years. PHS-II also evaluated vitamin E, vitamin C, and beta-carotene in addition to the multivitamin in a 2x2x2x2 factorial design. SU.VI.MAX (n=14,641),[71] conducted in France, studied the effects of a multivitamin that focused more narrowly on supplements with antioxidant properties, including vitamins A and E, selenium, beta-carotene, and zinc, taken daily for 8 years. Some non-vitamin or mineral substances were included in some supplements, such as lycopene in the PHI-II supplement,[80] and herbal substances such as ginkgo biloba in another trial.[100]

Three large cohorts provided additional evidence on harms with followup ranging from 8 to 18 years, and one study[140] examined several different use durations. Specific dosing was unknown in the cohort studies and was captured by self-report.

Detailed Results by Outcome

Eight RCTs reported KQ1 outcomes (n=30,503) [71, 80, 85, 95, 106, 122, 124, 133] and KQ2 outcomes were reported in 8 RCTs (n=30,172)[71, 80, 85, 100, 106, 122, 124, 133] and 3 cohort studies (n=188,027).[140, 142, 145] See **Appendix F Table 1** for a summary of findings for each trial and **Appendix F Table 2** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 3, 4, 5,** and **6**.

All-Cause Mortality (KQ1)

All-cause mortality was reported in eight trials.[71, 80, 85, 95, 106, 122, 124, 133] The largest trials showed small effect sizes in the direction of benefit that were not statistically significant.[71, 80] The largest effect was reported by SU.VI.MAX; after 7.5 years, 1.2 percent taking an antioxidant-focused multivitamin had died, compared with 1.5 percent taking a placebo.[71] This finding was very close to being statistically significant (RR, 0.77 [95% CI, 0.57 to 1.00]). The effect was smaller and not statistically significant after 12 years (RR, 0.87 [95% CI, 0.70 to 1.04]). PHS-II reported 18.4 percent all-cause mortality among those taking a broad-spectrum multivitamin after a median of 11.2 years, compared with 19.3 percent who were not taking the multivitamin (HR, 0.94 [95% CI, 0.88 to 1.02]).[80] The overall mortality rate was lower in SU.VI.MAX than PHS-II,

consistent with the mean age being 16 years younger in SU.VI.MAX than PHS-II. The pooled effect was consistent with these studies and was not statistically significant (OR 0.94 [95% CI, 0.85 to 1.03]; 8 RCTs [n=30,108]; I^2=0%, **Figure 2**). The effect size was very similar when limited to studies with full ascertainment and was not statistically significant (**Appendix F Table 2**).

SU.VI.MAX[71] examined the effect of multivitamin use on all-cause mortality by gender, and although the interaction term with gender was not statistically significant, it found reduced mortality in men at 7.5 year follow (RR, 0.63 [95% CI, 0.42 to 0.93]) but not women (RR, 1.03 [95% CI, 0.64 to 1.63]). This effect was less pronounced at the 12-year followup when the effect size for men was no longer statistically significant (RR, 0.78 [95% CI, 0.59 to 1.04]), vs. RR, 0.99 [95% CI, 0.71 to 1.38]) in women. No other studies reported outcomes in specific populations, such as by gender, age, race, or ethnicity.

Cardiovascular Events (KQ1)

Cardiovascular events were reported in four trials[71, 80, 85, 133] but only PHS-II[80] and SU.VI.MAX[71] reported full ascertainment of CVD outcomes (and had primary aims of CVD prevention). Both trials found no association between multivitamin use and CVD events. PHS-II reported no group differences in MI (HR, 0.93 [95% CI, 0.80 to 1.09]), stroke (HR, 1.06 [95% CI, 0.91 to 1.23]), or the composite CVD events outcome (HR, 1.01 [95% CI, 0.91 to 1.10]).[80] SU.VI.MAX similarly found no group differences in coronary heart disease events after 7.5 years (RR, 0.97 [95% CI, 0.77 to 1.20]) and 11.2 years (RR, 0.97 [95% CI, 0.80 to 1.17]).[71] The only outcome with sufficient data to pool was CVD mortality, which demonstrated no association with multivitamin use (OR, 0.95 [95 % CI, 0.83 to 1.09]; 3 RCTs; n=15,958; I^2=0%, **Figure 2, Appendix E Figure 2**).

SU.VI.MAX reported examination of differential effects on CVD outcomes for our a priori specific populations; it found that effects did not differ for men and women. In addition PHS-II[80] found a differential effect across age groups in cardiovascular events (interaction p=0.041). The largest difference was between men aged 50 to 59 (HR, 1.27; 95% CI 0.99 to 1.63) and men aged 70 years and older (HR, 0.91; 95% CI 0.81 to 1.03). PHS-II found no suggestion of variability in effect across other clinical, lifestyle, familial, biochemical or dietary risk factors. PH-II was limited to men, so could not examine differences by gender. No other studies reported outcomes in specific populations, such as by gender, age, race, or ethnicity.

Cancer (KQ1)

Four trials reported cancer outcomes,[71, 80, 85, 133] but again, only PHS-II[80] and SU.VI.MAX[71] reported full cancer ascertainment. SU.VI.MAX reported small, statistically non-significant effect sizes for any cancer incidence at 7.5 years (RR, 0.90 [95% CI, 0.76 to 1.06]) and 12.5 years (RR, 0.93 [95% CI, 0.82 to 1.05)]. At 7.5 years, 4.2 percent of participants taking the antioxidant supplement developed cancer, compared with 4.6 percent taking the placebo. SU.VI.MAX also reported a number of site-specific cancers, and effect sizes were wide ranging, reflecting the small number of events; most were in the direction of a benefit, but none were statistically significant.[71] PHS-II[80] specified both any cancer and prostate cancer as primary

outcomes, and their findings were similar to SU.VI.MAX. In PHS-II, overall cancer incidence demonstrated a small, statistically significant effect after 11.2 years (HR, 0.92 [95% CI, 0.85 to 1.00]). The pooled OR for cancer incidence was 0.92 (**Figure 2, Appendix E Figure 3**), but statistical significance differed between the random effects restricted maximum likelihood model with the Knapp-Hartung correction (95% CI, 0.84 to 1.01; I^2=0%) and the fixed effect model (95% CI, 0.85 to 0.99; 3 RCTs; n=27,417, **Appendix F Table 2**), which weights large studies more heavily than random effect models. Results were even more discrepant between pooling methods for cancer mortality, but neither had a statistically significant effect.

SU.VI.MAX[71] found an interaction between cancer incidence and gender, such that there was a protective effect of multivitamin use in men (RR, 0.69 [95% CI, 0.53 to 0.91] but not women (RR, 1.04 [95% CI, 0.85 to 1.29). In addition, PHS-II[80] found that the effect on any cancer incidence was largest among men age 70 and older (HR, 0.82 [95% CI, 0.72 to 0.93, vs. HRs 0.96 and 1.01 in among ages 50-59 and 60-69, respectively). However, this interaction was not statistically significant (p=0.06). No other studies reported outcomes in specific populations, such as by gender, age, race, or ethnicity.

Adverse Events (KQ2)

Four of the trials reported no group differences in any adverse effects,[106, 133] serious adverse effects,[85] or withdrawals due to adverse effects,[100] although very few events were reported for the serious adverse effects or withdrawals due to adverse effects (**Appendix F Table 6**). Small increases in cataracts[140, 145] and hip fractures[140] reported by cohort studies were not statistically significant and were not examined in any of the trials. There was evidence of no effect modification by age or smoking status on cataracts in NHS-I.[140] Several studies found no clear increased risk in gastrointestinal-related outcomes (nausea, constipation, GI symptoms, or GI-related hospitalizations), but most were hampered by small sample sizes and reported very few events.[100, 122, 124, 133] PHS-II found an increased risk of skin rash (29.0% among multivitamin users, 27.3% among non-multivitamin users; OR, 1.06 [95% CI, 1.01 to 1.12]) and epistaxis (21.6% among multivitamin users, 19.8% among non-multivitamin users; OR, 1.09 [95% CI, 1.02 to 1.16]).

KQ3. What Is the Efficacy of Supplementation With Single Nutrients or Functionally Related Nutrient Pairs for Reducing Cardiovascular Disease, Cancer, and Mortality in the General Adult Population?

KQ4. What Are the Harms of Supplementation With Single Nutrients in the General Adult Population?

Results for KQs 3 and 4 are organized by supplement, with results for KQ4 (harms) immediately following results for KQ3 (benefits) for each supplement or supplement group. The order of the supplements is: fat soluble (beta-carotene and vitamin A, vitamin D, vitamin E), water-soluble (B vitamins, vitamin C), and minerals (calcium, selenium, zinc, magnesium).

Beta-Carotene and Vitamin A

We discuss beta-carotene and vitamin A together since they are functionally related supplements. Beta-carotene is a vitamin A precursor, which is converted by the body into vitamin A.

Summary of Results

Beta-Carotene

Seven studies of beta-carotene supplementation with or without the use of other supplements were included (n=234,520, **Table 7**): 6 RCTs (n=112,820)[62, 72-75, 86] and one cohort study (n=121,700).[140] There are no newly included studies in this update. The included trials had a variety of study aims and primary outcomes. Two studies—PHS-I[74] and the Women's Health Study (WHS)[73] —had broad cancer and CVD prevention aims and the remaining focused more narrowly on the prevention of lung cancer[62, 75] and skin cancer,[72, 86] all but one study targeting populations at high risk for cancer.[72] Doses of beta-carotene ranged from 20 to 50 mg/day and was co-administered with high-dose vitamin A in CARET[62] (25,000 IU/day, exceeding the current recommended upper limit). Duration of use ranged from 4 years in a study terminated early due to harm,[62] to 12 years.[74] Five of seven included studies were conducted in the U.S.[62, 73, 74, 86, 140]

All 6 RCTs (n=112,820) reported both KQ3 and KQ4 outcomes, plus the 1 cohort study was included for KQ4 (n=121,700). Pooled estimates for several outcomes showed statistically significant paradoxical harm associated with beta-carotene use (**Figure 3**). The most pronounced risk increase was for lung cancer, with the pooled estimate showing a 20 percent increased risk over 3.7 to 12 years of followup (OR 1.20 [95% CI, 1.01 to 1.42]; 4 RCTs [n=94,830]; I^2=38.8%), including trials in general and high-risk populations. CVD mortality similarly showed an increased risk, however with a smaller magnitude (OR 1.09 [95% CI, 1.01 to 1.18]; 5 RCTs [n=94,506]; I^2=0%). Pooled estimates also suggested an increased risk of all-cause mortality associated with beta-carotene use, although the lower confidence interval was 1.00 (OR 1.06 [95% CI, 1.00 to 1.12]; 6 RCTs [n=112,820]; I^2=6.4%); estimates were statistically significant in a sensitivity analysis using an alternate pooling method and when a study of vitamin A supplementation was included (**Appendix F Table 7**). Trials generally showed no statistically significant findings for other adverse events other than hypercarotenodermia, a nonserious and reversible yellowing of the skin.

Vitamin A

Four studies of vitamin A supplementation with or without the use of other supplements were included (n=177,014): two RCTs (n=20,611)[62, 63] and two cohort studies (n=156,403)[140, 141] (**Table 8**). There are no newly included studies in this update. Two of these studies are also discussed for beta-carotene: CARET, which co-administered vitamin A and beta-carotene, and the NHS-I cohort study. The two studies that only address vitamin A were the SKICAP trial—reporting all-cause mortality and any adverse events—and an additional harms cohort . SKICAP was a fair-quality U.S-based skin cancer prevention trial (n=2,297) recruiting participants with a history of more than 10 actinic keratoses and at most 2 squamous cell carcinoma or basal cell

carcinoma skin cancers.[63] SKICAP evaluated supplementation with 7,500 retinol activity equivalents (RAE) alone (25,000 IU retinol) for 5 years. This is a large dose equating to more than double the upper intake levels for preformed vitamin A.[146]

Both RCTs (n=20,611) reported both KQ3 and KQ4 outcomes, plus the 2 cohort studies were included for KQ4 (n=156,403). In the SKICAP trial, there were 62 deaths (5.4%) in the supplementation group compared to 53 deaths (4.6%) in the placebo group during 5-years of followup (OR 1.16 [95% CI, 0.80 to 1.69]) (**Figure 4**).[63] The addition of the SKICAP trial to the beta-carotene pooled estimate for all-cause mortality resulted in the same point estimate, but did make the finding statistically significant for increased harm (OR 1.06 [95% CI, 1.01 to 1.12]; 7 RCTs [n=115,117]).

The incidence of any adverse effect was higher in participants in SKICAP randomized to vitamin A vs. those randomized to placebo (OR 1.77 [95% CI, 1.49 to 2.09]).[63] The cohort studies suggested a possible association between vitamin A use and hip fractures, but did not indicate an association with overall fracture risk or cataracts.

Detailed Study Characteristics

Beta-Carotene

Seven studies of beta-carotene supplementation with or without the use of other supplements were included (n=227,234).[62, 72-75, 86, 140] These studies include six RCTs[62, 72-75, 86] and one cohort study[140] evaluating harms only (**Table 7**). There are no newly included studies in this update. All of the RCTs were rated as good quality. While the included cohort study, the Nurses' Health Study,[140] is a large cohort study that generally used good methods, we rated it as fair quality because of self-reported supplement use and the inability of cohort studies to fully adjust for potential counfounders.

The included trials had a variety of study aims and primary outcomes. Two studies—PHS-I[74] and WHS[73]—had broad cancer and CVD prevention aims. Both were factorial design trials additionally evaluating aspirin, and also vitamin E in WHS. Two trials, ATBC[75] and CARET,[62] had primary aims of lung cancer prevention and evaluated beta-carotene supplementation in high-risk populations such as smokers and asbestos-exposed workers. ATBC was multifactorial, with additional randomization to 50 mg/day vitamin E. Two studies, NSCPS[72] and SCPS,[86] were focused on beta-carotene supplementation with the aim of skin cancer prevention. NSCPS was conducted in the general population and was a 2x2 trial also including a sunscreen intervention. SCPS was a secondary skin cancer prevention study and we only include outcomes other than skin cancer because of the primary prevention focus of this review. All trials except NSCPS reported full ascertainment for all main outcomes for our review. NSCPS described outcome ascertainment for only its primary outcome of incident skin cancer.[72] The included cohort for harms, NHS,[140] ascertained hip fractures from self-report.

Doses of beta-carotene ranged widely in included studies, from as low as 20 mg/day in ATBC[75] to as high as 50 mg/day in SCPS.[86] Duration ranged from as little as 4 years in CARET,[62] which was terminated early due to harm, to 12 years in PHS.[74] Five of seven included studies were

conducted in the U.S.[62, 73, 74, 86, 140] Additional studies were conducted in Finland,[75] and Australia.[72] Where race and ethnicity were reported, the vast majority of participants were White. Mean ages ranged from 49 to 63 years. In the RCTs, the percent of participants who were female ranged from 0% to 100%, and the cohort study was limited to women.

The trials with broader cancer and CVD prevention aims were very large, with 22,071 participants in PHS-I,[74] which were exclusively male and 39,876 participants in WHS, which was exclusively female.[73] Eleven to 13 percent were smokers in these trials and mean BMIs were 25 to 26 kg/m^2. The lung cancer prevention trials were also large, including 29,133 participants in ATBC[75] and 18,314 participants in CARET.[62] These trials were conducted primarily in men with ATBC being exclusively male and CARET 66 percent male.[62] ATBC recruited current smokers and CARET recruited individuals with workplace asbestos exposure or a 20 pack-year history of smoking who currently smoked or quit within the previous 6 years. The skin cancer prevention studies were smaller, with 1,621 participants in NSCPS[72] and 1,805 participants in SCPS.[86] These studies were 44 and 69 percent male, respectively. NSCPS was conducted in the general population whereas SCPS recruited individuals with prior biopsy-proven basal or squamous cell carcinoma. Nineteen percent of the SCPS population were smokers; smoking was not reported in NSCPS. Across all studies, baseline levels of beta-carotene were sparsely reported.

Vitamin A

Four studies of vitamin A supplementation with or without the use of other supplements were included (n=177,014).[62, 63, 140, 141] These studies include two RCTs[62, 63] and two cohort studies[140, 141] evaluating harms only (**Table 8**). There are no newly included studies in this update.

SKICAP is the only trial that was not included in the section above on beta-carotene. It reported all-cause mortality and any adverse events. SKICAP was a fair-quality U.S-based skin cancer prevention trial recruiting participants at moderate risk for new nonmelanoma skin cancer, defined as a history of more than ten actinic keratoses and at most two squamous cell carcinoma or basal cell carcinoma skin cancers.[63] SKICAP evaluated supplementation with 7,500 RAE alone (25,000 IU retinol) for 5 years. This is a large dose equating to more than double the upper intake levels for preformed vitamin A.[146] SKICAP included 2,297 participants, the mean age of which was 63 years; 30 percent were female, and 12 percent were current smokers. Ascertainment methods for all-cause mortality were not described. Two large U.S.-based cohort studies evaluating vitamin A supplementation were included for harms only—the Nurses' Health Study (n= 121,700)[140] and the Iowa Women's Health Study (IWHS, n= 34,703).[141] Both cohort studies used generally good methods, but were rated as fair quality because of self-reported supplement use and the inability to fully adjust for confounders. These cohorts consisted of women who were predominately White, with mean ages between 58 and 62 years. Mean BMIs were 26 to 27 kg/m^2. Twenty-six percent of those in the Nurses' Health Study were current smokers and 34 percent in IWHS had ever smoked. In the Nurses' Health Study, vitamin A exposure was ascertained every 2 years over 18 years of followup.[140] In IWHS, vitamin A exposure was ascertained at baseline only and reported after 9 years of followup.[141] Both cohorts ascertained the reported outcomes of fractures and cataracts through self-report.

Detailed Results by Outcome

All 6 RCTs (n=112,820) reported both KQ3 and KQ4 outcomes for beta-carotene, plus the 1 cohort study was included for KQ2 (n=121,700). Similarly, both RCTs (n=20,611) reported both KQ1 and KQ2 outcomes for vitamin A, plus the 2 cohort studies were included for KQ2 (n=156,403). See **Appendix F Tables 8 and 9** for a summary of findings for each trial for beta-carotene and vitamin A, respectively, and **Appendix F Table 7** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 10, 11, 12, 13, 14,** and **15**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in all six RCTs of beta-carotene.[62, 72-75, 86] The pooled effect showed a statistically non-significant increased risk for all-cause mortality associated with beta-carotene use over 4 to 12 years of followup (OR 1.06 [95% CI, 1.00 to 1.12]; 6 RCTs [n=112,820]; **Figure 3, Appendix E Figure 4**). The increased risk for all-cause mortality was statistically significant in ATBC,[75] a lung cancer prevention trial (ATBC: OR 1.09 [95% CI, 1.02 to 1.17], for the beta-carotene vs. no beta-carotene contrast). The odds ratio was above 1.0, although not statistically significant, in all other studies except NSCPS,[72] which did not have full ascertainment for this outcome. The pooled results became statistically significant when dropping this study in a sensitivity analysis (OR 1.06 [95% CI, 1.01 to 1.12], 5 RTCs [n=111,199]; **Appendix F Table 7**). We also conducted a sensitivity analyses that was limited to studies that did not include concomitant vitamin A supplementation, so dropping the CARET study. The result was identical to the full analysis (OR 1.06 [95% CI, 1.00 to 1.12], 5 RCTs [n=94,506]; **Appendix F Table 7**). CARET followed participants for 6 years after early termination of the randomized treatment period and an increased risk for all-cause mortality persisted (OR 1.13 [95% CI, 1.04 to 1.23]).[62] The slightly elevated but statically non-significant increase in risk for all-cause mortality was similar at the 5 year- and extended 8.2-year followup in SCPS.[86]

One additional study of vitamin A supplementation, SKICAP, reported all-cause mortality.[63] There were 62 deaths in the supplementation group compared to 53 deaths in the placebo group during 5-years of followup (OR 1.16 [95% CI, 0.80 to 1.69] (**Figure 4**). The addition of the SKICAP trial to the pooled estimate for all-cause mortality resulted in the same point estimate, but did make the finding statistically significant for increased harm (OR 1.06 [95% CI, 1.01 to 1.12]; 7 RCTs [n=115,117]).

CARET found that, among heavy smokers, effect sizes were similar for men and women, but the harmful effects were only clearly present for female heavy smokers after 10 years (RR, 1.37 [95% CI, 1.16 to 1.62] for women; RR, 1.00 [95% CI, 0.89 to 1.13] for men).[62] None of the other beta-carotene or vitamin A studies reported examination of effect modification for all-cause mortality by age, gender, race, or ethnicity. PHS-I reported that the effect of beta-carotene on all-cause mortality did not differ by smoking status (never, former, or current smoker), but no women were included in this study.[74] The ATBC study, also limited to men, did report some variability in effects by baseline daily cigarette use and age of smoking initiation, with the largest

association between beta-carotene and mortality in men who were heavier smokers and initiated smoking at age 21 years or older.[75]

Cardiovascular Outcomes (KQ3)

CVD mortality was the most commonly reported CVD outcome in this body of literature and was reported by all six RCTs of beta-carotene.[62, 72-75, 86] The pooled effect showed a statistically significant increased risk for CVD mortality associated with beta-carotene supplementation at 4 to 12 years of followup (Peto OR 1.10 [95% CI, 1.02 to 1.19]; 5 RCTs [n=94,506]; I^2=0%; **Figure 3, Appendix E Figure 5**). Results were identical using different pooling methods and were very similar when dropping one study without full outcome ascertainment[72] (**Appendix F Table 7**). However, this pooled estimate is likely an underestimate of increased risk as reporting for CARET at 3.7 year study termination was insufficient to include in pooled analyses, but suggested a larger magnitude of increased risk (RR 1.26 [95% CI, 0.99 to 1.61]).[62] Six-year post-intervention followup in CARET showed that the CVD mortality risk dissipated after supplementation stopped (RR 1.02 [95% CI, 0.88 to 1.19]).

In addition to CVD deaths, PHS-I[74] and WHS[73] also reported composite CVD events, MI, and stroke. For composite CVD events, defined in both trials as nonfatal MI, nonfatal stroke, and CVD deaths, results were not statistically significant in either trial (PHS: RR 1.00 [95% CI, 0.91 to 1.09]; WHS: RR 1.14 [95% CI, 0.87 to 1.49]). Neither MI nor stroke showed an association with beta-carotene in either trial; however, WHS did show a notably elevated point estimate for stroke (RR 1.42 [95% CI, 0.96 to 2.10]). The pooled effects were similarly not statistically significant for CVD event outcomes.

The SKICAP trial of vitamin A supplementation did not report CVD outcomes. None of the beta-carotene or vitamin A studies reported examination of effect modification for CVD outcomes by age, gender, race, or ethnicity. PHS-I reported that the effect of beta-carotene on CVD events and CVD mortality did not differ by smoking status (never, former, or current smoker).[74]

Cancer (KQ3)

Some type of cancer outcome was reported in all six trials of beta-carotene (alone or with vitamin E or vitamin A[62, 72-75, 86] and the one trial of vitamin A supplementation alone.[63] Pooled estimates showed a statistically significant increased risk of lung cancer associated with beta-carotene use, with or without other supplements at 3.7 to 12 years of followup (Peto OR 1.20 [95% CI, 1.01 to 1.42]; 4 RCTs [n=94,830]; I^2=38.8%; **Figure 3, Appendix E Figure 6**). Confidence intervals were tighter in a sensitivity analysis with the Mantel-Haenszel common effects model, but the point estimate was nearly identical (OR 1.21 [95% CI, 1.07 to 1.36], **Appendix E Table 7**).

Lung cancer risk was statistically significantly increased in both trials with a lung cancer prevention aim where populations were smokers or those with workplace asbestos exposure (ATBC: RR 1.18 [95% CI, 1.03 to 1.36]; CARET: adjusted RR 1.28 [95% CI, 1.04 to 1.57].[62, 75] In ATBC, 3.3 percent of participants taking beta-carotene developed lung cancer, compared with

2.8 percent who were not taking beta-carotene after a median of 6.1 years.[75] In ATBC, results of statistically significant harm for increased lung cancer risk persisted at 8 and 11 years of followup; at 14 and 24.1 years of followup, point estimates remained above 1 but no longer retained statistical significance.[75] When we dropped CARET to see the impact of beta-carotene without vitamin A, from the pooled analysis, the result was no longer statistically significant (OR 1.12 [95% CI, 0.96 to 1.31], 3 RCTs [n=76,516], **Appendix F Table 7**). This limited the meta-analysis to the 3 studies that investigated beta-carotene without vitamin A and included one high-risk study sample and two non-high-risk samples.

CARET also reported the incidence of lung cancer for the 6 years after the intervention period ended (when participants were no longer taking the study supplement), excluding cases that occurred during the main intervention phase of the study. In this post-intervention-only analysis, the increased lung cancer risk tempered somewhat after and was no longer statistically significant (RR 1.12 [95% CI, 0.97 to 1.31]). Results were not statistically significant in two trials conducted in healthier populations with lower lung cancer incidence, with point estimates both below and above 1.0 (PHS: OR 0.93 [95% CI, 0.69 to 1.26]; WHS: OR 1.48 [95% CI, 0.85 to 2.57)].[73, 74] An additional study focused on skin cancer, SCPS, reported lung cancer mortality and found no statically significant differences associated with beta-carotene use, but there were only 30 total lung cancer deaths over 8.2 years of followup (OR 0.74 [95% CI, 0.36 to 1.54]).

In trials reporting both lung cancer incidence and mortality, results were generally consistent between the two outcomes. Notably, six-year post-intervention followup in CARET showed that the increased lung cancer mortality risk persisted after supplementation stopped (RR 1.20 [95% CI, 1.01 to 1.43]), in contrast to lung cancer incidence.[62] ATBC found that the effect of beta-carotene on lung cancer was not affected by baseline serum levels.[75] That study also reported no differential impact of beta-carotene use by serum level on other site-specific cancers.

Pooled outcomes for all cancer mortality, any cancer incidence, colorectal, breast, and prostate cancer showed no statistically significant differences in risk associated with beta-carotene use with ORs ranging from 0.97 (95% CI, 0.80 to 1.16; 2 RCTs [n=46,165]; I^2=0%;) for breast cancer to 1.03 (95% CI, 0.92 to 1.14; 3 RCTs [n=48,665]; I^2=0%;) for prostate cancer. Prostate cancer neared statistical significance for increased risk in the beta-carotene vs. no beta-carotene comparisons in ATBC at 6.1 years of followup (OR 1.24 [95% CI, 0.96 to 1.59]; 0.9% with beta-carotene, 0.8% in the control group)].[75]

Two studies evaluating beta-carotene or vitamin A for primary skin cancer prevention showed mixed results. The NSCPS was a primary skin cancer prevention study in the general population evaluating beta-carotene supplementation and sunscreen in a 2x2 design.[72] Results showed no statistically significant association between beta-carotene supplementation and basal cell carcinoma or squamous cell carcinoma when analyzed either by number of participants or number of tumors. In SKICAP, a skin cancer prevention trial of vitamin A alone,[63] vitamin A supplementation was associated with a reduced risk of new squamous cell carcinoma (HR 0.74 [95% CI, 0.56 to 0.99]) but showed no statistically significant association with new basal cell carcinoma at 5 years of followup (HR 1.06 [95% CI, 0.86 to 1.32]).

ATBC found no impact of age on the association between beta-carotene use and cancer incidence.[75] No other studies of beta-carotene or vitamin A reported on differential effects on cancer outcomes by age, gender, race, or ethnicity.

Adverse Events (KQ4)

Overall, six RCTs[62, 72-75, 86] and one cohort study[140] report on the harms of beta-carotene supplementation, with or without the use of other supplements (**Appendix F Table 13**). The most substantial harms are the paradoxical harms of increased all-cause mortality, CVD mortality, and lung cancer described above. Trials generally showed no statistically significant findings for other adverse events other than hypercarotenodermia, and GI symptoms in the one trial reporting these outcomes.

For beta-carotene, there was a consistent and statistically significantly increased risk of hypercarotenodermia in the four trials reporting this adverse event at 2 to 12 years of followup.[73-75, 86] Odds ratios ranged from 1.11 to 6.84 in three trials reporting the incidence of hypercarotenodermia;[73-75] in the one trial reporting withdrawal due to this outcome, there were 12 withdrawals in those taking beta-carotene vs. 0 events in those not taking beta-carotene.[86] The only other harm for which there was a statistically significant increased risk from beta-carotene supplementation was GI symptoms in PHS which occurred in 2.5 percent of the intervention group compared to 1.1 percent of the control group at 12 years of followup (OR 2.25 [95% CI, 1.82 to 2.78]).[74] No other study reported this outcome.

The one cohort study of beta-carotene included for harms outcomes only was the Nurses' Health Study, which evaluated the association between the self-reported use of beta-carotene and hip fractures at 14 years of followup.[140] No association was seen between supplementation and this outcome (adjusted RR 0.91 [95% CI, 0.57 to 1.44]).

In the one trial of vitamin A supplementation without beta-carotene, the cumulative incidence of any composite clinical or laboratory adverse symptom was higher in participants randomized to vitamin A vs. those randomized to placebo (OR 1.77 [95% CI, 1.49 to 2.09], **Appendix F Table 15**).[63] Laboratory abnormalities were more common than clinical symptoms and showed generally higher serum cholesterol levels, elevated liver enzymes, and lower hemoglobin levels in the vitamin A group; however, group differences were not statistically significant for of any one type of abnormal lab value.

Two large cohort studies of vitamin A supplementation, conducted in women who were primarily White, both suggest a possible increased risk for hip fracture, although results were not statistically significant in the individual studies.[140, 141] In the Nurses' Health Study, current use of vitamin A supplements compared to no use was associated with an adjusted 40 percent increased risk for hip fracture at 18 years of followup (95% CI, 0.99 to 1.99);[140] however, there were only 36 hip fractures in women taking supplements. In IWHS, the adjusted increased risk for hip fracture associated with vitamin A supplementation was 18 percent at 9.5 years of followup (95% CI, 0.99 to 1.41).[141] No dose-response relationship was identified. There was no increased risk for all fractures associated with vitamin A supplementation at 9.5 years of followup (RR 1.00 [95% CI, 0.95 to 1.05]).

Evidence for the association between vitamin A supplementation and risk of cataract extraction is available from the Nurses' Health Study.[140, 147] Results are reported for past use and various durations of use compared to no use. No single comparison was statistically significant; however, a possible increased risk was detected in those with less than 2 years supplementation compared to no supplementation (adjusted RR 1.39 [95% CI, 0.97 to 1.98]). Only 32 cataract extractions occurred in those with this short duration of exposure, so confidence intervals are wide.

No studies reported on differential effects on adverse outcomes by age, gender, race, or ethnicity.

Vitamin D

Summary of Results

Thirty-eight studies of vitamin D supplementation with or without calcium were included (n=390,565, **Table 9**), comprising 35 RCTs (n=100,906)[64, 78, 82, 87, 88, 90-94, 99, 102, 107, 110-121, 123-125, 127, 128, 130, 134, 135, 138] and three cohort studies (n=289,659).[140, 143, 144] Only six of the RCTs[64, 78, 82, 87, 88] and one of the cohort studies[140] were included in the previous review.

Most of the studies had aims related to bone density, fractures, or falls and were primarily limited to adults aged 55 years and older. However, four explicitly aimed to prevent CVD[78, 88, 91, 93] and six had a cancer prevention aim.[78, 82, 88, 90, 92, 93] The two largest studies were the Women's Health Initiative (WHI, n=36,282)[78] which examined the effects of 400 IU vitamin D and 1000 mg calcium use daily, and VITamin D and OmegA-3 TriaL (VITAL, n=25,871),[93] which tested the effects of 2000 IU/day of vitamin D, with or without an Omega-3 fatty acid supplement in a 2x2 factorial design. Both studies had specific aims of cancer and CVD prevention among adults age 50 years and older. VITAL was newly published and not included in the previous review. In the RCTs, doses ranged from 20 to 5000 IU/day for 1 month to 7 years and followup time ranged from 1 month to 11.9 years. Studies administered D3 in all cases, as cholecalciferol, alfacalcidol, or calcitriol, among studies reporting the specific agent.

Thirty RCTs reported KQ3 outcomes (n=99,095) and KQ4 outcomes were reported in 30 RCTs (n=93,296) and 3 cohort studies (n=289,659). Evidence indicated that vitamin D, with or without calcium co-supplementation, reduced the risk of cancer-specific mortality (**Figure 5**) may have a small benefit for all-cause mortality. Pooled estimates indicated a statistically non-significant 6 percent lower odds of all-cause mortality (OR, 0.94 [95% CI, 0.89 to 1.00]; 24 RCTs [n=93,003]; I^2=0%; **Figure 5, Appendix E Figure 7**) and an 11 percent lower odds of cancer mortality (OR, 0.89 [95% CI, 0.80 to 0.99]; 6 RCTs [n=74,237]; I^2=0%; **Figure 5, Appendix E Figure 8**). However, evidence suggested no benefit for the incidence of cancer (**Figure 5, Appendix E Figures 8, 9**) or CVD events (**Figure 5, Appendix E Figure 10**). For example, the pooled effects for the composite outcomes of any CVD events (OR, 1.00 [95% CI, 0.95 to 1.05]; 6 RCTs [n=72,430]; I^2=0%) and incidence of any cancer (OR, 0.97 [95% CI, 0.92 to 1.03]; 17 RCTs [n=82,019]; I^2=0%) were both fairly precise estimates demonstrating no benefit. Both trial and cohort studies suggested an increased risk of kidney stones with 7 years or more of vitamin D use, particularly with doses of 1000 IU/day or more, with or without concomitant calcium use.

Point estimates were very similar when limited to studies with full ascertainment, those examining vitamin D without calcium, and those examining vitamin D and calcium combined (**Appendix F Table 16**). Findings were also robust to different pooling methods. In addition, for all-cause mortality, composite CVD events, and any cancer incidence there was no clear association between effect size and vitamin D dose or the use of bolus dosing (e.g., 100,000 IU monthly), nor was there a difference in effect size between the studies in the previous review and newly-included studies.

Detailed Study Characteristics

Thirty-five RCTs (n=100,906)[64, 113, 123 78, 82, 87, 88, 90-94, 99, 102, 107, 110-112, 114-121, 124, 125, 127, 128, 130, 134, 135, 138] and three cohort studies[140, 143, 144] (n= 289,659) of vitamin D use were included, for a total of 390,565 participants (**Table 9**). Six of these studies were included in the previous review.[64, 78, 82, 87, 88, 140] Twenty of the 32 newly included studies became eligible due to our slightly broader inclusion criteria rather than recent publication, and these studies typically collected CVD and cancer outcomes as part of their adverse events reporting, if at all, rather than having robust ascertainment of these outcomes from medical records or other comprehensive sources. However, some newly included trials did have CVD or cancer aims, including the large VITAL study[93] (n=25,871) for CVD and cancer prevention, ViDA[91] (n=5,110) for CVD prevention, and a study by Lappe and colleagues[92] (n=2,303) for cancer prevention.

Eleven[64, 78, 90-94, 118, 135, 138, 139] of the included studies (all RCTs) were rated as good quality and the remaining studies were fair quality. Many of the fair-quality RCTs were downgraded because they lacked robust ascertainment of the outcomes pertinent to our review (cancer, CVD), since most were designed to address other outcomes. Full ascertainment of the main outcomes for this review were reported by 10[78, 87, 88, 91-93, 111, 117, 121, 138] trials for all-cause mortality, 6[78, 88, 90, 91, 93, 138] for CVD events, and 7[78, 82, 88, 90-93] for cancer incidence. The cohort studies were large and generally used good methods, however we rated them as fair quality because of their reliance on self-reported supplement use and inability to fully control for confounders.

Four studies[78, 88, 91, 93] had an explicit aim of CVD prevention and three additional trials aimed to improve CVD risk factors.[99, 114, 119] Six had a cancer prevention aim,[78, 82, 88, 90, 92, 93] plus one additional trial examined markers of apoptosis in colorectal mucosa.[113] All three of the cohort studies examined the association between varying levels of self-reported vitamin D supplement use and kidney stones.[140, 143, 144] Among the RCTs, 23 (65.7%) examined the use of vitamin D without calcium, nine (22.5%) examined the use of vitamin D and calcium together, and three[88, 90, 113] had factorial designs examining vitamin D and calcium use alone and in combination. The most common doses were 800 and 1000 IU daily, and doses ranged from 20 to 5000 IU/day taken for 1 month to 7 years, with followup ranging from 1 month to 11.9 years post-baseline. Seven studies[87, 91, 99, 115, 116, 118, 138] used bolus dosing, administering 100,000 to 500,000 IU at once, with periodicity ranging from monthly to annually. Only one of these had a study aim pertinent to this review, the VIDA study,[91] which administered 100,000 IU per month for CVD prevention. Almost all doses were within the recommended daily upper limit of 4000 IU, including the bolus dosing when divided by the number of days between doses. The only exception was one small study that only reported harms and was included in the previous review, which administered 5000 IU daily for one month to promote optimal cognitive and emotional

functioning.[64] Calcium doses ranged from 93 to 2000 mg/day. The cohort studies included participants taking a range of daily doses and duration of vitamin D use, with supplement use based on self-report.

Fourteen of the studies were conducted in the U.S., and the remaining were conducted in Canada, Europe, Australia, and New Zealand. The mean ages were in the 60s or older (weighted average age of 66 years), most studies were majority or entirely female (75% of participants across all trials were female), and mean BMIs were most commonly in the overweight range (weighted average BMI of 28.5 kg/m^2). The samples were predominantly of White race, however some studies of bone loss were limited to Black women.[102, 130] In the very large VITAL study, 20 percent of participants were Black, but that study had very limited representation of other people of color or Hispanic persons.[93] Across all studies reporting baseline 25(OH)D, the median (interquartile range [IQR]) for baseline serum level was 63 nmol/L (52 to 72 nmol/L), suggesting few participants had vitamin D deficiency.

Detailed Results by Outcome

Thirty RCTs reported KQ3 outcomes (n=99,095) and KQ4 outcomes were reported in 30 RCTs (n=93,296) and 3 cohort studies (n=289,659). See **Appendix F Table 16** for a summary of findings for each trial and **Appendix F Table 17** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 18, 19, 20,** and **21**.

Across all outcomes, there was no apparent effect modification related to the comprehensiveness of outcome ascertainment, whether vitamin D was used alone or in combination with calcium, or whether the supplement was given in a large bolus (e.g., 100,000 IU monthly) or taken daily in smaller doses. In addition, differing statistical pooling methods had almost identical results. Evidence for an association between all-cause mortality and dose was conflicting in meta-regression and stratified analyses, and no association was identified between dose and either CVD events or cancer incidence. Sensitivity analysis results are shown in **Appendix F Table 17.** Results from factorial studies indicated similar effects for vitamin D with or without calcium, but these comparisons are not discussed in detail. Subgroup analyses within trials also demonstrated no effect modification by baseline vitamin D serum levels.[91, 93]

All-Cause Mortality (KQ3)

All-cause mortality was reported in 24 RCTs, and on balance suggests a small benefit.[78, 87, 88, 90-93, 102, 110-112, 115, 120, 121, 124, 125, 127, 128, 130, 134, 135, 138, 139] Although none of the studies reported a statistically significant reduction on all-cause mortality, most point estimates were smaller than 1.0 and the pooled effect indicated a small statistically non-significant reduction associated with vitamin D use (OR, 0.94 [95% CI, 0.89 to 1.00]; 24 RCTs [n=93,003]; I^2=0%; **Figure 5, Appendix E Figure 7**) after 6 months to 6.2 years of followup. The results were very similar for vitamin D alone and vitamin D with calcium, and neither of these effects were statistically significant when pooled separately (**Appendix F Table 17**). The overall pooled estimate was identical using different pooling methods for rare events, however the effect was statistically significant when using the restricted maximum likelihood method. The proportion of participants

dying was highly variable across these studies, ranging from 0 to 33 percent in the control groups, leaving the best pooling method unclear. In addition, the prediction interval, which indicates the likely effect range predicted for newly published studies, suggested a likely small effect (prediction interval, 0.88 to 1.00, pooling the Peto OR). The results were also very similar when the analysis was limited to studies with full ascertainment of all-cause mortality, although confidence intervals were slightly wider and the pooled estimate was not statistically significant. In WHI, 4.1 percent of those taking vitamin D and calcium had died after 7 years, compared with 4.5 percent taking placebo, but this difference was not statistically significant (HR, 0.91 [95% CI, 0.83 to 1.01]). The effect in VITAL suggested no benefit after 5.3 years (HR, 0.99 [95% CI, 0.87 to 1.12]); 3.8 percent in each group had died. Meta-regression indicated a possible association between vitamin D dose and all-cause mortality (p=.04, controlling for the use of bolus dosing). Follow-up exploratory analyses suggested a larger effect at doses lower than 2000 IU/day (p=.06), however stratified analyses did not demonstrate an association (p=.30). There was no association between effect size and the use of bolus dosing (p=.68), versus vitamin D taken daily in smaller doses, nor was there a difference in effect size between the previous and newly-included studies (p=.19)

Subgroup analyses for all-cause mortality were sparsely reported. Two studies found no differences in effect sizes for all-cause mortality by age,[78, 87] and one of these also found no effect modification by gender.[78]

Cardiovascular Outcomes (KQ3)

A CVD outcome was reported in 15 of the 35 trials (**Figure 5, Appendix E Figure 10**).[78, 87, 88, 90, 91, 93, 99, 102, 112, 115, 116, 121, 125, 128, 138] Pooled effects showed no group differences for CVD mortality, the composite CVD event outcome, MI, and stroke. Point estimates for these outcomes ranged from 0.96 to 1.02, including sensitivity and subgroup analyses, and no pooled result was statistically significant. Very few individual study results showed a statistically significant benefit. Point estimates were in a similar range as the pooled effects for WHI and VITAL across a number of CVD-related outcomes. Meta-analyses included three to eight trials and 33,484 to 73,236 participants, with little to no statistical heterogeneity among the individual study effects. Two of these trials tested vitamin D and calcium use combined compared with placebo, and neither found any reduction in CVD deaths or events.[78, 88]

The included studies found no effect modification by age,[78, 87, 93] gender,[87, 93] or race,[93] as well a number of other health-related characteristics such as smoking status[78, 93] and BMI.[78, 93] In addition, pooled analyses demonstrated no association between effect size for the composite CVD events outcome and vitamin D dose (interaction p=.88) or the use of bolus dosing (p=.82), versus vitamin D taken daily in smaller doses, nor was there a difference in effect size between the previous and newly-included studies (p=.76)

Cancer (KQ3)

Cancer outcomes were reported by 18 of the RCTs.[78, 82, 87, 88, 90-93, 102, 112, 114-116, 118, 119, 121, 125, 138] The meta-analysis showed a small benefit of vitamin D use for cancer mortality (pooled OR, 0.89 [95% CI, 0.80 to 0.99]; 6 RCTs; n=74,237; I^2=0%; **Figure 5, Appendix E Figure 8**). The

prediction interval supporting this finding and indicated that the plausible range for future studies is a likely a small to moderate benefit (prediction interval, 0.77 to 1.03). WHI and VITAL[78, 93] did not find statistically significant group differences, however both had point estimates in the direction of benefit (WHI[78]: HR, 0.89; 95% CI, 0.77 to 1.03; VITAL[93]: HR, 0.83; 95% CI, 0.67 to 1.02). In VITAL, 1.2 percent of participants taking vitamin D had died of cancer, compared with 1.4 percent taking placebo.

Despite the benefit for cancer mortality in pooled analyses, there were very few trials with statistically significant effects of vitamin D use on cancer incidence, overall or site-specific, with or without concomitant calcium use (**Appendix E Figures 8 and 9**). The pattern of effects more strongly in the direction of benefit for cancer mortality than cancer incidence was consistent for all studies that reported both outcomes, although confidence intervals within each study were highly overlapping (**Table 10**). WHI reported extensively on site-specific cancers and generally found statistically non-significant ORs between 0.90 and 1.10 for cancers with more than ten events per study group. The only statistically significant site-specific cancer finding for WHI was a reduction in breast cancer in situ after 11.9 years (HR, 0.82 [95% CI, 0.68 to 0.99], 1.1% in supplement group vs. 1.3% in the placebo group). However, WHI found no reduction in breast cancer overall (HR, 0.96 [95% CI, 0.86 to 1.07]) or invasive breast cancer (HR, 1.04 [95% CI, 0.94 to 1.14], 4.7% in the supplement group vs. 4.5% in the placebo group).

The included studies found no effect modification for cancer by age,[78, 87, 93] gender,[87, 93] or smoking status.[78, 93] The VITAL study did find an interaction with BMI (p=0.002).[93] That study found greater a protective effect associated with lower BMI (<25.0 kg/m^2: HR, 0.76 [95% CI, 0.63 to 0.90], 25.0 to <30.0 kg/m^2: HR,1.04 [95% CI, 0.90 to 1.21], ≥30.0 kg/m^2: HR,1.13 [95% CI, 0.94 to 1.37]). In addition, subgroup analyses suggested a larger benefit for cancer incidence among Black participants (HR, 0.77 [95% CI, 0.59 to 1.01] than Non-Hispanic White participants (HR, 0.99 [95% CI, 0.89 to 1.11]), but the interaction term was not statistically significant (p=0.21).[148] In addition, meta-regression analyses demonstrated no association between effect size for the any cancer incidence and vitamin D dose (interaction p=.74) or the use of bolus dosing (p=.36), versus vitamin D taken daily in smaller doses, nor was there a difference in effect size between the previous and newly-included studies (p=.39)

Adverse Events (KQ4)

Twenty-eight of the RCTs reported some kind of adverse event outcome, as did all three of the cohort studies. Several RCTs reported no differences in the percent of participants experiencing any adverse event[64, 91, 113, 115, 117, 128, 139] any serious adverse events[82, 92, 102, 135, 138] or withdrawal due to adverse events.[92, 94, 102, 119, 123, 127, 135, 138]

While most trials reporting kidney stones had very few events, the largest trials indicated a small increased risk.[82, 90-93, 110, 125] In WHI, 2.5 percent of participants taking 400 IU vitamin D and 1000 mg calcium daily developed a kidney stone after 7 years, compared with 2.1 percent in the placebo group (HR, 1.17 [95% CI, 1.02 to 1.34). VITAL found a similar effect size, although it was not statistically significant (HR, 1.12 [95% CI, 0.99 to 1.28]); 3.7 percent in those taking 2000 IU/day vitamin D vs. 3.3 percent in the placebo group after 5.3 years developed a kidney stone. In addition, two of the cohort studies[143, 144] found an increased risk of kidney stones with

use of 1000 IU/day or more of vitamin D after 20 to 26 years, compared with no vitamin D use, but only one of these findings was statistically significant. There was no suggestion of increased risk with lower doses in either of these studies. The third cohort study, NHS-I,[140] found no association between any dose of vitamin D and kidney stones.

A wide range of non-serious harms were reported, but the only one with reported group differences was GI symptoms, and only in one study. Of ten studies reporting some type of serious or non-serious GI-related outcome[88, 93, 94, 99, 102, 107, 119, 123-125] ranging from nausea to gastrointestinal bleeding.

We found no evidence related to effect modification on harms of vitamin D use by age, sex, race, ethnicity, or dose.

Vitamin E

Summary of Results

Eleven studies of vitamin E supplementation were included (n=265,511, **Table 11**): nine RCTs (n=116,468)[73, 75, 76, 79, 80, 103, 126, 129, 131] and two cohort studies (n=149,043).[140, 142] Seven of the RCTs had an explicit aim to prevent CVD[73, 79, 80, 103] or related outcomes,[76, 126, 131] most among adults at increased risk for CVD, due to either smoking history[75, 131] or the presence of CVD risk factors.[76, 103, 126] Four of the trials with CVD aims also had a cancer prevention aim.[73, 75, 79, 80] In the RCTs, dose ranged from 111 to 666 IU daily (50 to 300 mg/day) for 3 to 10 years, and followup time ranged from 3 to 24 years. Five of the studies were conducted in the US[73, 80, 126, 140] or the US and Canada,[79] primarily among adults aged 45 years and older.

Nine RCTs reported KQ3 outcomes (n=116,468) and KQ4 outcomes were reported in seven RCTs (n=115,576) and two cohort studies (n=149,043). Most evidence indicated that vitamin E, with or without vitamin C, had no benefit for mortality**,** CVD, or cancer (**Figure 6, Appendix E Figures 11, 12,** and **13**), and also no clear increased risk of serious harm. For example, pooled evidence demonstrated no association between vitamin E use and all-cause mortality (OR, 1.02 [95% CI, 0.97 to 1.07]; 9 RCTs [n=107,772]; I^2=0%) or the composite outcomes of any CVD events (OR, 0.96 [95% CI, 0.90 to 1.04]; 4 RCTs [n=62,136]; I^2=0%) or incidence of any cancer (OR, 1.02 [95% CI, 0.98 to 1.08]; 5 RCTs [n=76,777]; I^2=0%). A cohort study of 27,343 Swedish men found a higher incidence of cataracts among men reporting any vitamin E use on a one-time survey than those who reported no use.[142] However, no differences in cataract incidence were identified in the other, better-quality cohort study of postmenopausal American women that had biennial reporting of supplement use.[140]

Detailed Study Characteristics

Nine RCTs[73, 75, 76, 79, 80, 103, 126, 129, 131] and two cohort studies[140, 142] were included (n= 265,511, excluding participants randomized to take other supplements in factorial RCTs; **Table 11**). Five of these studies were newly identified and not included in the previous review: four RCTs[103, 126, 129, 131] and one cohort study.[142] Only one[103] of the newly-included studies had a primary aim of CVD and none had a primary aim of cancer. Both of the cohort studies were only included for

harms, covering hip fractures, kidney stones, and cataracts.[140, 142] Six of the studies (all RCTs) were rated as good quality[73, 75, 79, 80, 103, 129] and the remaining trials were fair quality. The Nurses' Health Study is a large cohort study that generally used good methods, however we rated it as fair quality because of its reliance on self-reported supplement use and inability to fully adjust for confounders.

Eight studies had an explicit aim of prevention of CVD[73, 75, 79, 80, 103] or atherosclerosis progression,[76, 126, 131] and four of these had a cancer prevention aim as well.[73, 75, 79, 80] Three studies aimed to explore the association between vitamin E and age-related cataracts,[129, 140, 142] and one of these also explored hip fractures and kidney stones as potential harms of vitamin E use.[140] Three of the studies did not describe having full ascertainment of the main outcomes for our review of all-cause mortality, CVD outcomes, or cancer incidence.[76, 126, 131]

In the trials, dosing was fairly wide-ranging, from 111 to 666 IU daily (50 to 300 mg/day), and duration of use ranged from 3 to 10 years. In the large Nurse's Health Study cohort study, [140] a variety of use durations were examined, compared with no use, with no restriction on dose. Two trials examined vitamin E with or without 500 mg of vitamin C[76] and 200 mcg of selenium[79] daily. However, the trial with concomitant vitamin C use was too small to allow conclusions with regard to all-cause mortality and did not report CVD or cancer outcomes. Five of the studies were conducted in the U.S.[73, 80, 126, 140] or the U.S. and Canada,[79] and the others were conducted in Europe. Across all studies, the mean ages were in the 50s or 60s, mean BMIs were in the overweight range, and the samples were predominantly of White race. One of the largest trials, SELECT, reported the highest proportion of Black participants, which was only 13 percent.[79] Two studies were limited to women[73, 140] and four were limited to men.[75, 79, 80, 142] Two studies were limited to smokers[75, 131] and three others selected patients based on other CVD risk factors.[76, 103, 126] Most studies did not report baseline serum levels.

Detailed Results by Outcome

Nine RCTs reported KQ3 outcomes (n=116,468) and KQ4 outcomes were reported in seven RCTs (n=115,576) and two cohort studies (n=149,043). See **Appendix F Table 22** for a summary of findings for each trial and **Appendix F Table 23** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 24, 25, 26,** and **27**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in all nine RCTs. The pooled effect demonstrated no benefit of vitamin E use (OR, 1.02 [95% CI, 0.97 to 1.07]; 9 RCTs [n=107,772]; **Figure 6, Appendix E Figure 11**) after 3 to 10 years of followup. The results were identical using different pooling methods, and very similar when dropping four studies without full ascertainment of this outcome (**Appendix F Table 23**). Studies that reported additional longer term followup consistently reported similar findings to those shown in the **Appendix E Figure 11**,[75, 79] and no study found statistically significant group differences in all-cause mortality at any timepoint. None of the studies reported on effect modification by age, gender, race, or ethnicity. Effect sizes were very similar when vitamin E was used with or without selenium in SELECT.[79]

Cardiovascular Outcomes (KQ3)

CVD outcomes were reported in eight of the nine trials (**Figure 6, Appendix E Figure 12**). Pooled effects showed no group differences for CVD mortality, the composite CVD event outcome, MI, and stroke, and very few individual study results showed a statistically significant benefit. Several results shown in the forest plot were in the direction of benefit for CVD mortality, and WHS, a large good-quality trial of postmenopausal women,[73] reported a statistically significant 24 percent reduction in the likelihood of CVD mortality after 10 years of 300 IU/day of vitamin E daily (study-reported RR=0.76 [95% CI, 0.59 to 0.98]). However, the pooled effect for CVD mortality was not statistically significant (OR, 0.88 [95% CI, 0.74 to 1.04]; 6 RCTs [n=77,114]) and effect sizes across all studies were wide-ranging, particularly when considering the broader set of related outcomes. Additionally, both PHS-II[80] and ATBC showed an increased risk of hemorrhagic stroke. In PHS-II, 0.5 percent among those taking vitamin E and 0.3 percent among those taking placebo experienced a hemorrhagic stroke (HR, 1.74 [95% CI, 1.04, 2.9]). In the ATBC study of smokers, hemorrhagic stroke death was similarly elevated (calculated OR, 1.50 [95% CI, 1.03 to 2.20]; vitamin E: 0.5%, placebo: 0.3%).[75] Effect sizes across all pooled outcomes were very similar when limited to studies reporting full ascertainment of CVD outcomes. In SELECT, effect sizes for CVD outcomes were generally similar when vitamin E was taken with or without selenium, with the exception of stroke. Effect sizes suggested a less harmful impact when vitamin E was paired with selenium.[79]

WHS reported beneficial effects on CVD events among women age 65 years and older (RR, 0.74 [95% CI, 0.59 to 0.93]), which differed from the effect in younger women (interaction p=0.008; age 45-54: RR, 1.13 [95% CI, 0.91 to 1.4]; age 55-64: RR, 0.95 [95% CI, 0.77 to 1.16].[73] No other studies reported effect sizes by age, and none of the studies reported effect modification by gender, race, or ethnicity.

Cancer (KQ3)

Cancer outcomes were reported by seven of the RCTs.[73, 75, 79, 80, 103, 126, 131] Pooled effects showed no benefit of vitamin E use for cancer mortality, incidence of any cancer, or the incidence of colorectal, lung, breast, or prostate cancer (**Figure 6, Appendix E Figure 13**). Pooled ORs ranged from 0.98 (95% CI, 0.82 to 1.16; 3 RCTs [n=71,950]; I^2=0%;) for colorectal cancer to 1.02 (95% CI, 0.98 to 1.08; 5 RCTs [n=76,777]; I^2=0%;) for any incident cancer. For all outcomes, results were very similar when limited to trials with full ascertainment of cancer outcomes. However, the results for prostate cancer were inconsistent across studies. The ATBC study[75] found a reduced risk of prostate cancer with 111 IU (50 mg) daily use for a median of 6.1 years, with or without concomitant beta-carotene use. For example, the ORs for prostate cancer for vitamin E (alone) were 0.64 (95% CI, 0.44 to 0.94) at 6.1-year followup and 0.88 (95% CI, 0.78 to 0.98) at the 24-year followup. On the other hand, no group differences were found in other large, good-quality trials (study-reported HR of 0.97 [95% CI, 0.85 to 1.09] in the PHS-II[80] and 1.13 [95% CI, 0.95 to 1.35] in the SELECT study).[79] Effect sizes for cancer outcomes were generally similar when vitamin E was taken with or without selenium.[79] PHS-II found no effect modification by age, nor by several other health behaviors such as BMI, smoking status, physical activity, alcohol consumption, and parental history of cancer.[80]

Adverse Events (KQ4)

Three trials reported no group differences in the total number of adverse events, [103, 129] serious adverse events,[129] or withdrawals due to adverse events.[76, 129] Trial evidence also supported no group differences in hospitalization from pneumonia,[75] gastrointestinal disease,[103] several bleeding outcomes,[80, 103] fatigue,[79] nail changes,[79] halitosis,[79] easy bruising[80] and noncataract ophthalmic events.[129] However, some of these results were based on a very small or unknown number of events. Isolated statistically significant paradoxical (harmful) findings were reported for hemorrhagic stroke in two trials, as described above under CVD events.[75, 80]

PHS-II found no increase in the incidence of cataracts with vitamin E use (HR, 0.99 [95% CI 0.88 to 1.11) after 8 years. Among the two cohort studies examining cataract incidence,[140, 142] the NHS[140] found no group differences among 121,700 post-menopausal women for less than 2 years' use, 2−4 years' use, 5−9 years' use, or 10 or more years' use, compared with no use. Surveys were completed every 2 years to determine vitamin E use. However, a cohort study of 27,343 Swedish men age 49 to 79 years found a higher incidence of cataracts among men reporting any vitamin E use on a one-time survey than those who reported no use 8.4 years after completing the survey (HR, 1.57, 95% CI, 1.10 to 2.22; 22.2% of vitamin E users vs. 8.8% of non-users).[142] Both of these studies relied on self-report to determine supplement use, which is subject to inaccuracy and recall bias.

Folic Acid

Summary of Results

We identified five RCTs[83, 96, 108, 109, 132] (n=6,370) of folic acid supplementation (**Table 12**). Three RCTs[83, 108, 109] had primary aims relevant to this review; all three had an explicit aim to prevent colorectal cancer in persons with a previous adenoma, which were included for all outcomes, including colorectal cancer. Participants were randomized to use 1,000 mcg, 800 mcg, or 500 mcg of folic acid daily or to 400 mcg daily along with 500 mcg per day of vitamin B12.[96] Four trials[96, 108, 109, 132] were newly identified and not included in the previous review. Two trials[83, 109] were conducted in the US, and across all trials, mean ages ranged from 57 to 74 years.

Five RCTs reported KQ3 outcomes (n=6,370) and four reported KQ4 outcomes (n=5,854). Evidence indicated that folic acid had no benefit for mortality (**Appendix E Figure 14**), but increased the risk of any cancer incidence in 2 of 3 studies, which were limited to people with a history of adenomas or with elevated homocysteine concentrations (**Figure 7**). There were too few events to draw conclusions about CVD mortality and CVD composite outcomes (**Appendix E Figure 15**) or site-specific cancers, although one trial did report an increased risk of prostate cancer[83] (**Appendix E Figure 16**). The pooled effect for all-cause mortality was in the direction of benefit, but was not statistically significant and most studies had fewer than 20 deaths in either group (Peto OR 0.71 [95% CI, 0.49 to 1.03]; 5 RCTs [n=6,370]; I^2=21.1%, **Appendix E Figure 14**). On the other hand, the pooled effect for any cancer incidence demonstrated an increased risk at or beyond 2 years of followup (Peto OR, 1.42 [95% CI, 1.10 to 1.84]; 3 RCTs [n=4,612]; I^2= 0%, **Appendix E Figure 16**). Evidence suggested no benefit for MI and stroke (**Appendix E Figure 15**). For example, the pooled effects for the composite outcomes for MI and stroke were

OR 1.26 (95% CI, 0.86 to 1.85); 4 RCTs [n=3,201]; I^2=43.8%) and OR 0.79 ([95% CI, 0.54 to 1.14]; 4 RCTs [n=3,201]; I^2=13.1%), respectively, although both estimates were imprecise.

There was no clear increased risk of other serious harm aside from the cancer incidence findings.

Detailed Study Characteristics

We identified five RCTs[83, 96, 108, 109, 132] (n=6,370) of folic acid supplementation among adults with mean ages ranging from 57 to 74 years. One trial[83] was included for benefits only, the other four trials[96, 108, 109, 132] were included for benefits and harms. Four trials[96, 108, 109, 132] were newly identified and not included in the previous review.

Three RCTs[83, 108, 109] had an explicit aim to prevent colorectal cancer and all three were limited to adults with a history of colorectal adenomas. The other two RCTs aimed to explore the effects of folic acid on cognitive performance[132] and osteoporotic fractures,[96] both limited to adults with slightly[132] to moderately[96] elevated homocysteine concentration. Participants in three RCTs received folic acid only in doses of 500 mcg/day,[108] 800 mcg/day,[132] and 1,000 mcg/day[109] or placebo for 3 to 6.5 years. Participants in the Aspirin/Folate Polyp Prevention Study (AFPPS)[83] were randomized to 1,000 mg/daily of folic acid or placebo, then separately randomized to receive aspirin (81 mg or 325 mg daily) or placebo (3x2 factorial design). This was the only study included in the previous review. The Wu 2009[109] trial was conducted among participants of two large prospective cohorts—the Health Professionals Follow-Up Study and the Nurses' Health Study, and was the only study rated as good quality. The remaining four trials[83, 96, 108, 132] were rated as fair quality, all were downgraded because ascertainment for outcomes relevant to our review were not reported; some had additional methodologic concerns.

The largest included trial, B Vitamins for the Prevention of Osteoporotic Fractures (B-PROOF),[96] randomized 2,919 men and women aged ≥65 years and with moderately elevated homocysteine concentrations (12–50 micromol/L) to 400 mcg/day of folic acid and vitamins B12 and D3 (500 mcg/day and 15 mcg/day, respectively), or placebo supplementation with 15 mcg of vitamin D3 for 2 years. Trials were conducted in the US,[83, 109] The Netherlands[96, 132] and the UK and Denmark. [108, 132] Only one trial reported race or ethnicity, and only 8 percent of participants in this trial were Black.[83] Among the four studies reporting baseline serum folic acid levels, the range was from 3.8 [132] to 10.5 ng/mL,[83] values that are all considered normal (above 3.0 ng/mL).[149]

Detailed Results by Outcome

Five RCTs reported KQ3 outcomes (n=6,370) and four report KQ4 outcomes (n=5,854). See **Appendix F Table 28** for a summary of findings for each trial and **Appendix F Table 29** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 30, 31, 32,** and **33**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in all five trials—70 (2.2% of 3,191) deaths occurred in

intervention groups and 95 deaths (3.0% of 3,179) occurred in control groups altogether. None of the trials demonstrated a statistically significant effect of 400 mcg to 1,000 mcg folic acid daily on all-cause mortality after 2 to 6.5 years of followup and 2 to 6.5 years of folic acid use. The pooled effect was not statistically significant (Peto OR, 0.71 [95% CI, 0.49 to 1.03]; five RCTs [n=6,370]; I^2=21.1%, **Figure 7, Appendix E Figure 14**); however, our sensitivity analysis using an alternate pooling method demonstrated significant association between the use of folic acid and reduction in all-cause mortality when using the Mantel-Haenszel model (OR, 0.73 [95% CI, 0.73 to 0.99]; **Appendix F Table 29**). Most studies had fewer than 20 events per study group, so as few as two to three additional deaths in either group could substantially change a study's effect size. All studies either did not report[83, 108, 132] the ascertainment methods for all-cause mortality or deaths were reported by relatives.[96, 109] The study with the most deaths was B-PROOF, with 37 (2.5%) deaths in the intervention group taking folic acid combined with vitamin B12 and 42 (2.9%) deaths in the placebo group (OR, 0.88 [95% CI 0.56 to 1.37], n=2,919). No studies reported on effect modification by age, gender, race, or ethnicity.

Cardiovascular Outcomes (KQ3)

Four trials[83, 96, 108, 109] reported CVD outcomes (**Appendix E Figure 15**). The incident rates for CVD mortality,[109] MI,[83, 96, 108, 109] stroke,[83, 96, 108, 109] and the composite CVD event outcome[109] were wide-ranging and did not differ between the intervention and control groups in any the individual studies. Pooled effects showed no group differences for MI (OR 1.26 [95% CI, 0.86 to 1.85]; 4 RCTs [n=3,201]; I^2=43.8%) and stroke (OR 0.79 [95% CI, 0.54 to 1.14]; 4 RCTs [n=3,201]; I^2=31.1%). However, there were too few events in three[83, 108, 109] out of four trials to draw conclusions about the effects of folic acid on CVD. For example, there were only a total of 32 MIs and 23 strokes across these three studies. Only a sub-analysis conducted on a random sample of 569 persons from the B-PROOF study reported a substantial number of events, finding no statistically significant difference for MI and stroke in older persons with an increased level of homocysteine.[150]

Cancer (KQ3)

Four trials reported a cancer outcome.[83, 96, 108, 109] In the pooled analysis, folic acid, either alone[83, 109] or with vitamin B12,[96] was associated with higher rates of any cancer incidence (Peto OR 1.42 [95% CI, 1.10 to 1.84]; 3 RCTs [n=4,612]; I^2=0.0%) at 2 to 6 years of followup, after 2 to 6 years of supplement use. Two[83, 96] of the three trials reported statistically significant increases in cancer incidence for at least one followup timepoint. The study with the most events for any cancer outcome was the B-PROOF[96] trial, which was limited to people with elevated homocysteine levels. B-PROOF was the only study reporting on cancer that was not limited to people with a previous colorectal adenoma. B-PROOF found a higher rate of any cancer incidence at two years of followup (HR, 1.56 [95% CI, 1.04 to 2.31]), particularly for women (HR, 2.35 [95% CI, 1.23 to 4.50]. However, this effect was no longer statistically significant at 6.5 years followup (HR, 1.25 [95% CI, 1.00 to 1.57]) for both women and men combined, and results were not reported separately by gender. At the 2-year followup, there were 63 (4.3%) newly diagnosed cancer cases in the group taking folic acid and vitamin B12, compared with 42 (2.9%) in those taking placebo. After 6.5 years, the number cases were 171 (13.6%) with folic

acid and vitamin B12, and 143 (11.3%) with the placebo. Excess cancer cases appeared to be primarily driven by colorectal cancer in B-PROOF and prostate cancer in AFPPS.

Although there were few site-specific cancer cases in any trials, B-PROOF was the largest study and had the most events with 19 cases of colorectal cancer.[96] B-PROOF reported a statistically significant increase in the risk for colorectal cancer at 2 and 6.5 years of followup (HR, 1.77 [95% CI, 1.08 to 2.90] at 6.5 years). B-PROOF was the only study reporting colorectal cancer incidence that was not limited to people with a previous adenoma, however the other three studies were all underpowered for this outcome and only reported between 1 and 5 events per study arm. The pooled effect for colorectal cancer combining all four trials was not statistically significant (Peto OR, 1.16 [95% CI, 0.50 to 2.66]; 4 RCTs [n=5,538]; I^2=37.3%; **Figure 7, Appendix E Figure 16**).

Two trials[83, 109] examined the effect of 1,000 mcg of folic acid daily on the incidence of prostate cancer at 6.5- and 7-years of followup. The number of prostate cancer diagnoses was small in the Wu 2009[109] trial (11 cases total) and groups did not differ (OR, 0.79, 95% CI, 0.23 to 2.65). However, the AFPPS [83] trial reported an increased risk for prostate cancer with folic acid use. Over a median of 7 years, the adjusted probability of prostate cancer diagnosis was 9.7 percent (95% CI, 6.5% to 14.5%) in the intervention group and 3.3 percent (95% CI, 1.7 to 6.5%) in the control group (multivariable-adjusted HR, 2.58 [95% CI, 1.14 to 5.86]), although this is based on a total of only 34 cases.[151]

None of the trials found evidence of benefit of folic acid, either alone or with vitamin B12 on the incidence of breast,[96, 109] lung,[96 109] hematological,[96] musculoskeletal,[96] melanoma,[96] ear, nose, throat,[96, 109] reproductive system (both male and female) cancer,[96] or urinary cancer either at 2 or 6 years of followup, with few events reported for site-specific cancers.

Adverse Events (KQ4)

All five trials reported on adverse events or potential harms with folic acid supplementation. None of the studies reported any increased risk of serious adverse events associated with folic acid, except the increased risk of prostate cancer in the AFPPS[83](n=1,021) trial described above.

In B-PROOF,[96] 1.0 percent of intervention group participants withdrew from the study due to perceived side effects attributed to the study tablets during the 2 years of followup, compared with 0.9 percent in the control group. In the good-quality study, one person (0.3%) in the intervention and seven people (2.1%) in the control group stopped taking study tablets due to patient-perceived symptoms attributed to the study tablets.[109] There were no group differences in gastrointestinal-related outcomes,[108, 132] including gastrointestinal bleeding (0.8% taking folic acid vs. 1.3% taking the placebo) and peptic ulcer (0.2% taking folic acid vs. 0.6% taking the placebo), although there were too few events to draw firm conclusions.[108]

Vitamin B3

Detailed Study Characteristics and Summary of Results

We included one RCT[101] evaluating nicotinamide (a form of vitamin B3), which was included for KQ3 and KQ4. This study was a small, good-quality RCT that randomized 386 Australian men and women aged 30–91 years with at least two nonmelanoma skin cancers in the previous five years to nicotinamide (12 months of 1,000 mg/day) or placebo (**Table 13**). The purpose of this RCT was to test the protective effect of nicotinamide to reduce new nonmelanoma skin cancers and actinic keratoses in a high-risk population. This trial was newly identified and not included in the previous review. The full ascertainment was reported for the incidence of skin cancer only, which we did not retain since we did not address tertiary prevention in this review. Ascertainment of other cancers, mortality and CVD events was not reported; outcomes relevant to our review were captured as part of the adverse events reporting.

In this trial, with only a few events reported, data were insufficient to draw conclusions for the impact on mortality, CVD, (non-skin) cancer outcomes, or serious harms (**Table 14**).

Detailed Results by Outcome

The included trial was included for both KQ3 and KQ4. See **Appendix F Table 34** for a summary of findings for the included trial. A full listing of all relevant results is available in **Appendix F Tables 35, 36, 37, and 38**.

All-Cause Mortality (KQ3)

Data were insufficient to evaluate all-cause mortality, with only one death in the intervention group and two deaths in the control group over the 12-month study period.

Cardiovascular Outcomes (KQ3)

Data were insufficient to evaluate CVD outcomes (i.e., myocardial infarction, stroke, and heart failure); only a very small number of events was reported (no more than 3 participants experienced any of these outcomes in either group).

Cancer (KQ3)

Data were insufficient to evaluate cancer outcomes, including, colorectal, lung, prostate, duodenal cancer, non-Hodgkin's lymphoma, or any neoplasm. The outcome with the most events was any neoplasm, experienced by eight individuals (4.1%) who took nicotinamide and four (2.1%) individuals taking a placebo (OR, 2.04 [95% CI, 0.60 to 6.90]).

Adverse Events (KQ4)

Only very few adverse events were reported. The most common adverse event reported was cardiac chest pain experienced by eight (4.1%) individuals in the placebo group and one (0.5%)

person in the nicotinamide group.

Vitamin B6

Study Characteristics and Results

We found no studies examining all-cause mortality, CVD, or cancer for vitamin B6. Only one fair-quality cohort study of vitamin B6 supplementation met the inclusion criteria for harms of supplementation—the Nurses' Health Study (NHS-I, n=121,700)[140] initiated in 1976[140, 152] (**Table 13**). The sub-analysis[140, 152] of this study included 75,864 women and examined the risk for hip fracture in postmenopausal female registered nurses in the US receiving vitamin B6 supplements in excess of dietary intake. The median cumulative intake of vitamin B6 was 3.6 mg/day (intake raged <2 to ≥35 mg/day). The doses of vitamin B6 received from a supplement ranged from <2 to ≥25 mg/day. The mean followup time was 20.9 years. This was a newly published result, although the Nurse's Health Study was included in the previous review for vitamin A, multivitamins, and beta-carotene. See **Appendix F Table 34** for a summary of findings for the included study.

All-Cause Mortality, CVD, Cancer (KQ3)

No evidence was included.

Adverse Events (KQ4)

This study demonstrated that an intake of high cumulative doses of vitamin B6 (≥35 mg/day) was associated with an increased risk of hip fracture (RR, 1.29 [95% CI, 1.04 to 1.59], p-value for linear trend, 0.06), compared to the reference category of total vitamin B6 <2 mg/day. Women who consumed no vitamin B6 supplements had the lowest risk for hip fractures, compared to women receiving from less than 2 mg/day (RR, 1.37 [95% CI, 1.12 to 1.69]) to more than 25 mg/day (RR, 1.41 [95% CI, 1.10 to 1.80]). A listing of all relevant results reported in this study is available in **Appendix F Table 38.**

Vitamin C

Summary of Results

Six studies of vitamin C use were included (n=254,587, **Table 15**): two RCTs (n=15,031)[76, 80] and four cohort studies (n=239,556).[140, 142, 144, 145] Three of the cohort studies are newly identified and not included in the previous review.[142, 144, 145] Studies were conducted in the U.S. and Scandinavian countries and included adults primarily in their late 50s to mid-60s. Most evidence for CVD and cancer is from a single large and good-quality U.S-based study of male physicians (n=14,641), PHS-II, which had CVD and cancer prevention as primary aims.[80] A smaller RCT of fair quality evaluated the effect of vitamin C on progression of carotid atherosclerosis and reported a very small number of deaths and adverse events.[76] Vitamin C doses were 500 mg per day in both RCTs, with followup times of 3 and 8 years.

Both RCTs (n=15,031) reported KQ3 and KQ4 outcomes, and KQ4 outcomes were also reported in the 4 cohort studies (n=239,556). This small body of trial evidence suggests that vitamin C supplementation of 500 mg/day for 3 to 8 years has no benefit for mortality, CVD, or cancer outcomes and no serious harm (**Figure 8**). For example, PHS-II found no benefit for all-cause mortality (HR 1.07 [95% CI, 0.97 to 1.18]), cardiovascular events (HR 0.99 [95% CI, 0.89 to 1.11], or total cancer incidence (HR 1.01 [95% CI, 0.92 to 1.10]) at 8 years of followup. Evidence from cohort studies was inconsistent for a possible increased risk for cataracts and suggests increased risk of kidney stones in men.

Detailed Study Characteristics

Six studies of vitamin C use were included (n=254,587).[76, 80, 140, 142, 144, 145] These studies include two RCTs[76, 80] and four cohort studies[140, 142, 144, 145] evaluating harms only (**Table 15**). Three studies are new in this update and all are cohort studies reporting harms.[142, 144, 145]

The largest RCT (n=14,641), PHS-II, was a good-quality trial conducted in the U.S. that recruited male physicians age 50 years or older that also evaluated vitamin E, multivitamin, and beta-carotene in addition to vitamin C in a 2x2x2x2 factorial design.[80] The other much smaller RCT (n=390 for vitamin C-related supplements), ASAP, was a fair-quality trial conducted in Finland of men and women aged 45 to 69 years with mildly elevated cholesterol. This trial tested an intervention of vitamin C alone and an intervention of combined vitamin C and vitamin E.[76] All four cohort studies were rated fair quality. Two were conducted in the U.S.[140, 144] and two were conducted in Sweden.[142, 145] Each cohort was large and was population-based or recruited from the health professions. Vitamin use was obtained by self-report in each cohort.

PHS-II had the primary aim of evaluating supplementation on total and prostate cancer, CVD, and the age-related eye diseases of cataract and macular degeneration. Outcome ascertainment was valid and robust for the main outcomes of our review. The smaller ASAP trial had the study aim of evaluating progression of carotid atherosclerosis. Outcome ascertainment is not described for the six deaths reported in this trial (3 deaths occurring in vitamin C or placebo groups). All cohort studies had broad aims about chronic disease. The two Swedish cohorts ascertained outcomes using registries and the two U.S. cohorts ascertained outcomes based on self-report with medical record confirmation.

Vitamin C doses were 500 mg per day in both RCTs, with followup times of 3 and 8 years for ASAP and PHS-II, respectively. In the cohort studies evaluating harms, followup ranged from 8 to 14 years, with sub-analyses reported by duration of use. Dose information in the harms studies, which was captured by self-report, was varied.

The trials were conducted in the U.S. and Finland and the cohort studies were conducted in the U.S. and Sweden. Across all studies, mean ages were in the late 50s to mid-60s. With the exception of the smaller trial,[76] studies were conducted either exclusively in men or women. BMI was reported only in the largest trial and largest cohort, with a mean of 26 kg/m^2 in both studies.[80, 140] Smoking rates were highly variable, ranging from 4 percent in the U.S.-based PHS-II trial,[80] to 40 percent in the Finnish trial.[76] Specific data on race/ethnicity was not reported for

any study and was described only as predominately White in the large PHS-II trial. No study reported baseline vitamin C levels.

Detailed Results by Outcome

Both RCTs (n=15,031) reported KQ1 and KQ2 outcomes, and KQ2 outcomes were also reported in 4 cohort studies (n=239,556). See **Appendix F Tables 39** for a summary of findings for each trial. Comprehensive and detailed study-level results are available in **Appendix F Tables 40, 41, 42,** and **43**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in two trials.[76, 80] The vast majority of evidence is from the PHS-II trial of exclusively men, which showed that 500 mg/day vitamin C was not associated with all-cause mortality (HR 1.07 [95% CI, 0.97 to 1.18], **Figure 8**) at 8 years of followup.[80] At 8 years of followup, 11.7 percent of those in the vitamin C group died compared to 11.0 percent who were not taking vitamin C). The much smaller ASAP trial (n=390) was not powered to evaluate mortality. Three deaths occurred; one each in the vitamin C, vitamin C plus vitamin E, and placebo groups.[76] None of the studies reported on effect modification by age, gender, race, or ethnicity.

Cardiovascular Outcomes (KQ3)

Cardiovascular events were reported in two trials.[76, 80] In PHS-II, vitamin C was not associated with cardiovascular events (HR 0.99 [95% CI, 0.89 to 1.11], **Figure 8**) at 8 years of followup.[80] Similarly, results suggested no difference for CVD mortality (HR 1.02 [95% CI, 0.85 to 1.21], **Figure 8**), or any individual CVD event at 8 years of followup. For example, 3.5 percent of those in the vitamin C group experienced an MI compared with 3.4 percent in the no vitamin C group (HR 1.04 [95% CI, 0.87 to 1.24], **Figure 8**). For stroke, 3.0 percent in the vitamin C group experienced this event compared with 3.4 percent in the no vitamin C group (HR 0.89 [95% CI, 0.74 to 1.07], **Figure 8**). The three deaths that occurred in the smaller ASAP trial were CVD deaths; one each in the vitamin C, vitamin C + vitamin E, and placebo groups.[76] PHS-II found no effect modification for CVD outcomes by age or CVD risk factors, including BMI, smoking status, physical activity, alcohol consumption, and parental history of CVD prior to age 60.

Cancer (KQ3)

Cancer was reported only in PHS-II, which had total and prostate cancer as co-primary outcomes (**Figure 8)**.[80] Vitamin C was not associated with total cancer incidence (HR 1.01 [95% CI, 0.92 to 1.10]) or total cancer death (HR 1.06 [95% CI, 0.97 to 1.18]) at 8 years of followup. Incident prostate cancer occurred in 6.9 percent in the vitamin C group and 6.8 percent in the group not receiving vitamin C with no statistically significant differences between groups (HR 1.02 [95% CI, 0.90 to 1.15]). Prostate cancer death occurred in 0.6 percent of the vitamin C group and 0.4 percent of the group not taking vitamin C with no statistically significant differences between groups (HR 1.46 [95% CI, 0.92 to 2.31]). There were no differences for any other reported individual cancer (colorectal and lung). PHS-II found no effect modification by age, nor by

several other health behaviors such as BMI, smoking status, physical activity, alcohol consumption, and parental history of cancer.[80].

Adverse Events (KQ4)

All six studies reported on the harms of vitamin C use. The included trials found no increase in serious or nonserious harms from long-term vitamin C use.[76, 80] Furthermore, there were no statistically significant paradoxical findings for mortality, cancer, or CVD in either trial. PHS-II reported no statistically significant effects on minor bleeding (including hematuria, easy bruising, and epistaxis) or gastrointestinal symptoms (peptic ulcer, constipation, diarrhea, gastritis, and nausea), fatigue, drowsiness, skin discoloration, rashes, and migraine.[80] The smaller ASAP trial reported only withdrawals due to adverse events and found similar numbers in all groups: six in those on vitamin C, seven in those on vitamin C plus vitamin E, and eight in the placebo group.[76]

Three cohort studies[140, 142, 145] and one trial[80] evaluated the association of vitamin C use with cataract extraction, with mixed results. The two Swedish cohorts, one in women and one in men, each found that vitamin C supplementation of an estimated dose of 1,000 mg/day was associated with a statistically significant increased risk of cataract extraction over 8 years of followup when compared to no supplementation.[142, 145] The magnitude of increased risk was similar in both cohorts: a hazard ratio of 1.25 (95% CI, 1.05 to 1.50) in the Swedish Mammography Cohort,[145] and a hazard ratio of 1.21 (95% CI, 1.04 to 1.41) in the Cohort of Swedish Men.[142] However, vitamin C use was assessed only by a one-time questionnaire. The NHS cohort study,[140] which assessed vitamin C use every 2 years by questionnaire, found that vitamin C supplementation was not associated with cataract extraction for any duration of current use (<2 years: RR 1.08 [95% CI, 0.88 to 1.32], 2-4 years: RR 1.01 [95% CI, 0.76 to 1.33], 5−9 years: 1.05 [95% CI, 0.84 to 1.31], ≥10 years: RR 0.95 [95% CI, 0.76 to 1.20]). Vitamin C dose in NHS was not reported. Similarly, the very large PHS-II trial found no association of 500 mg/day vitamin C and cataracts (HR 1.02 [95% CI, 0.91 to 1.14]) at 8 years of followup.[80] All three cohort studies reported no effect modification by age on likelihood of cataracts.

Two cohort studies,[142, 144] both conducted exclusively in men, evaluated the association of vitamin C use with kidney stones and suggest an association between supplementation and this harm. In the Cohort of Swedish Men, vitamin C use of an estimated dose of 1,000 mg/day was associated with the risk of a first kidney stone at 11 years of followup (RR 1.92 [95% CI, 1.33 to 2.77]).[142] The Health Professionals Follow-up Study reported the risk of kidney stones for no vitamin C use compared to various doses at 14 years of followup.[144] While no single dose category comparison was statistically significant, the overall trend across dose was statistically significant (p=0.01). The risk ratio for no use compared to 1,000 mg/day or more was 1.16 (95% CI, 0.97 to 1.39). Both cohorts performed one-time assessments of vitamin C use by questionnaire.

Calcium

Summary of Results

Nine studies of calcium use were included (n=134,661, **Table 16**): 8 RCTs[81, 82, 84, 88, 90, 104, 105, 113] (n=12,961) and one large cohort study[140] (n= 121,700). Two studies had an explicit cancer prevention aim,[82, 88] and two additional trials aimed to prevent colorectal adenoma recurrence among patients with a recent adenoma.[84, 90] Two studies aimed to prevent CVD.[88, 105] Four[90, 104, 105, 113] trials were newly identified and not included in the previous review; none of these newly-included trials had a specific cancer or CVD prevention aim. The most common doses were 1000 and 1200 mg/day, and duration of use ranged from six months to five years. Followup time ranged from 6 months to 12 years post-baseline. Across all trials, participants were generally aged 40 years and older, and five of the studies were conducted in the US.[82, 84, 90, 113, 140] The best evidence came from the RECORD trial (n=5,292), which examined the effects of 1000 mg/day of calcium, with or without 800 IU/day of vitamin D in a 2x2 factorial design, on CVD and cancer outcomes among older adults with fragility fractures.[88]

Seven RCTs reported KQ3 outcomes (n=11,884) and KQ4 outcomes were reported in eight RCTs (n=11,930) and one cohort study (n=121,700). Most of the included evidence indicated that calcium had no benefit for mortality, CVD, or cancer (**Figure 9, Appendix E Figures 17, 18, and 19**). Pooled effects uniformly indicated no group differences (**Appendix F Table 44**), and very few individual study findings demonstrated an effect of calcium supplementation on cancer, CVD, or mortality. For example, pooled estimates for all-cause mortality (OR, 1.05 [95% CI, 0.92 to 1.21]; 6 RCTs [n=8,394]; I^2=0%), CVD events (OR, 1.11 [95% CI, 0.90 to 1.36]; 4 RCTs, n=4,076, I^2= 0%), and any incidence of cancer (OR, 0.94 [95% CI, 0.41 to 2.14, 3 RCTs, n=5,051, I^2=49.2%) all showed no association with calcium use. RCTs supported an increased risk of GI effects, but no clear increase in risk of fractures. The cohort study of women only suggested an increased risk of kidney stones, but most effects exploring various dose levels were not statistically significant. Evidence was too sparse to draw conclusions about other adverse events.

Detailed Study Characteristics

Eight RCTs[81, 82, 84, 88, 90, 104, 105, 113] of calcium use were included (n=12,961 randomized, excluding participants randomized to take other supplements), examining nine active intervention groups (**Table 16**). In addition, we included one large cohort study (n= 121,700) that examined the risk of kidney stones,[140] for a total of 134,707 participants across all studies. Two studies had broad cancer prevention aims,[82, 88] two aimed to prevent colorectal adenoma recurrence among patients with a recent adenoma,[84, 90] and two aimed to prevent CVD.[88, 105] Four[90, 104, 105, 113] of these trials were newly identified and not included in the previous review, and none of these newly included had a specific cancer or CVD prevention aim. One trial was only included for harms.[113]

Three trials were rated good quality[88, 90, 104] and the remaining were rated fair quality. The best evidence came from a good-quality trial that including almost half of the included participants (n=5,292), the RECORD trial.[88] RECORD had primary aims of cancer and CVD prevention, but

was limited to older adults (age 70 years or older) with a fragility fracture. RECORD was included in the previous review. RECORD was a factorial trial that crossed 1000 mg/day calcium use with 800 IU/day of vitamin D. They reported both the calcium vs. no calcium contrast and provided data to calculate the effects of calcium alone compared with placebo. We included results comparing calcium (alone) with placebo in the meta-analyses.

Doses ranged from 600 to 2000 mg/day, and the most common doses were 1000 and 1200 mg/day. Duration of use ranged from six months to five years. Five of the studies were conducted in the US[82, 84, 90, 113, 140] and the others were conducted in the UK, New Zealand, and Australia. Across all studies, the mean ages ranged from the late 50s to the late 70s, mean BMIs were generally in the overweight range, and the samples were predominantly of White race and women. Four studies were limited to women[81, 82, 104, 140] and one smaller trial was limited to men;[105] 85 percent of the participants in RECORD[88] were women. The smoking rate ranged from 3 to 27 percent of participants, and was highest in the study limited to men.[105]

Detailed Results by Outcome

Seven RCTs reported KQ3 outcomes (n=11,884) and KQ4 outcomes were reported in eight RCTs (n=11,930)and one cohort study (n=121,700). See **Appendix F Table 45** for a summary of findings for each trial and **Appendix F Table 44** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 46, 47, 48,** and **49**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in six trials.[81, 84, 88, 90, 104, 105] None of the trials found group differences in all-cause mortality and the pooled effect did not demonstrate a benefit (OR, 1.05 [95% CI, 0.92 to 1.21]; 6 RCTs [n=8,394]; I^2=0%, **Figure 9, Appendix E Figure 17**). In RECORD, 34.1 percent of participants taking calcium (without vitamin D) and 32.6 percent of participants taking a placebo had died after a median of 6.2 years, after using calcium for a median of. 3.75 years.[88] Pooled estimates were similar across pooling methods (**Appendix F Table 44**). None of the studies reported on effect modification for cancer by age, gender, race, or ethnicity.

Cardiovascular Outcomes (KQ3)

CVD outcomes were reported in five trials.[81, 84, 88, 104, 105] Almost no CVD outcome showed a statistically significant difference at any timepoint, and none of the pooled effects indicated an association between calcium use and CVD events or CVD mortality (**Figure 9, Appendix E Figure 18, Appendix F Table 44**). For example, the pooled OR for CVD events was 1.11 (95% CI, 0.90 to 1.36, 4 RCTs, n=4,076, I^2= 0%). In RECORD, 14.8 percent of participants taking calcium and 13.7 percent of those taking a placebo had died from CVD after 6.2 years (OR, 1.10 [95% CI, 0.88 to 1.37]). RECORD reported no group differences in CVD events (HR, 0.92 [95% CI, 0.80 to 1.08]), MI (HR, 0.97 [95% CI, 0.75 to 1.26]), or stroke (HR, 1.06 [95% CI, 0.85 to 1.32], **Appendix F Table 47**). RECORD did, however, find a reduction in congestive heart failure with calcium use (HR, 0.75 [95% CI, 0.58 to 0.97]; 102 events/2649 persons taking

calcium vs. 136 events/2643 person taking placebo). The only other statistically significant finding was an increase in CVD events in postmenopausal women with 1000 mg/day of calcium for 5 years in one trial (IRR, 1.43 [95% CI, 1.01 to 2.04]; 23.3 events/1000 person-years with calcium use vs. 16.3 events/1000 person-years; n=1,471).[81] None of the studies reported on effect modification for cancer by age, gender, race, or ethnicity for CVD.

Cancer (KQ3)

Cancer outcomes were reported by four trials (**Appendix E Figure 19**).[82, 84, 88, 90] The meta-analysis showed no association between calcium use and the composite outcome of any incidence of cancer (OR, 0.94 [95% CI, 0.41 to 2.14, 3 RCTs, n=5,051, I^2=49.2%; **Figure 9, Appendix F Table 44**). Statistical heterogeneity was fairly high, limiting our confidence on the pooled result, given the small number of studies pooled. RECORD found no group differences in incidence of or mortality from lung, colorectal, breast, prostate, or any type of cancer combined. For example, RECORD reported 12.4 percent in the calcium group and 11.4 percent in the placebo group developed new cancer cases (OR, 1.10 [95% CI, 0.87 to 1.39]) over 6.2 years.[88] The only cancer-related finding that was statistically significant was a reduction in prostate cancer at one of three followup timepoints in the smaller trial of adenoma recurrence prevention (RR, 0.52 [95% CI, 0.28 to 0.98]; 4.3% taking calcium vs. 8.3% taking placebo after 6 years, **Figure 9**, **Appendix F Table 47**).[84] None of the studies reported on effect modification for cancer by age, gender, race, or ethnicity for cancer.

Adverse Events (KQ4)

The included studies that reported on the occurrence of any adverse events,[113] any serious adverse events,[82] and withdrawals due to adverse events[84, 105] identified very few events and found no group differences. Constipation and gastrointestinal symptoms were generally increased with calcium use, but findings were only statistically significant in three studies, both indicating higher risk with calcium use.[81, 88, 104] Evidence from five trials suggested no increased risk of fractures.[81, 88, 90, 104, 105] The cohort study, NHS-I, reported an increased incidence of kidney stones for any calcium use compared with no calcium use, but no dose-response trend was identified.[140] Evidence on kidney stones from the trials was inconclusive due to the small numbers of events. See **Appendix F Table 49** for detailed results. None of the studies reported on effect modification for cancer by age, gender, race, or ethnicity for adverse events.

Selenium

Summary of Results

Five RCTs[77, 79, 89, 97, 98] (n= 29,909) of selenium use by adults primarily aged 50 years and older were included (**Table 17**). All studies had an explicit cancer or colorectal adenoma prevention aim. The most common dose was 200 mcg/day. Duration of use ranged from 6 months to 5.5 years, and followup time ranged from 6 months to 15.9 years. Most evidence derived from a single large study of males only (Selenium and Vitamin E Cancer Prevention Trial [SELECT][79], n=25,984), which also had the longest duration of selenium use at a median of 5.5 years.[79] Two

of the trials were newly identified and not included in the previous review,[97, 98] but SELECT[79] was included in the previous review.

Four RCTs reported KQ3 outcomes (n=29,408) and KQ4 outcomes were reported in all five RCTs (n=29,909). Most of the included evidence indicated that selenium had no benefit for mortality, CVD, or cancer outcomes (**Figure 10, Appendix E Figures 20, 21, and 22**), and no clear increased risk of serious harm. For outcomes with sufficient evidence for pooling, no association was found between use of 200 mg daily of selenium and all-cause mortality (OR, 0.94 [95% CI, 0.83 to 1.07]; 4 RCTs [n=20,832]; I^2=4.7%) or CVD mortality (OR, 0.93 [95% CI, 0.75 to 1.14]; 3 RCTs [n=19,008]; I^2=0%). The SELECT trial demonstrated no benefit of 200 mcg/day of selenium for a median of 5.5 years on all-cause mortality, cancer incidence or mortality, and cardiovascular events or mortality at up to 7.1 year followup, with or without concomitant use of 400 IU/day of vitamin E.[79] These results were generally supported by the other trials, with the exception of one smaller trial[77] (n=1312) among persons with a history of basal or squamous cell carcinoma. This trial found benefits for a number of non-skin cancer outcomes at up to 7.4 years' followup. The included studies found no increased risk of serious harm at doses at or below 200 mg/day, and withdrawals due to adverse events did not differ between subgroups defined by dose level.

Detailed Study Characteristics

Five RCTs[77, 79, 89, 97, 98] of selenium use were included (n= 29,909 randomized, excluding participants randomized to take other supplements), examining ten active intervention groups (**Table 17**). Two of these trials were newly identified and not included in the previous review.[97, 98] One trial was only included for harms.[89] The largest trial, SELECT, was conducted exclusively in men, was rated good quality, and included most of the observations in this body of literature (n=25,984, excluding the vitamin E-only group).[79] The remaining trials were fair quality.

All studies had an explicit cancer[77, 79, 89, 97] or colorectal adenoma[98] prevention aim, and two were limited to patients with an increased risk of cancer due to a personal history of basal or squamous cell carcinoma (Nutritional Prevention of Cancer Study [NPC])[77] or a colorectal adenoma in the previous 6 months (Selenium and Celecoxib Trial [Sel/Cel]).[98] The largest study[79] also had CVD prevention as a study aim. All of these trials described full ascertainment of our main review outcomes except the Sel/Cel trial,[98] which nevertheless had very similar effect sizes to the SELECT trial.

The most common dose was 200 mcg/day and ranged from 100 to 300 mcg daily. The SELECT trial examined selenium with and without 400 IU/day of vitamin E.[79] Duration of use ranged from 6 months[89] to a median of 5.5[79] years. Three of the trials were conducted in the U.S.[77, 98] or the U.S. and Canada,[79] and the others were conducted in Great Britain[89] and Denmark.[97] Across all studies, the mean ages were in the 60s, mean BMIs were in the overweight range, and the samples were predominantly of White race. The smoking rate was high in two of the smaller studies, at 28.2 percent[77] and 29.7 percent.[97] Among the four studies reporting baseline serum selenium levels, the range was from 86.5 to 135.3 ng/mL, values that are all considered normal (above 70 ng/mL).[153]

Detailed Results by Outcome

Four RCTs reported KQ3 outcomes (n=29,408) and KQ4 outcomes were reported in all five RCTs (n=29,909). See **Appendix F Table 50** for a summary of findings for each trial and **Appendix F Table 51** for a listing of results from all pooled analyses. Comprehensive and detailed study-level results are available in **Appendix F Tables 52, 53, 54, and 55**.

All-Cause Mortality (KQ3)

All-cause mortality was reported in four trials.[77, 79, 97, 98] The pooled effect did not demonstrate a benefit (OR, 0.94 [95% CI, 0.83 to 1.07]; 4 RCTs [n=20,832]; I^2=4.7%, **Figure 10, Appendix E Figure 20**). The SELECT trial of men only had effects ranging from HR, 0.94 (95% CI, 0.77 to 1.13) to 0.99 (95% CI, 0.82 to 1.19) on a daily dose of 200 mcg, covering both intervention groups (with or without 400 IU of vitamin E) and followup assessments at 5.5 and 7.1 years.[79] For example, at 7.1 years of followup, 6.3 percent had died in the selenium group (without vitamin E) compared to 6.5 percent among those taking the placebo (HR, 0.98 [95% CI, 0.84 to 1.14]). Effects were wide-ranging in the smaller trials, falling in the direction of both benefit and harm. The only statistically significant finding was an increased risk of all-cause mortality at 15 years of followup after 5 years of 300 mcg daily (HR, 1.59 [95% CI, 1.02 to 2.46]; 39.5% in the selenium group vs. 27.8% in the placebo group); the effect size was similar but not statistically significant at the 5-year followup.[97] This study found that the harmful effect was limited to participants younger than 65 years when they began the study (HR, 3.12 [95% CI, 1.51 to 6.44]; HR, 0.93 [95% CI, 0.53 to 1.63] in those ≥ 65 years, interaction p=0.04). No other studies reported on effect modification for all-cause mortality by age, gender, race, or ethnicity.

Cardiovascular Outcomes (KQ3)

CVD outcomes were reported in three trials.[77, 79, 97] Effect sizes for CVD mortality were wide ranging, reflecting the relatively few number of events in many cases, and no effects were statistically significant. The pooled estimate indicated no association between 200 mg/day selenium use and CVD mortality (OR, 0.93 [95% CI, 0.75 to 1.14]; 3 RCTs; n=19,008; I^2=0%, **Figure 10, Appendix E Figure 21**). Two studies reported on CVD events;[77, 79] across all timepoints and intervention groups, effect sizes for the composite outcome of any CVD events ranged from HR, 0.97 (95% CI, 0.86 to 1.09) to 1.04 (95% CI, 0.73 to 1.49). Results were similar but more wide ranging for MI and stroke, and no effects for any CVD event outcome were statistically significant. No studies reported on effect modification by age, gender, race, or ethnicity for CVD. Two trials found that the effect of vitamin D on CVD events was similar across baseline serum selenium level.[77, 89]

Cancer (KQ3)

Cancer outcomes were reported by four studies.[77, 79, 97, 98] Cancer mortality was reduced only in the trial limited to those with a history of basal or squamous cell carcinoma (n=1312).[77] This trial reported reductions in overall cancer mortality (HR, 0.48 [95% CI, 0.31 to 0.76]; 4.4% in the selenium group vs. 8.6% in the placebo group) and lung cancer deaths (HR, 0.47 [95% CI, 0.23 to 0.93]; 1.8% in the selenium group vs. 3.8% in the placebo group) at a median 6.3 years'

followup after taking 200 mcg/day for a median of 4.4 years. This is despite having no impact on the incidence of recurrent basal or squamous cell carcinoma. Effects were wide-ranging and none were statistically significant in the other trials. In the largest trial, 1.5 percent taking selenium and 1.4 percent taking placebo died from cancer (HR, 1.02 [95% CI, 0.74 to 1.41]) after 5.5 years, with a similar effect size among those also taking vitamin E.[79] The pooled OR for cancer mortality was 0.86 ([95% CI, 0.69 to 1.06]; 3 RCTs; n=19,008; I^2=71.6%; **Figure 10, Appendix E Figure 22**), however the high degree of statistical heterogeneity and the small number of pooled trials limits our confidence in these results (**Appendix F Table 51**). The wide range of effect sizes could be related to variable underlying risk, and one study had very few events (a total of 4 cancer deaths after 5 years), which limited the reliability of their findings.[97]

Similar to cancer mortality, cancer incidence was reduced only in the trial of persons with a history of basal or squamous cell carcinoma (n=1312).[77] In this study, reductions were seen at 7.4 years of followup in the incidence of: any cancer (HR, 0.75 [95% CI, 0.58 to 0.97]; 16.9% vs 21.8%), colorectal cancer, lung cancer, prostate cancer, and any carcinoma, but not breast, esophageal, head and neck, leukemia, melanoma, or urinary bladder cancer. Although an interaction test did not indicate a differential effect by gender, subgroup analyses suggested a benefit for men (HR, 0.67 [95% CI, 0.50 to 0.89]; n=932) but not women (HR, 1.20 [95% CI, 0.66 to 2.20]; n=318) for the composite outcome of any cancer incidence. The other studies did not find reductions in cancer, including no reduction in colorectal cancer among persons with a recent colorectal adenoma (n=1824), after 3 years followup and taking 200 mcg daily for an average of 2.8 years, with very few events (OR, 1.26 [95% CI, 0.34 to 4.70]; selenium: 0.5% vs placebo: 0.4%).[98] In the largest trial, 9.6 percent taking selenium and 9.5 percent taking placebo had developed cancer of any kind (HR, 1.01 [95% CI, 0.89 to 1.15])[79] Pooled effect size for colorectal cancer, reported in three studies,[77, 79, 98] was limited due to the relatively high statistical heterogeneity and the small number of studies (OR, 0.82 [95% CI, 0.44 to 1.51]; 3 RCTs; n=20,584; I^2=53.8%). Effect modification was not reported in any studies by age, race, or ethnicity.

Adverse Events (KQ4)

The included studies found no increased risk of serious harm at 200 mg/day of selenium use. Two small trials reported zero serious adverse effects at doses of 100 to 300 mg/day[89] or no group differences in serious adverse events.[98] Statistically significant paradoxical findings on mortality, cancer, and cardiovascular disease events were rare despite the large number of outcomes reported, often across multiple doses and followup timepoints. However, the smallest trial (n=491)[97] found a higher likelihood of all-cause mortality with 300 mg selenium use daily, at 15.9 years of followup (39.5% among selenium users and 27.8% in the placebo group, HR, 1.59 [95% CI, 1.02 to 2.46]). The effect size was similar at the 5-year followup but with only 20 deaths altogether, group differences were not statistically significant (10.1% among selenium users and 6.3% in the placebo group, HR, 1.62 [95% CI, 0.66 to 3.96]). The only other adverse event that differed between groups in any trial was dermatitis in the SELECT trial, only when delivered without vitamin E (6.9% among those taking selenium vs. 5.9% with placebo, RR, 1.17 [95% CI, 1.0 to 1.35]; study-reported p<0.01).[79] SELECT did not report on serious adverse events or withdrawals due to adverse events; the study reported no group differences in alopecia, halitosis, fatigue, and nausea.[79] Two[77, 97] studies suggested higher numbers of withdrawals due to

adverse effects with selenium, but group differences were not statistically significant and a third trial[89] reported similar rates between groups with very few withdrawals related to adverse effects. One study reported interaction between selenium use and gender by serious adverse effects (p=0.39) or brittle or hard nails (p=0.78).[98]

Zinc

Study Characteristics and Results

We found no studies examining all-cause mortality, CVD, or cancer for zinc. One small fair-quality RCT met the inclusion criteria for harms of supplementation (n=87)[137](**Table 18**). The study included adults aged 18 years and older (median, 49 years) who self-reported that they usually had 1 or more colds each winter. Ninety percent were women. Participants were randomized to 78 mg/day of elemental zinc or placebo upon the onset of cold symptoms, for at most 5 days, with the purpose of testing whether the use of a commercially available zinc acetate lozenge shortens the duration of the common cold.[137] See **Appendix F Table 56** for a summary of findings for the included study.

All-Cause Mortality, CVD, Cancer (KQ3)

No evidence was included.

Adverse Events (KQ4)

Zinc acetate (78 mg/day) was associated with an increased risk of having any adverse events, including stomachache, taste alteration, teeth and mouth roughness or dryness, and aching in the mouth, compared to placebo, OR, 3.81 (95% CI, 1.57 to 9.24).[137] The study also reported that 1 participant in the zinc group (2.2%) and no participants in the placebo group withdrew due to adverse events, OR, 2.8 (95% CI, 0.11 to 70.68).[137]A listing of all relevant results reported in this study is available in **Appendix F Table 56.**

Magnesium

Study Characteristics and Results

We found no studies examining all-cause mortality, CVD, or cancer for magnesium. Only one small fair-quality RCT met the inclusion criteria for harms of supplementation (n=59)[136] (**Table 19**). The study included adults aged 55 years and older randomized to either an oral magnesium supplement (400 mg/daily) or matching placebo for 12 weeks. The purpose of this RCT was to study the effects of oral magnesium supplementation on supraventricular arrhythmias.[136] See **Appendix F Table 57** for a summary of findings for the included study.

All-Cause Mortality, CVD, Cancer (KQ3)

No evidence was included.

Adverse Events (KQ4)

Oral magnesium (400 mg/day) was associated with an increased risk of gastrointestinal symptoms, OR, 15.00 (95% CI, 3.00 to 4.96) compared to placebo.[136] The study also reported that 1 participant in the magnesium group (3.4%) and no participants in the placebo group withdrew due to adverse events, OR, 3.21 (95% CI, 0.13 to 82.07).[136] A listing of all relevant results reported in this study is available in **Appendix F Table 57.**

Chapter 4. Discussion

Summary of Evidence

We conclude that most vitamin and mineral supplements provide no clinically important protective effects for CVD, cancer, or all-cause mortality in healthy adults without known nutritional deficiencies (**Table 20, Figure 11**), with vitamin E having the strongest body of evidence demonstrating no benefit for most outcomes relevant to this review. These conclusions are generally consistent with those of the previous review for the USPSTF on this topic.[52] In contrast to the previous review, we found a benefit for cancer mortality (OR, 0.89 [95% CI, 0.80 to 0.99]; 6 RCTs [n=74,237]; I^2=0%) with Vitamin D supplementation (with or without calcium). In addition, a small effect for all-cause mortality that was nearly statistically significant (OR, 0.94 [95% CI, 0.89 to 1.00]; 24 RCTs [n=93,003]; I^2=0%), and was statistically significant in a sensitivity analysis using a pooling method that is not specific to rare events. However, the effect size was very small for all-cause mortality and in addition to being statistically non-significant, its clinical significance is uncertain. In WHI, the individual study which came the closest to finding a statistically significant effect for all-cause mortality, there was an absolute risk reduction (ARD) of 0.4 percent, which translates to a number needed to treat (NNT) of 250 persons for 7 years to avoid one death. For cancer-specific mortality, where again there were almost no individual study findings that were statistically significant, studies reported ARDs on the order of 0.2 percent (NNT, 500 people). There was evidence for little to no impact of vitamin D on the incidence of cancer and CVD outcomes. Further, evidence suggested a small increased risk in kidney stones with long-term use of 1,000 IU or more daily. In both WHI and VITAL the absolute increase in risk was 0.4 percent, which translated, again, to an NNT of 250 for one excess case of kidney stones after 5 to 7 years.

Our findings confirm the previous review's finding that beta-carotene supplementation, especially with concomitant vitamin A use, likely increases the risk of lung cancer incidence in those at high risk for lung cancer. We extended these findings to note that cardiovascular mortality may also be increased with beta-carotene use. We found some information on additional harms that was not identified in the previous review, including weak evidence that the risk of kidney stones may be increased for women with calcium supplementation and for men with vitamin C supplementation. These and all findings in our review are relevant only to micronutrients taken in the form of supplements, and not to dietary intake.

The current review included substantially more evidence on folic acid, however this was still a small body of evidence with most studies reporting only a small number of events, showing weak evidence that folic acid (with or without concomitant vitamin B12), may be associated with an increased risk of cancer incidence. For the first time, we included evidence related to the benefits and harms of vitamin B3 and harms of vitamin B6, zinc, and magnesium. We found weak evidence that vitamin B6 may increase the risk of hip fracture, however the findings were otherwise inconclusive for these supplements so add little of substance to the findings of the previous review. For all supplements, the findings of our review are consistent with other systematic reviews of supplementation use,[58, 154-163] including some reviews of observational studies.[164, 165]

Other Evidence Supporting Our Findings

Vitamin D

Our findings for vitamin D are generally consistent with other reviews, which have found small benefits for all-cause mortality,[157-159] generally with pooled estimates in the range of 0.93 to 0.97, and slightly larger relative reductions in cancer-specific mortality.[58, 158, 160] The review for the USPSTF on vitamin D and calcium supplementation for the prevention of fractures did not find a benefit for all-cause mortality, but found an effect size that was very similar to ours and very close to being statistically significant for vitamin D alone (RR, 0.91 [95% CI, 0.82 to 1.01]).[65] Although observational studies of serum vitamin D levels tend to show increased risk of CVD[166, 167] and some cancers[168-172] with deficient serum levels, other reviews of trial evidence have concluded that vitamin D supplementation does not appear to reduce the risk of cancer[58, 157] or CVD events.[65]

The findings from our pooled analyses that showed a beneficial association with cancer mortality but no association with cancer incidence were surprising. In the studies that reported both outcomes, all showed the same pattern: point estimates suggested a larger benefit for cancer mortality than cancer incidence (although none of the findings were statistically significant). Post-hoc analyses of the findings from VITAL suggested an even stronger impact on cancer mortality when excluding cases in the first 1 year and the first 2 years post-randomization.[93]

The enzyme that converts vitamin D to calcitriol and the vitamin D receptor are expressed in most human tissues. Binding of the vitamin D receptor by calcitriol modifies the expression of over 200 genes that support a wide range of biological functions.[138] A number of these functions inhibit tumor progression, through means such as increased apoptosis (normal cell death as a part of tissue growth) and differentiation (from tumorous into benign tissue), and reduced cell proliferation, inflammation, and vascularization of tumors.[138] Indeed, there are some laboratory, animal, and observational study findings that support a role for vitamin D in tumor progression.[173-176] For example, preclinical and in vivo evidence suggests that vitamin D may suppress tumor growth.[176, 177] In addition, a meta-analysis of 64 studies of 44,165 people with cancer found that higher 25OHD concentration was associated with better cancer outcome.[174] Thus, we concluded that it is possible that there could be a differential impact on cancer incidence and mortality. There are currently two trials of vitamin D underway with primary outcomes of cancer, along with and all-cause mortality or CVD (**Appendix G**). These trials are examining two different dosing regimens and plan to include 2500 and 21,000 participants. Results are expected as soon as 2021 for the smaller of these studies. These studies may help elucidate the discrepancy between cancer incidence and cancer mortality.

Beta-Carotene and Vitamin A

Our results on the potential harms of supplemental beta-carotene are also supported by the broader evidence base in addition to the previous USPSTF review. We found that beta-carotene supplementation (with or without other supplements) was associated with statistically significant paradoxical harm for CVD mortality, lung cancer, and when combined with the vitamin A results, all-cause mortality. The highest magnitude of increased risk was for lung cancer. The

most robust evidence for increased lung cancer risk was from the two studies included in our review of populations at high-risk for lung cancer (ATBC[75] and CARET[62]), which showed that increased lung cancer risk was statistically significant only for current smokers. This finding was supported by another meta-analysis, which did a more detailed examination of subgroup analyses by smoking status provided by the four largest studies in our review.[178] However, study-level subgroup analyses are confounded by heterogeneity of dose and duration and are limited by reduced power due to a small number of events in subgroups by smoking status, particularly in WHS. There was no signal of benefit for any health outcome associated with supplemental beta-carotene use, and limited data from the intermediate outcomes of diabetes incidence and colorectal adenoma further suggest no benefit.[75, 179]

The addition of one vitamin A trial reporting all-cause mortality to the beta-carotene studies rendered the point estimate statistically significant for an increased risk (OR 1.06 [95% CI, 1.01 to 1.12]; 7 RCTs [n=115,117]). Further, two large cohort studies in women suggest a possible increased risk for hip fracture associated with vitamin A supplementation.[140, 141] Guidance from the Institute of Medicine (IOM) states that high beta-carotene intake is not known to cause hypervitaminosis A, however, an upper limit of 3,000 RAE is established for preformed vitamin A which is based on liver abnormalities as the critical endpoint.[7] This guidance also notes that chronic vitamin A toxicity may also be associated with reduced bone mineral density. This is consistent with our finding of a signal for possible increased risk of hip fracture in two cohort studies. Of note, the two trials evaluating supplementation with preformed vitamin A, CARET and SKICAP, both used a dose of 7,500 RAE, which is twice the upper limit.

Other Evidence That Contrasts With Our Findings

Vitamin E

There are a few minor points of departure between our findings and other systematic reviews that underscore the uncertainty of some of our findings. While we found clear evidence that vitamin E had no impact on all-cause mortality and CVD events, another review of primary prevention in adults concluded that vitamin E may reduce the risk of CVD mortality.[180] Our pooled analysis for CVD mortality was not statistically significant, although the point estimate was in the direction of benefit (OR, 0.88 [95% CI, 0.74 to 1.04]). The point estimate in the other review was identical to ours but was statistically significant (RR, 0.88 [95% CI, 0.80 to 0.96]).[180] Their analysis included studies of multivitamins that contained vitamin E in addition to vitamin E alone, in contrast to our meta-analysis that was limited intervention arms examining vitamin E alone. While this might indicate a relatively small effect that is only detectable in very large pooled analyses, the clear lack of association with all-cause mortality CVD events, and cancer incidence led us to conclude that vitamin E most likely has little to no effect on CVD mortality as well.

B Vitamins

Regarding folic acid, in contrast to our review, one network meta-analysis[181] reported a reduction in stroke with folic acid when combined with B6 and with the combination of B6 and B12. However, most of the studies in this analysis were limited to individuals with CVD or a history

of stroke or transient ischemic attack. We found two meta-analyses examining the impact of folic acid on CVD outcomes, although both primarily included persons with pre-existing CVD, so provided little information on prevention in a general population. One of these found no association between folic acid and CVD events (RR, 1.04 [95% CI, 0.98 to 1.11]) in persons with CVD, stroke, or diabetes mellitus.[182] The other meta-analysis found a benefit of folic acid for stroke (RR, 0.79 [95% CI, 0.69 to 0.92]) and a composite CVD outcome (RR, 0.83 [95% CI, 0.73 to 0.93]), although this analysis was limited to trials with persons with known chronic conditions only (e.g., CVD, end-stage renal disease) and trials not eligible for our review (e.g., conducted in China).[183] Thus, we believe evidence for folic acid supplementation for CVD prevention in general populations, with or without vitamin B6 and B12, suggests no effect on MI and stroke and is inconclusive for other CVD outcomes due to the very small number of events in our included studies.

Two of the three folic acid studies reporting cancer incidence in our review found an increased risk with folic acid supplementation. While another meta-analysis showed no such association (RR, 1.06 [95% CI, 0.99 to 1.1]), this meta-analysis was published prior to B-PROOF,[96] the trial with the most cancer outcome events in our review, and which showed an increased risk. One (AFPPS[83]) of two studies reporting prostate cancer included in our review detected an increased risk for prostate cancer with folic acid use. Two other reviews of prospective cohort studies found that higher serum folate levels were associated with higher prostate cancer risk.[184, 185] For example, one reported a 13 percent increase in the odds of prostate cancer for the highest vs. lowest 20% of serum folate levels (OR 1.13, 95% CI, 1.20 to 1.26), and a similar findings for serum B_{12} levels (OR, 1.12 (95% CI, 1.01 to 1.25).[184] However, one of these reviews found no association between high dietary folate (with or without vitamin B12 intake) and increased risk for prostate cancer.[185]

While we find very limited evidence related to vitamin B3, four systematic reviews[183, 186-188] evaluated the evidence for the use of vitamin B3 with or without statins for prevention of CVD events and all-cause mortality. The authors of the Cochrane report[187] found high to moderate quality of evidence of no statistically significant effect of vitamin B3 for all-cause mortality, CVD mortality, and MI, and low quality of evidence of no effect for non-fatal stroke. This review included a mix of primary prevention and secondary prevention studies. Three other reviews were limited to studies in persons with or at increased risk for CVD (e.g., with CVD risk factors).[183, 186, 188] These studies found that the use of vitamin B3 was associated with an increased risk of worsening of diabetes,[186, 188] skin,[186, 188] gastrointestinal,[186] and musculoskeletal adverse events,[186] and increased risk for all-cause mortality.[183] Also, the Cochrane review[187] found that persons who used vitamin B3 were more likely to discontinue treatment, compared with persons randomized to control.

Selenium

While we found no evidence that serious harms are increased with selenium use in the included studies, two systematic reviews[189, 190] showed a small association between selenium supplementation and increased risk for incident diabetes with 200 mcg/day selenium use. This finding was statistically significant in only one of the reviews, however (pooled RR, 1.11 [95% CI, 1.01 to 1.22]; I^2=0%, 5 RCTs).[21] The upper level for safe consumption is currently 400

mcg/day for adults. The IOM report describing the evidence used to establish safe upper limits identified the most common effects associated with excess selenium intake to be hair and nail brittleness and loss (most frequently reported symptoms), gastrointestinal disturbances, skin rash, garlic breath odor, fatigue, irritability, and nervous system abnormalities.[7] They concluded that doses of up to 388 mcg/day for "short periods of time" did not appear to be associated with adverse effects.

Limitations of Our Approach

Our review had several limitations. Due to our focus on CVD and cancer, our review does not address other potential benefits of supplemental vitamins and minerals on other outcomes. There may be some benefits of some supplements that are not covered in our review. For example, folic acid in women who are pregnant or soon to be pregnant is known to be valuable for prevention of neural tube defects in their offspring.[191] In addition, our non-systematic examination of precursor cardiovascular and cancer outcomes suggested possible small effects on blood pressure and lipids for some vitamins or minerals (**Appendix D**). In addition, because we focused on studies in predominantly healthy populations without known nutritional deficiencies, our review also does not cover therapeutic use of supplements in persons with physical symptoms, medical conditions, or nutritional deficits.

We did not do an extensive analysis of the exact formulations of the supplements studied, such as whether they were synthetically produced or naturally derived, or the type of vitamin D provided (cholecalciferol vs. other forms of D3). Given the many dimensions along which studies displayed heterogeneity, we felt it unlikely that this factor would elucidate variability in effect sizes, especially since these types of details were not always provided.

We did not address the effects of vitamin D and calcium on bone health since our focus was on the prevention of CVD and cancer. Although some included studies of vitamin D reported on outcomes such as fractures and bone mineral density, and some found an increased risk of harm, we believe a better source of information on this association are systematic reviews designed to examine this association, such as the review commissioned by the USPSTF to support their recommendation on use of vitamin D and calcium to prevent fractures.[65] This review concluded that Vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence among community-dwelling adults without known vitamin D deficiency, and also found no clear indication of an increased risk.

In addition, due to our focus on serious harms, our review of non-serious harms is not comprehensive. We limited extraction of non-serious harms to those that were experienced by at least 5 percent of participants taking the supplement or those that appeared to have been specified a priori due to known risk. Because some studies reported dozens of specific harms that were reported by participants, most experienced by only a small number of individuals, a substantial number of outcomes were not included for some studies. We believe these data provided little additional value; these outcomes were non-serious and presumably reversible, and there was limited power to detect group differences in these outcomes that were not commonly reported. We also did not address risks of high doses, which are most comprehensively

explicated in the reviews conducted by the IOM for setting tolerable upper limits.[7] One exception is that we included studies with vitamin A and vitamin D doses above the recommended upper limit, for consistency with the previous review. We recommend that these studies be excluded in future USPSTF reviews.

Finally, due to the large number of analyses we conducted, there is a risk of false positive findings due to chance.

Limitations of the Literature

In general, the impacts of individual micronutrients on human health are very difficult to detect in generally healthy populations with adequate nutrition. Supplement exposure is complicated by exposure to nutrients through dietary intake, and some studies reported fairly high levels of independent use of supplements among their study populations. There is variability in how individuals absorb and metabolize nutrients, and interactions among nutrients and between nutrients and myriad enzymes and hormones in the human body complicate our ability to detect their effects. Relatedly, many of the included studies used factorial designs with other background chemoprevention agents in some participants, such as other vitamins and minerals, aspirin, and omega-3 fatty acids. Another limitation is that we had minimal evidence available to explore the impact of dose for most supplements. Supplement doses were wide ranging and the only supplement with sufficient data to explore dose-response associations was vitamin D.

In addition, there are some limitations related to the reporting of outcomes. First, many studies did not report full ascertainment of the primary outcomes for our review. This was primarily the case in studies where CVD and cancer prevention were not primary aims, in which CVD and cancer outcomes were collected through adverse event reporting, sometimes in an open-ended manner. Despite this, many supplements had evidence in more directly relevant studies that were adequately powered for the outcomes relevant to our review, so while these studies add some "noise" to the review, we were still able to draw conclusions with moderate or high strength of evidence for several supplements, including vitamin D, vitamin E, and calcium. Second, many studies reported dozens of outcomes, so some statistically significant findings may be occurring due to chance. Third, effects on such long-term outcomes as cancer, CVD, and all-cause mortality are likely subtle in otherwise healthy adults with reasonably healthy eating patterns, and are presumed to take many years to manifest. Most trials followed patients for less than 10 years, many less than three years, so effects may not yet be realized. One the other hand, there were some large studies with long-term follow-up, particularly among trials of beta-carotene and vitamin E.

Evidence on the impact of supplementation in some important populations was lacking. There was minimal representation of people who are Black, Indigenous, or people of color across all supplements. Some vitamin D trials were limited to older Black women, however these were focused on bone density and provided minimal evidence for CVD and cancer prevention. In addition, although women were generally well-represented for most supplements, there is no large trial of a broad-spectrum multivitamin that included women. Fortunately, there is currently a large trial of approximately 20,000 participants examining the use of a broad-spectrum

multivitamin for cancer and CVD prevention that includes both men and women. Results are expected in the fall of 2021 (**Appendix G**).

Future Research Needs

Continued long-term surveillance of participants in the large included trials of vitamin D would be valuable, since effects on cancer, CVD and mortality may take a decade or more to manifest. Large studies with long-term followup of vitamin D and a broad-spectrum multivitamin for cancer and CVD prevention are underway, which are addressing gaps in the evidence for those supplements (**Appendix G**). However, the degree to which people of color will be represented in these studies is unclear. We urge the investigators conducting these studies to report on the impact of supplement use in racial and ethnic groups, particularly for vitamin D, given an intriguing (albeit post-hoc) signal that vitamin D supplementation may reduce the risk of cancer in Black adults.[93] In the United States, Black adults experience disproportionately high incidence of some cancers and a higher risk for vitamin D deficiency due to the impact of melanin on the synthesis of vitamin D.[192-194] We acknowledge, however, that racial and ethnic inequities in health outcomes are multifactorial and also involve nonbiologic factors.

The evidence base demonstrating no benefit of vitamin E on cancer and CVD is robust and does not warrant resource investment in major new de novo studies. However, examination of CVD mortality with robust ascertainment in the included vitamin E studies that did not report this outcome would be valuable, as well as continued followup of CVD mortality in the existing trials. Such additional followup could be valuable to elucidate the long-term impact on this important outcome with a signal for possible benefit. In addition, the contradictory findings for prostate cancer among between ATBC (which showed an increased risk) and SELECT (which showed a decreased risk) warrants continued followup in these studies and examination in other large vitamin E studies that did not report this outcome.

Most research to date on folic acid for CVD and cancer prevention has been focused on secondary prevention in persons with known CVD, which were not included in our review. Because these reviews suggest a possible reduction in CVD events, particularly stroke, it remains plausible that folic acid could help prevent CVD in general populations as well. Therefore, studies sufficiently powered for CVD outcomes with long-term followup could be valuable. Also, the effect of folic acid administered with other B vitamins on CVD and cancer outcomes remains understudied. There is some evidence that folic acid coupled with vitamins B6 and B12 may reduce homocysteine levels, and therefore large, long-term controlled trials to examine the impact of these B vitamins on CVD may warrant further investigation. However, these possible benefits must be weighed against the weak evidence we found that folic acid may increase the risk of cancer incidence. Examination of overall cancer incidence, colorectal cancer, and prostate cancer as outcomes in studies that have not yet reported them would be valuable first steps before planning larger CVD prevention studies, as would longer-term followup on cancer outcomes in studies that did report them.

Studies of the effects of vitamin C in preventing cancer and CVD for women and people of color may be valuable, given the paucity of this evidence. However, careful monitoring of participants

for early indications of kidney stone formation may be important, since we found weak evidence of an increased risk of kidney stones in men.

Given the risks identified for beta-carotene, we see no need for further research on the role of beta-carotene in CVD and cancer prevention, nor, by extension, for vitamin A.

Conclusions

Vitamin and mineral supplementation provides little to no benefit in preventing cancer, CVD, and death, with the exception of a benefit for cancer-related mortality and a possible small benefit for all-cause mortality with vitamin D use. Beta-carotene increases the risk of lung cancer and other harmful outcomes in persons at high risk of lung cancer. Data were absent or insufficient to draw conclusions for any of the B vitamins, iron, zinc, or magnesium.

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Figure 2. Meta-Analysis or Best Evidence Summary for Multivitamins*†

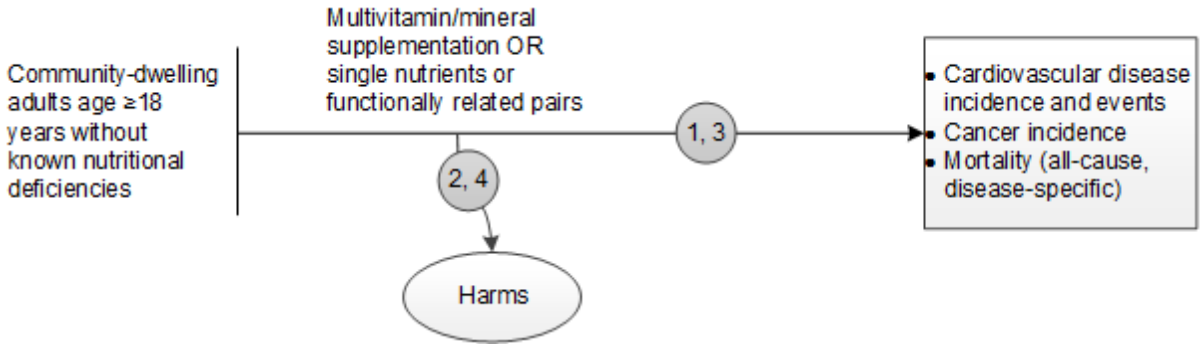
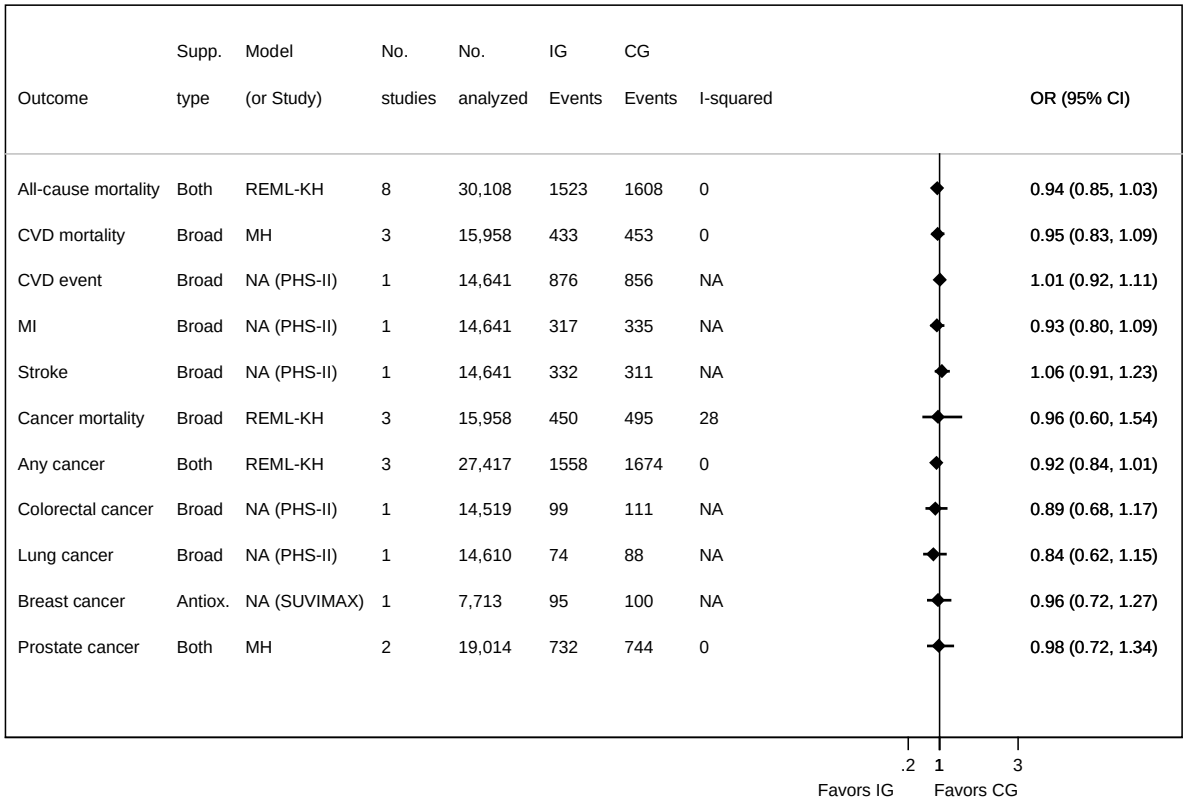


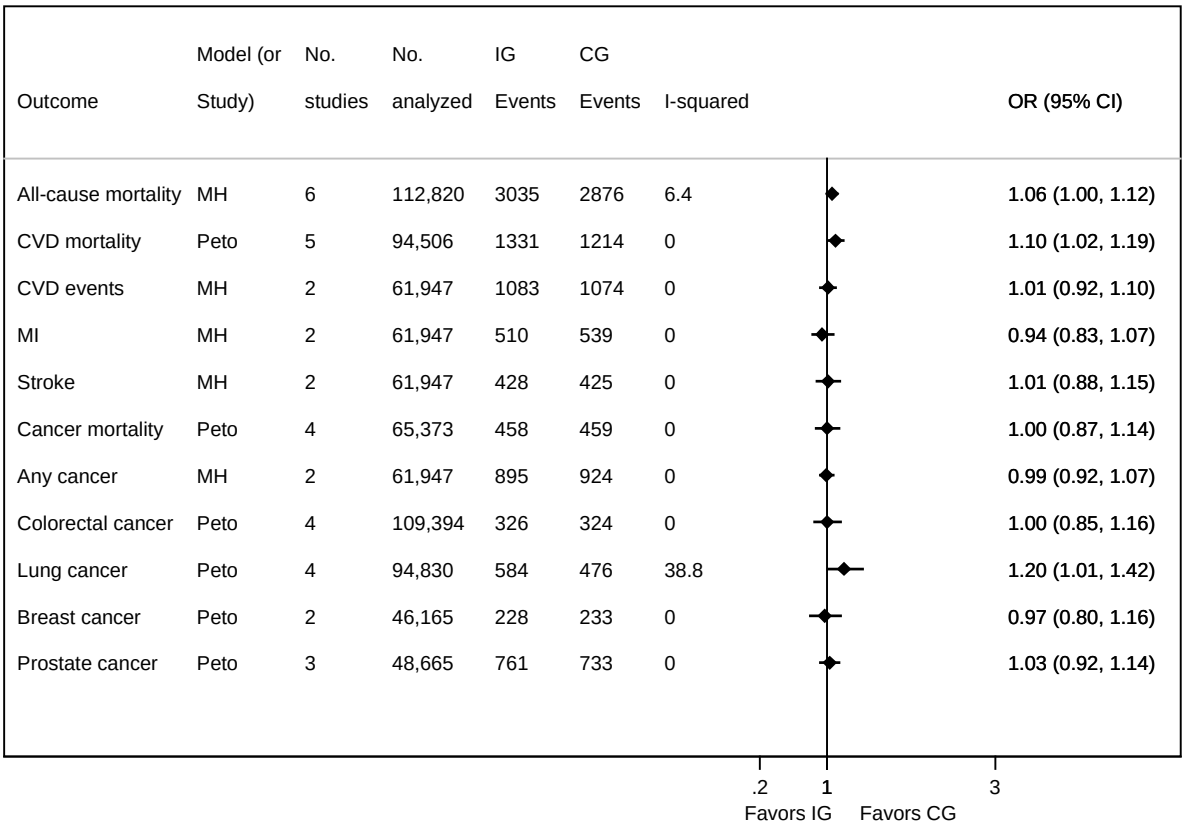
Figure 2. Meta-Analysis or Best Evidence Summary for Multivitamins*†



*Supplement type (column 2) refers to whether the included studies examined broad spectrum multivitamins ("Broad"), antioxidant focused multivitamins ("Antiox."), or both ("Both").
†I-squared values shown for analyses using the MH model are taken from sensitivity analyses using random effects models; the MH model is based on a fixed effect model where calculation of I-squared is not applicable because it is assumed to be 0. If data were insufficient for meta-analysis, findings from the largest and most comprehensive study reporting the outcome are presented.

Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; MH = Mantel-Hantzel; MI = Myocardial infarction; NA = Not applicable; OR = Odds ratio; PHS-II = Physicians' Health Study II; REML-KH = Restricted Maximum Likelihood model with the Knapp-Hartung adjustment; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntioXydants

Figure 3. Meta-Analysis Summary for Beta-Carotene*



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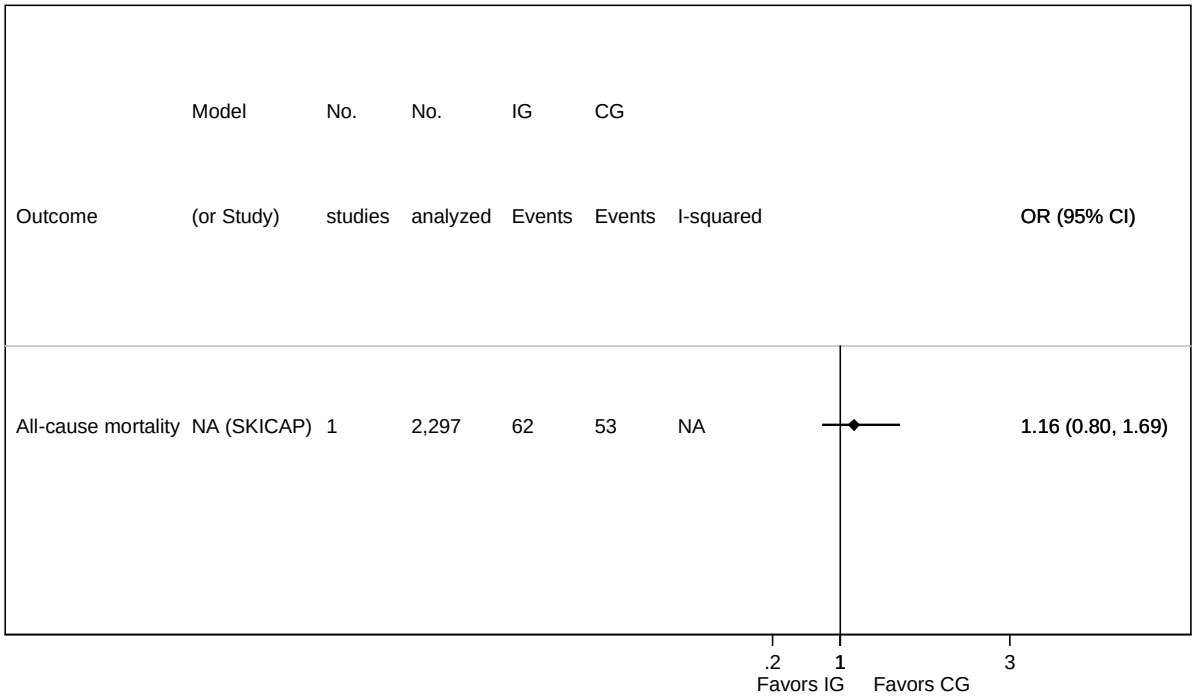
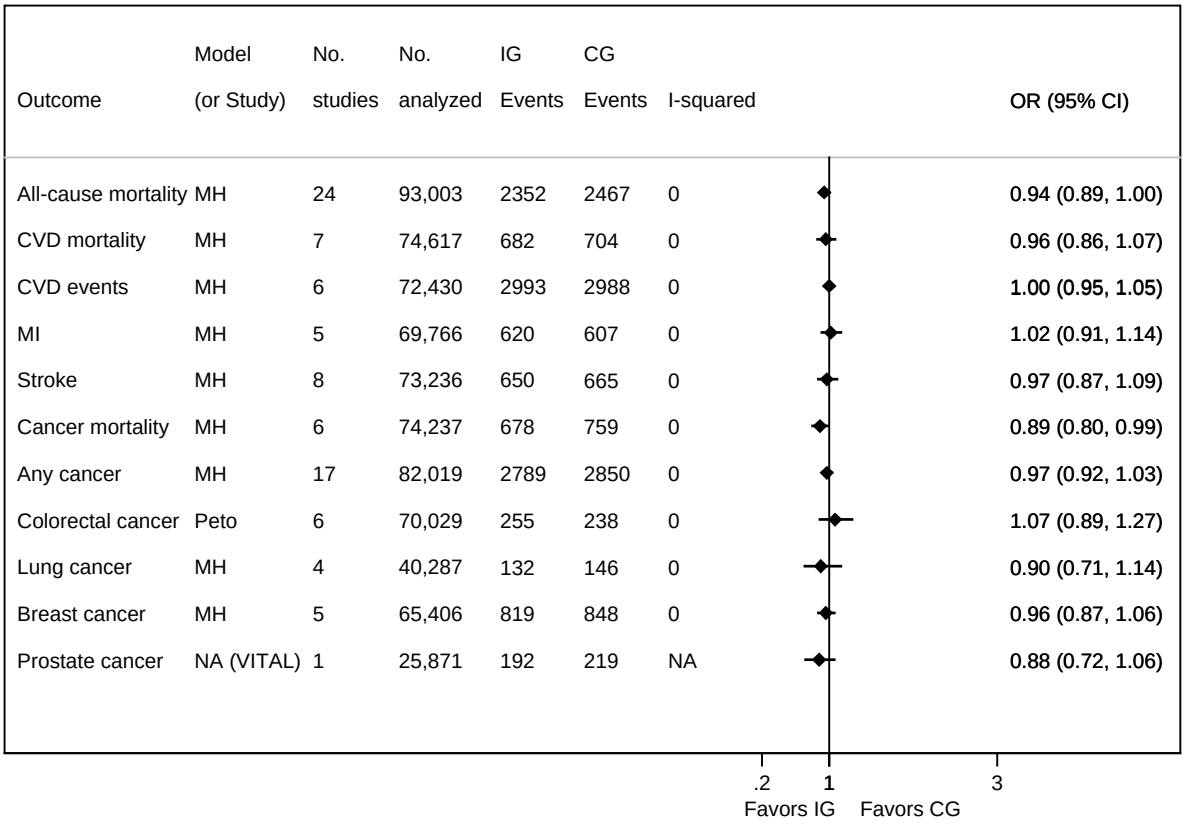
Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; MH = Mantel-Haenszel common (fixed) effects model; MI = Myocardial infarction; OR = Odds ratio; Peto = Peto odds ratio

Figure 4. Evidence Summary for Vitamin A



Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; OR = Odds ratio; SKICAP = SKIn CAncer Prevention

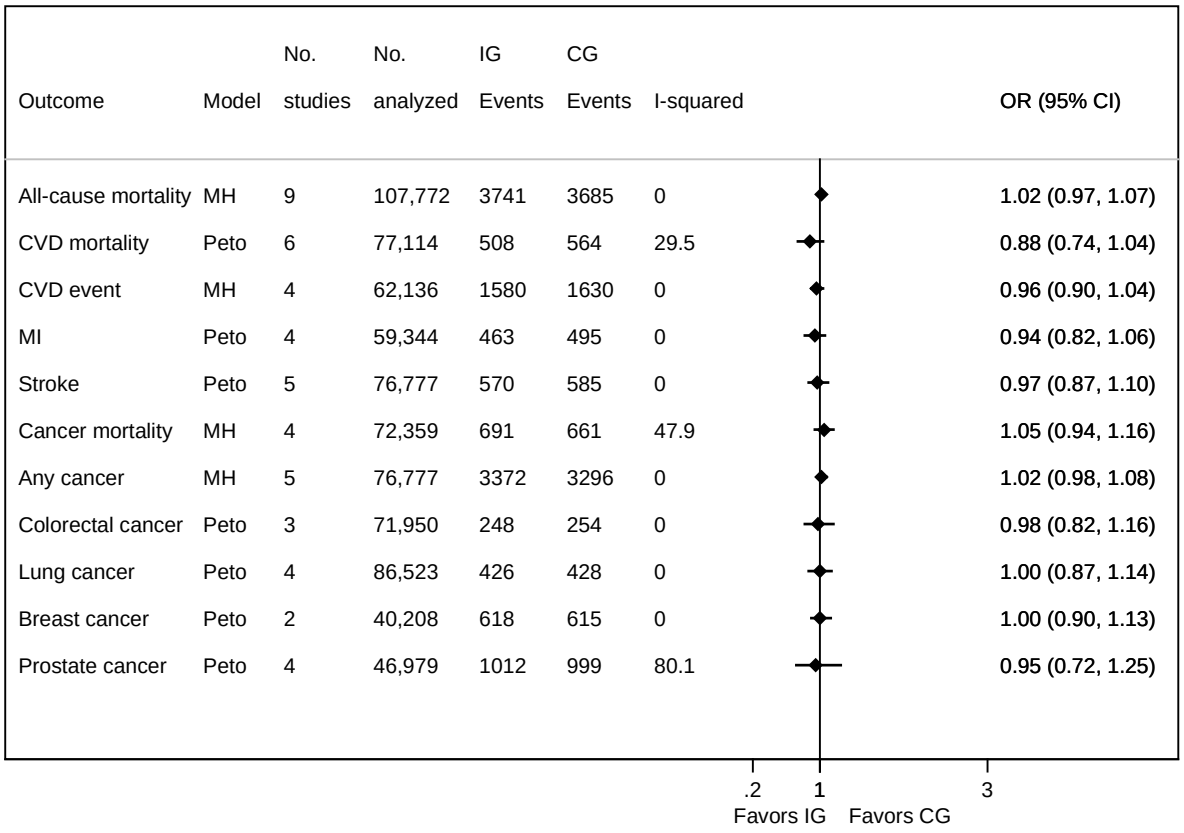
Figure 5. Meta-Analysis or Best Evidence Summary for Vitamin D (With or Without Calcium)*



*I-squared values shown for analyses using the MH model are taken from sensitivity analyses using random effects models; the MH model is based on a fixed effect model where calculation of I-squared is not applicable because it is assumed to be 0. If data were insufficient for meta-analysis, findings from the largest and most comprehensive study reporting the outcome are presented.

Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; MH = Mantel-Haenszel common (fixed) effects model; MI = Myocardial infarction; NA = Not applicable; OR = Odds ratio; Peto = Peto odds ratio; VITAL = VITamin D and OmegA-3 TriaL

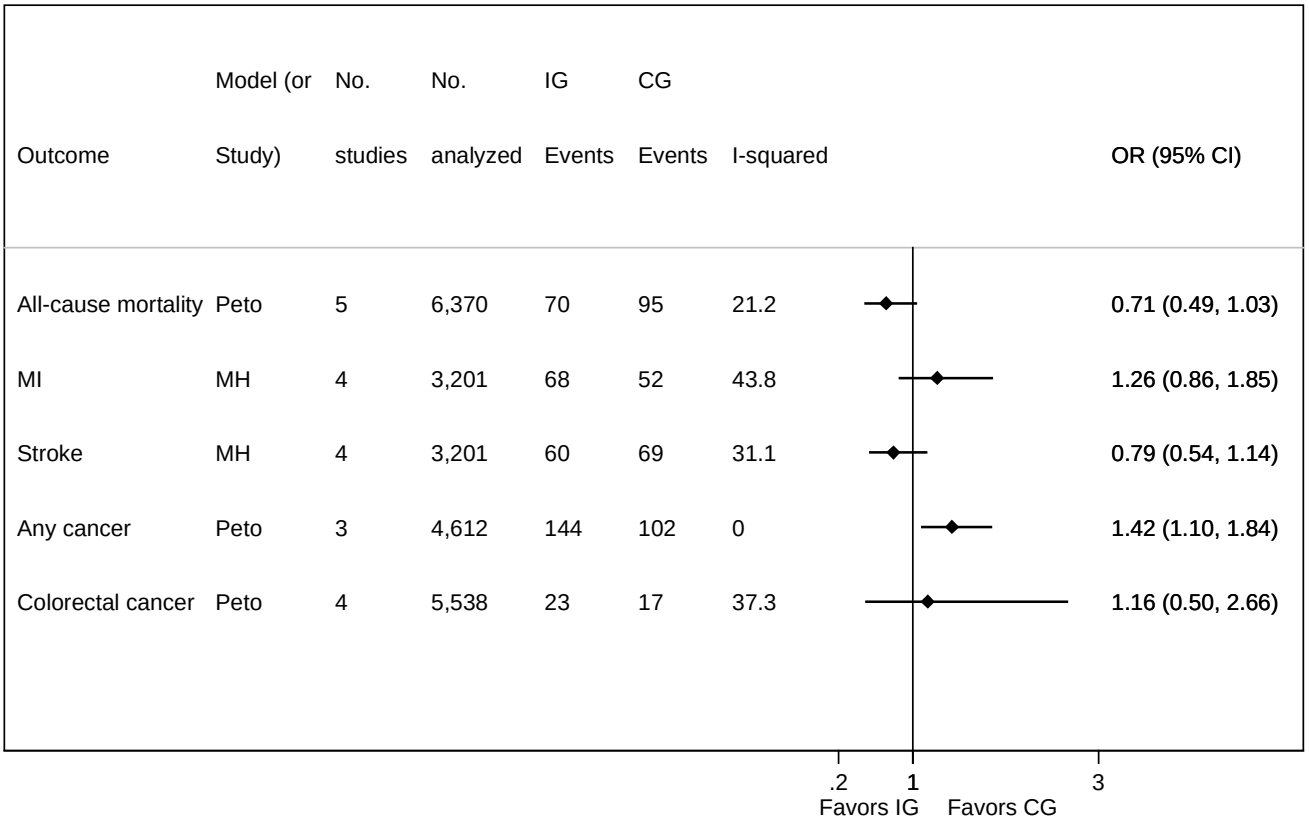
Figure 5. Meta-Analysis or Best Evidence Summary for Vitamin D (With or Without Calcium)*



*I-squared values shown for analyses using the MH model are taken from sensitivity analyses using random effects models; the MH model is based on a fixed effect model where calculation of I-squared is not applicable because it is assumed to be 0.

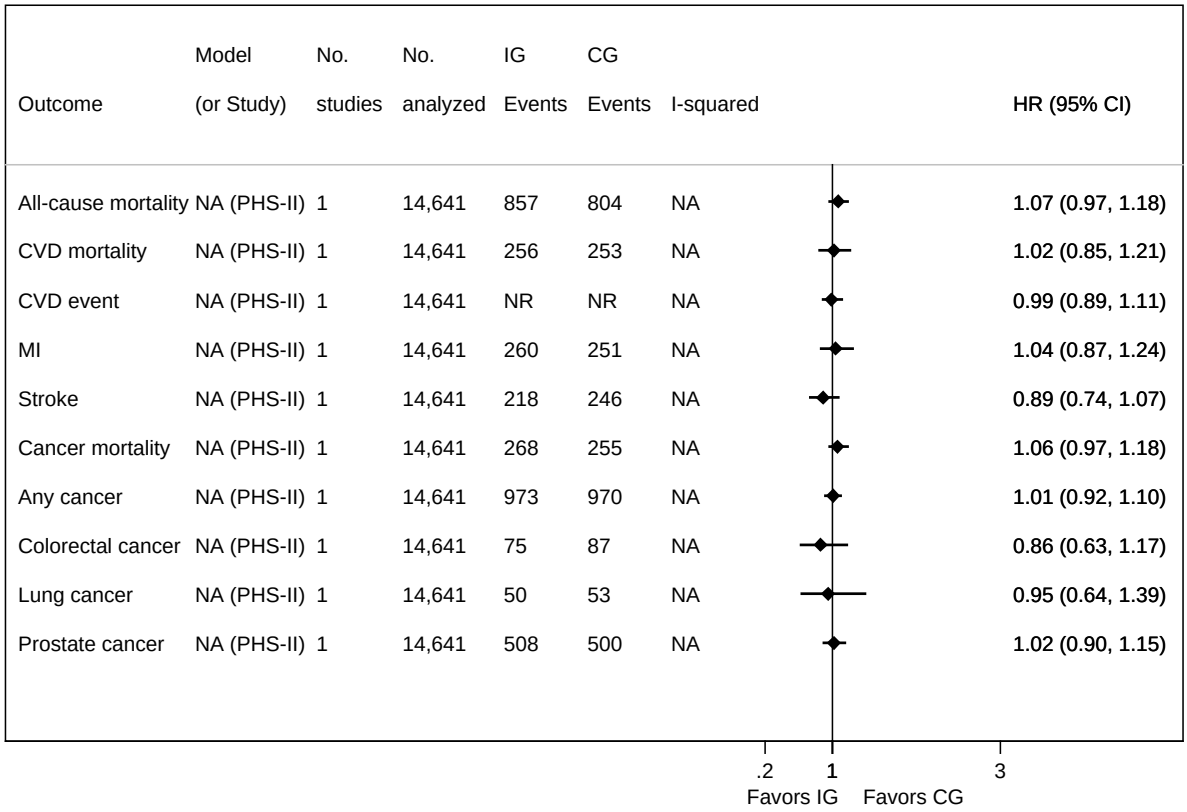
Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; MH = Mantel-Haenszel common (fixed) effects model; MI = Myocardial infarction; OR = Odds ratio; Peto = Peto odds ratio

Figure 7. Meta-Analysis Summary for Folic Acid



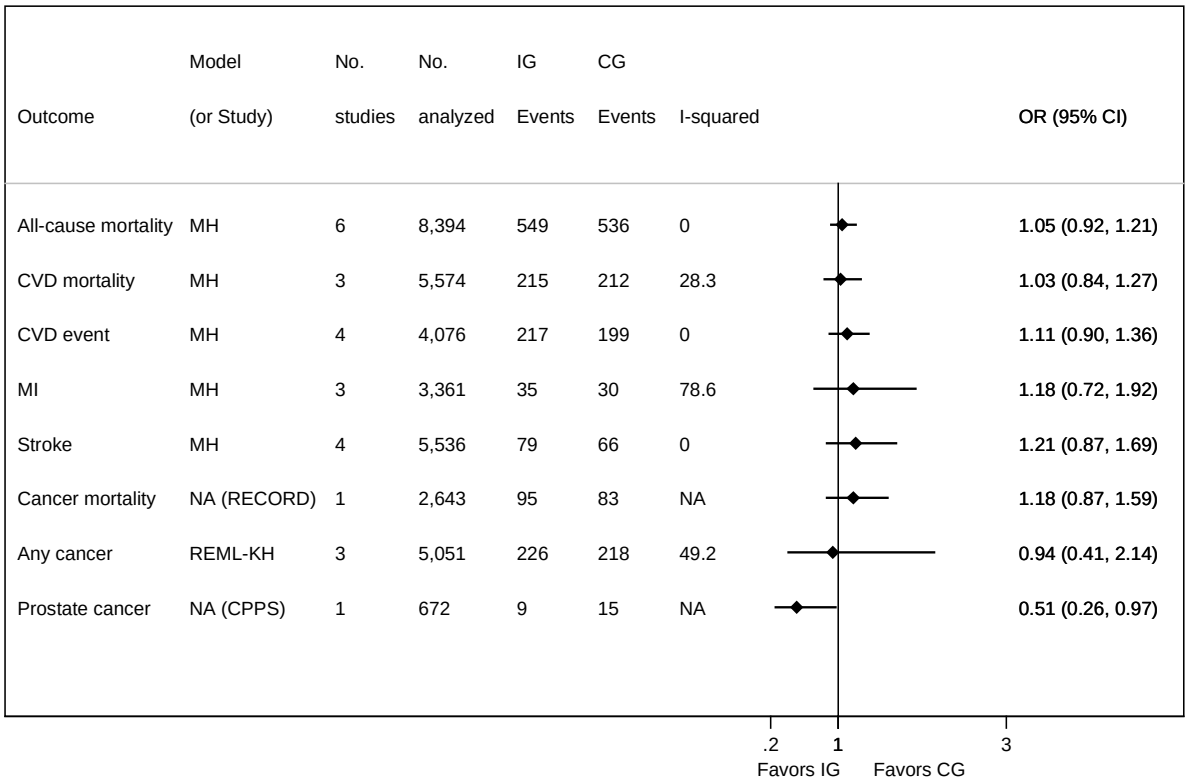
Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; OR = Odds ratio; Peto = Peto odds ratio

Figure 8. Evidence Summary for Vitamin C



Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; MI = Myocardial infarction; NA = Not applicable; PHS-II = Physicians' Health Study II

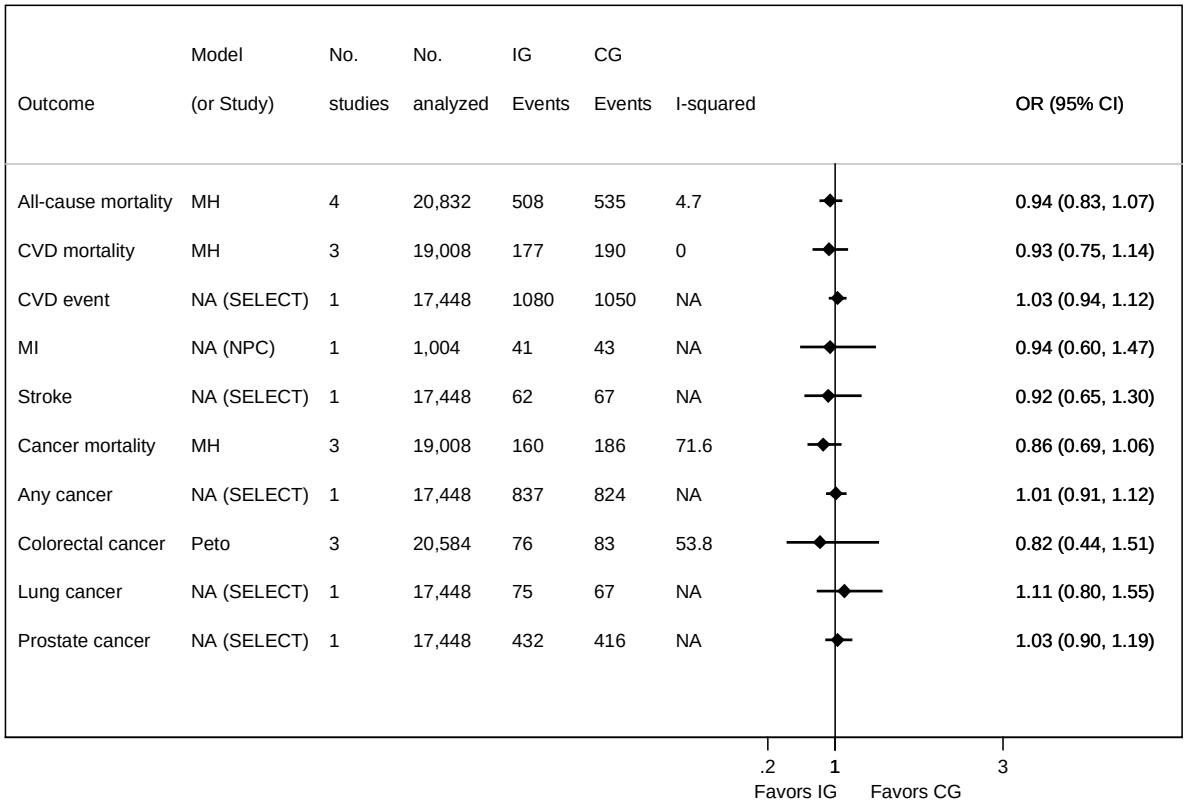
Figure 9. Meta-Analysis or Best Evidence Summary for Calcium (Without Vitamin D)*



*I-squared values shown for analyses using the MH model are taken from sensitivity analyses using random effects models; the MH model is based on a fixed effect model where calculation of I-squared is not applicable because it is assumed to be 0. If data were insufficient for meta-analysis, findings from the largest and most comprehensive study reporting the outcome are presented.

Abbreviations: CG = Control group; CI = Confidence interval; CPPS = Calcium Polyp Prevention Study; CVD = Cardiovascular disease; IG = Intervention group; MI = Myocardial infarction; NA = Not applicable; OR = Odds ratio; RECORD = Randomized Evaluation of Calcium OR vitamin D; REML-KH = Restricted Maximum Likelihood model with the Knapp-Hartung adjustment

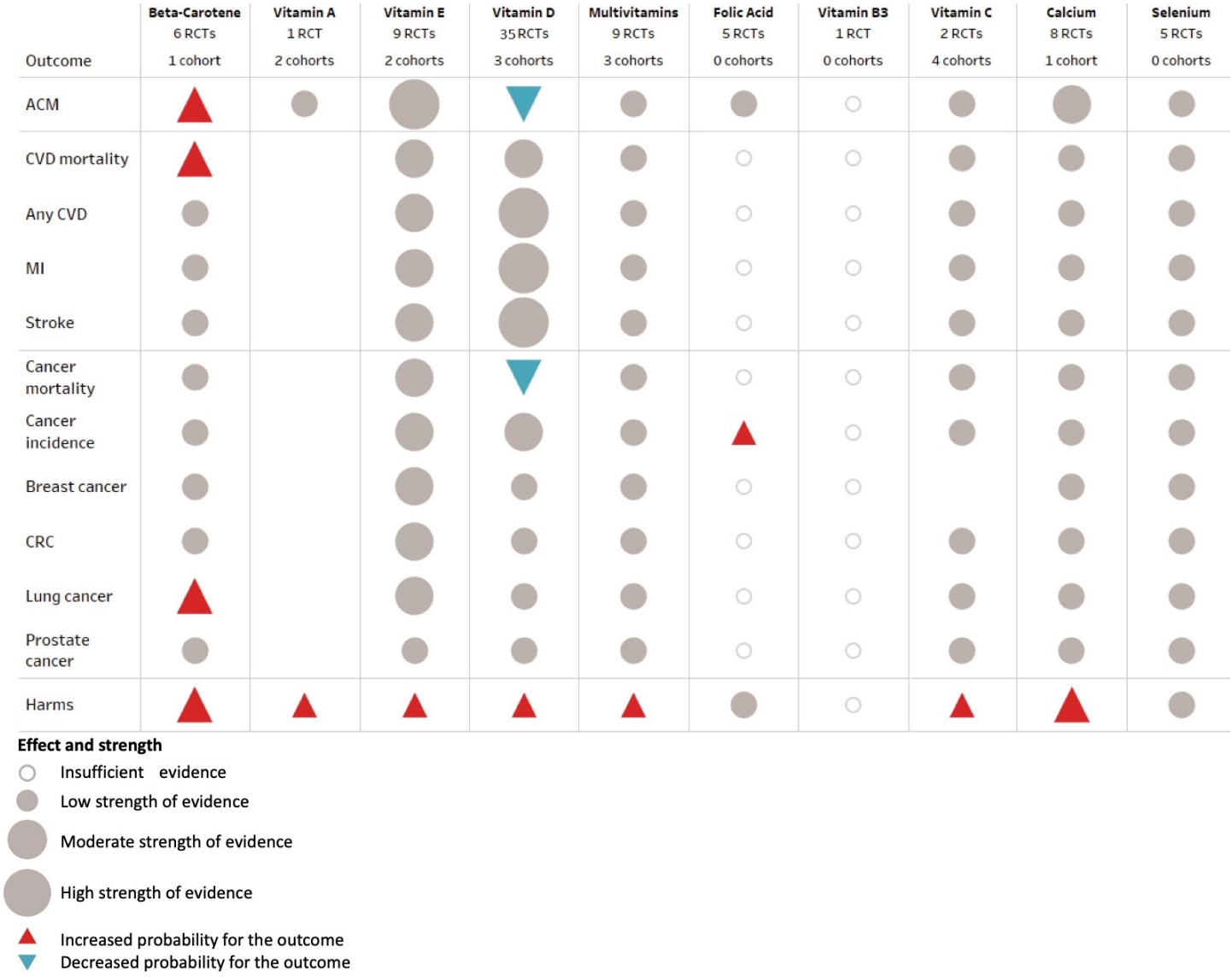
Figure 10. Meta-Analysis or Best Evidence Summary for Selenium*



*I-squared values shown for analyses using the MH model are taken from sensitivity analyses using random effects models; the MH model is based on a fixed effect model where calculation of I-squared is not applicable because it is assumed to be 0. If data were insufficient for meta-analysis, findings from the largest and most comprehensive study reporting the outcome are presented.

Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; MH = Mantel-Haenszel common (fixed) effects model; MI = Myocardial infarction; NPC = Nutritional Prevention of Cancer; OR = Odds ratio; Peto = Peto odds ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial

Figure 11. Overview of Evidence Base and Strength of Evidence for Multivitamin Supplements and Single or Paired Nutrient Supplements*



*Not shown in the figure are one study of harms for each of vitamin B6, zinc, and magnesium; insufficient strength of evidence in all three cases.

Abbreviations: ACM = All-cause mortality; CRC = Colorectal cancer; CVD = Cardiovascular disease; RCT = Randomized controlled trial

Table 1. Past 30-Day Use of Any Dietary Supplement or Multivitamin-Minerals by Demographic and Socioeconomic Characteristics (NHANES 2011–2014; N=11,024)[13]

Category	Any dietary supplement*			Multivitamin-minerals†		
	Total (%)	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)
Overall	52.1	45.4	58.6	31.2	28.3	34.0
Age group (years)						
19–30	35.5	31.6	40.0	22.6	19.5	26.1
31–50	45.2	38.4	51.7	29.1	25.1	33.0
51–70	63.3	56.3	69.8	35.4	34.5	36.2
≥71	74.9	69.3	79	42.7	40.9	44.0
Race/ethnicity						
White	58.2	51.3	64.8	35.7	32.8	38.5
Black	40.3	33.9	45.5	22.6	20.3	24.6
Hispanic	35.3	27.5	43.2	19.7	15.3	24.2
Asian	53.5	47.3	58.9	28.8	28.2	29.2
Education						
< HS	37.8	30.2	45.9	20.6	17.7	23.7
HS diploma/GED	47.2	36.7	58.2	25.2	19.2	31.6
> HS	58.1	53.5	62.3	36.3	35.0	37.5
Poverty-income ratio						
PIR ≤130%	38.6	30.2	45.7	20.5	15.5	24.6
PIR 131–350%	50.3	41.9	58.3	29.1	25.4	32.6
PIR ≥350%	63.5	58.3	69.1	40.7	38.8	42.9
Food security						
Food-insecure	36.4	29.1	48.3	18.9	15.5	22.1
Food-secure	55.1	43.2	61.6	33.5	30.6	36.3
SNAP Participation						
SNAP Participant	32.1	23.7	38.9	16.4	12.4	19.5
Income ineligible for SNAP	59.0	52.8	65.2	36.6	34.1	39.1

*Any single-nutrient supplement, multivitamin-multimineral, multivitamin, or botanical
†A product containing three or more vitamins and one or more mineral counts per supplement
Abbreviations: HS = high school; PIR = poverty-income ratio; SNAP = Supplemental Nutrition Assistance Program

Table 2. Age-Adjusted Prevalence (Percentage) of Participant-Reported Cancers and Cardiovascular Disease (NHIS 2018)[18]*

Population	Cardiovascular disease			Cancer			
	All types of heart disease†	Stroke		Any cancer	Breast cancer	Cervical cancer	Prostate cancer
Total	11.2	2.8		8.3	1.6	0.9	2.1
Age (years)							
18–44	4.8	0.6		1.8	0.2	0.8	‡
45–64	11.8	3.1		9.6	1.7	1.2	1.4
65–74	23.6	6.9		22.2	4.7	1.2	7.4
75+	37.3	11.8		31.3	7.0	0.7	12.3
Sex							
Males	12.6	3.1		7.6	0.0	NA	2.1
Females	10.1	2.6		9.1	3.0	0.9	NA
Race/ethnicity							
White	11.5	2.6		9.1	1.6	1.0	2.0
Black	10.0	3.9		5.1	1.7	0.9	2.8
AI/AN	14.6	3.0		7.1	1.0	‡	‡
Asian	7.7	2.7		3.9	1.1	0.1	1.7
Hispanic	8.2	2.5		4.2	0.7	0.4	1.5
Education							
< High school	12.9	5.1		6.8	1.3	1.4	1.6
High school/GED	13.1	3.6		8.7	1.9	1.4	2.3
Some college	13.3	3.2		10.5	2.1	1.4	1.9
≥ College degree	10.9	2.2		10.5	1.9	0.6	3.1
Poverty status							
<100% FPL	13.5	5.6		7.3	1.5	1.7	1.6
100-200% FPL	12.9	4.1		7.2	1.4	1.2	1.6
>200% FPL	10.9	2.3		8.8	1.7	0.7	2.3

* Estimates based on respondent-reported data
† Includes coronary heart disease, angina, heart attack, or any other heart condition or disease
‡ Estimate is considered unreliable, as specified in National Center for Health Statistics Data Presentation Standards for Proportions

Abbreviations: AI/AN = American Indian/Alaska Native; FPL = Federal Poverty Level; GED = General Educational Development high school equivalency diploma; NA = not applicable; NHIS = National Health Interview Survey

Table 3. Age-Standardized Cancer Incidence and Mortality per 100,000 Population by Sex and Race/Ethnicity (SEER 2012–2016 for Incidence and 2013–2017 for Mortality)[21]

Population	All Races		White		Black		Asian/PI		AI/AN		Hispanic	
	Inc.	Mort.	Inc.	Mort.	Inc.	Mort.	Inc.	Mort.	Inc.	Mort.	Inc.	Mort.
Any cancer												
Overall	447.9	158.2	467.5	162.9	466.9	186.4	293.6	98.9	401.4	166.0	348.9	111.8
Males	487.9	189.3	503.0	193.8	547.6	233.2	296.5	117.4	420.0	200.3	377.8	135.6
Females	421.4	135.5	444.5	139.9	412.8	157.5	295.7	85.7	391.9	141.0	333.6	95.1
Prostate cancer												
Males only	108.1	19.1	101.7	18.0	182.3	38.7	56.3	8.6	75.7	21.2	98.2	15.7
Lung and bronchial cancer												
Males	69.5	49.3	73.4	51.8	83.9	60.4	44.4	29.3	62.9	46.5	36.2	24.1
Females	51.8	33.2	57.5	36.8	49.3	31.9	28.2	16.9	51.2	32.6	23.1	12.6
Breast cancer												
Females only	126.8	20.3	133.0	20.3	129.6	28.4	96.5	11.5	102.5	16.6	96.1	14.0
Colorectal cancer												
Males	45.1	16.6	44.7	16.3	55.0	23.8	36.2	11.5	51.9	23.1	42.9	14.1
Females	34.4	11.7	34.4	11.7	40.8	15.6	26.3	8.1	41.8	15.0	30.0	8.7

Abbreviations: AI/AN = American Indian/Alaska Native; Inc. = incidence; Mort. = mortality; PI = Pacific Islander

Table 4. Recommendations From Other Organizations

Organization	Year	Recommendation Statement
Academy of Nutrition and Dietetics[39]	2018	It is the position of the Academy of Nutrition and Dietetics that micronutrient supplements are warranted when requirements are not being met through the diet alone. Those with increased requirements secondary to growth, chronic disease, medication use, malabsorption, pregnancy and lactation, and aging may be at particular risk for inadequate dietary intakes. However, the routine and indiscriminate use of micronutrient supplements for the prevention of chronic disease is not recommended, given the lack of available scientific evidence.
Canada Cancer Society[43]	2018	The best way to get all the vitamins and minerals you need is to make healthy food choices; however, individuals are encouraged to discuss supplementation with vitamin D (1,000 IU) during the fall and winter months with their physician.
World Cancer Research Fund/American Institute for Cancer Research[40]	2018	Do not use dietary supplements for cancer prevention. Aim to meet nutritional needs through diet alone.
National Osteoporosis Foundation and the American Society for Preventive Cardiology[41]	2017	The expert panel concluded that calcium, with or without vitamin D intake, and from food or supplements, has no relation (beneficial or harmful) to risks for CVD, cerebrovascular disease, or mortality in generally healthy adults. Therefore, they recommend that calcium intake from food and supplements that does not exceed the tolerable upper level of intake (2000 to 2500 mg/d defined by the National Academy of Medicine) be considered safe from a cardiovascular perspective.
Dietary Guidelines 2015-2020 for Americans (U.S. Department of Health and Human Services and U.S. Department of Agriculture)[4]	2015	Nutrient needs should be met primarily from nutrient-dense foods because, in addition to vitamins and minerals, they contain fiber and other naturally occurring substances with beneficial health effects.
American Heart Association[42]	2014	We recommend that healthy people get adequate nutrients by eating a variety of foods in moderation, rather than by taking supplements.

Table 5. Table of Study, Intervention, and Population Characteristics for Studies of Multivitamin Use, Sorted by Study Design, Then Author (KQs 1 and 2)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Type	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ1	KQ2	Ascertain-ment
RCT												
Avenell, 2005 (MAVIS)[106] Fair		910 (91.6%)	Broad	1 (1)	GBR	Other: Infection-related morbidity	Adults age ≥65 years	Mean age: 72 % Female: 47 % White: NR % Black: NR Mean BMI: 28.0 % Curr. smoker: 13		X	X	ACM: NR Ca: NA CVD: NA
Baeksgaard, 1998[124] Fair		240 (82.9%)	Broad	2 (2)	DNK	Other: Bone mineral density	Women aged 58-67 years	Mean age: 62 % Female: 100 % White: 100 % Black: 0 Mean BMI: NR % Curr. smoker: NR	Vit D: NR Ca: 2.3 mmol/L	X	X	ACM: NR Ca: NA CVD: NA
Bonelli, 2013[95] (NA) Fair		411 (80.3%)	Antiox.	5 (5)	ITA	Other: Recurrent colorectal adenoma	Adults aged 25-75 years with at least one adenoma recently removed from colon	Mean age: 58 % Female: 38 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR		X		ACM: NR Ca: NR CVD: NA
Chylack, 2002 (REACT)[85] Fair	X	297 (100%)	Antiox.	2.8 (2.8)	USA, GBR	Other: Age-related cataracts	Adults age ≥40 years with early cataract	Mean age: 66 % Female: 59 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 19		X	X	ACM: NR Ca: NR CVD: NR
CTNS Study Group, 2008 (CTNS)[133] Good		1020 (99.3%)	Broad	13 (13)	ITA	Other: Age-related cataract	Adults aged 55 to 75 years with early cataract or no cataract	Mean age: 68 % Female: 45 % White: NR % Black: NR Mean BMI: 27.9 % Curr. smoker: 18		X	X	ACM: Full Ca: Self-report CVD: Self-report

Table 5. Table of Study, Intervention, and Population Characteristics for Studies of Multivitamin Use, Sorted by Study Design, Then Author (KQs 1 and 2)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Type	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ1	KQ2	Ascertain-ment
Hercberg, 2004 (SU.VI.MAX)[71] Good	X	13017 (93.5%)	Antiox.	8 (7.5, 8.9, 12.5)	FRA	CVD, Cancer	Adults age 35-60 years	Mean age: 48 % Female: 60 % White: NR % Black: NR Mean BMI: 23.8 % Curr. smoker: 16		X	X	ACM: Full Ca: Full CVD: Full
Pike, 1995[122] Fair		47 (74.5%)	Broad	1 (1)	CAN	Other: Immune function	Adults age 60 or older	Mean age: 69 % Female: 72 % White: 100 % Black: 0 Mean BMI: NR % Curr. smoker: NR		X	X	ACM: Full Ca: NR CVD: NA
Rucklidge, 2014[100] Fair		80 (92.5%)	Broad	0.15 (0.15)	NZL	Other: ADHD	Age ≥16 years with ADHD	Mean age: 35 % Female: 34 % White: 80 % Black: NR Mean BMI: NR % Curr. smoker: NR			X	ACM: NA Ca: NA CVD: NA
Sesso, 2008 (PHS-II)[80] Good	X	14641 (98.0%)	Broad	11.2	USA	CVD, Cancer	US male physicians aged ≥ 50 years	Mean age: 64 % Female: 0 % White: NR % Black: NR Mean BMI: 26 % Curr. smoker: 4	Vit E: NR Vit C: NR	X	X	ACM: Full Ca: Full CVD: Full
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies)	Varied	<2 2-4 <5 5-9 ≥10 10-14 ≥15 (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	Vit E: NR Vit D: NR Ca: NR BC: NR Vit C: NR		X	ACM: NA Ca: NA CVD: NA

Table 5. Table of Study, Intervention, and Population Characteristics for Studies of Multivitamin Use, Sorted by Study Design, Then Author (KQs 1 and 2)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Type	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ1	KQ2	Ascertain-ment
Rautiainen, 2010 (SMC)[145] Fair		38984 (63.1%)	Varied	8.2 (8.2)	SWE	Other: Cataract	Women aged 49-83 years	Mean age: 61 % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 25			X	ACM: NA Ca: NA CVD: NA
Zheng Selin, 2013 (COSM)[142] Fair		27343 (100%)	Varied	11 (8.4, 11)	SWE	Other: Cataracts	Men age 45-79 years	Mean age: 58 % Female: 0 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 25	Vit E: NR Vit C: NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than multivitamins

Abbreviations: ACM = All-cause mortality; ADHD = Attention hyper deficit disorder; Antiox. = Antioxidant; BC = Beta carotene; BL = Baseline; BMI = Body mass index; Ca = Calcium; COSM = Cohort of Swedish Men; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; Curr. = Current; CVD = Cardiovascular disease; FUP = Follow up; MAVIS = Mineral and Vitamin Intervention Trial; NA = Not applicable; NHS-I = Nurse' Health Study; NR = Not reported; PHS-II = Physicians' Health Study; RCT = Randomized controlled trial; REACT = Roche European American Cataract Trial; SMC = Swedish Mammography Cohort; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants; Vit E = Vitamin E; Vit C = Vitamin C

Table 6. Vitamin and Mineral Components in the Multivitamin Trials

Vitamin/mineral	Units	Bonelli, 2013[95]	REACT[85]	SU.VI.MAX[71]	Baeksgaard, 1998[124]	CTNS[133]	MAVIS[106]	Pike, 1995[122]	PHS-II[80]	Rucklidge, 2014[100]
Number of components		4	3	5	13	26	16	16	31	27
Multivitamin Type		Antioxidant	Antioxidant	Antioxidant	Broad	Broad	Broad	Broad	Broad	Broad
Beta-carotene	IU/day		30,006	1,000					*	
Boron	mg/day								0.15	2.4
Calcium	mg/day					162		162	200	1,320
Chloride	mg/day					36.3			72.6	
Chromium	mcg/day					25			130	624
Copper	mg/day					2	0.75	1.5	2	7.2
Iodine	mcg/day					150	150	225	150	204
Iron	mg/day					18	14	27	4	13.7
Magnesium	mg/day					100	0	100	100	600
Manganese	mg/day					2.5	1		3.5	9.6
Molybdenum	mcg/day					25			160	144
Nickel	mcg/day								5	29.4
Phosphorus	mg/day					125			48	840
Potassium	mg/day					40			0.08	240
Selenium	mcg/day	200		100		25			20	204
Silicon	mg/day								2	
Vanadium	mcg/day								10	1,194
Vitamin A	IU/day	6,666			2,666	5,000	2,326	2,668	5,000	5,760
Vitamin B1 (Thiamin)	mg/day					1.5	1.4	2.18	1.5	18
Vitamin B12	mcg/day				1,400	6	1	9	25	900
Vitamin B2 (Riboflavin)	mg/day				1.6	1.7		2.6	1.7	13.5
Vitamin B3 (Niacin or Nicotinamide)	mg/day				18	20	18	30	20	90

Table 6. Vitamin and Mineral Components in the Multivitamin Trials

Vitamin/mineral	Units	Bonelli, 2013[95]	REACT[85]	SU.VI.MAX[71]	Baeksgaard, 1998[124]	CTNS[133]	MAVIS[106]	Pike, 1995[122]	PHS-II[80]	Rucklidge, 2014[100]
Vitamin B5 (Pantothenic acid)	mg/day				6	10	6		10	12.6
Vitamin B6	mg/day					2		3.65	3	36
Vitamin B7 (Biotin)	mcg/day				150	30			30	1,080
Vitamin B9 (Folic acid)	mcg/day				100	400	200	400	400	1,440
Vitamin C	mg/day	180	750	120	60	60	60	90	60	600
Vitamin D	IU/day					400	200	200 (D2)	400	1,440
Vitamin E	IU/day	44.7	330	30 mg†	14.9	30	11	67.05	45	360
Vitamin K	mcg/day					25			10	
Zinc	mg/day	30		20	0	15	15	22.5	15	48
Other					Participants also received 1000 mg calcium carbonate and 560 IU cholecalciferol		2 mg pyridoxine			Choline bitartrate (540 mg), dl-Phenylalanine (360 mg), Citrus bioflavonoids (240 mg), Inositol (180 mg), Glutamine (180 mg), Methionine (60 mg), Grape seed (45 mg), Ginkgo biloba (36 mg), Germanium sesquioxide (20.7 mg)

*40 percent as beta-carotene supplemented as vitamin A
†Unknown type of vitamin E
Empty cells mean that the vitamin/mineral was not a part of the pill or capsule

Abbreviations: CTNS=Clinical Trial of Nutritional Supplements; IU = international unit(s); MAVIS = Mineral and Vitamin Intervention Trial; mcg = microgram(s); mg = milligram(s); PHS-II = Physicians' Health Study II; REACT = Roche European American Cataract Trial; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntioXydants

Table 7. Table of Study, Intervention, and Population Characteristics for Studies of Beta-Carotene Use (With or Without Vitamin A), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
ATBC Study Group, 1994 (ATBC)[75] Good	X	29133 (100%)	IG1: 40000 mcg RAE + 111 IU Vitamin E IG2: 40000 mcg RAE	6.1 (6.1, 8, 11, 14, 22.1, 24.1)	FIN	Cancer	Male smokers age 50-69 years	Mean age: 57 % Female: 0 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 100	BC: 0.32 mcmol/L Vit A: 2.01 mcmol/L Vit E: 26.7 mcmol/L	X	X	ACM: Full Ca: Full CVD: Full
Green, 1999 (NSCPS)[72] Good	X	1621 (85.3%)	60000 mcg RAE	4.5 (4.5)	AUS	Cancer	Adults, age 20-69 years	Mean age: 49 % Female: 56 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR	X	X	ACM: NR Ca: Full CVD: NR
Greenberg, 1990 (SCPS)[86]	X	1805 (100%)	100000 mcg RAE	4.3 (2, 5, 8.2)	US	Cancer	Adults aged <85 years with prior biopsy-proven basal or squamous cell carcinoma	Mean age: 63 % Female: 31 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 19	BC: 0.42 mcmol/L	X	X	ACM: Full Ca: Full CVD: Full
Hennekens, 1996 (PHS-I)[74] Good	X	22071 (99.9%)	50000 mcg RAE	12 (12, 12.9)	US	CVD, Cancer	Male physicians age 40-84 years	Mean age: 53 % Female: 0 % White: NR % Black: NR Mean BMI: 24.9 % Curr. smoker: 11	NR	X	X	ACM: Full Ca: Full CVD: Full
Lee, 2005 (WHS)[73] Good	X	39876 (99.4%)	50000 mcg RAE	4.1 (10)	US	CVD, Cancer	Adult females, aged ≥45 years, postmenopausal or not planning to become pregnant	Mean age: 55 % Female: 100 % White: 95 % Black: NR Mean BMI: 26.0 % Curr. smoker: 13	NR	X	X	ACM: Full Ca: Full CVD: Full

Table 7. Table of Study, Intervention, and Population Characteristics for Studies of Beta-Carotene Use (With or Without Vitamin A), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Omenn, 1996 (CARET)[62] Good	X	18314 (100%)	60000 mcg RAE + 7500 mcg RAE Vitamin A	4 (3.7, 10, 11)	US	Cancer	Men age 45-69 years with a history of asbestos exposure or adults age 50-69 years with a history of at least 20 years of smoking	Mean age: 58 % Female: 34 % White: 93 % Black: 3 Mean BMI: NR % Curr. smoker: 60	NR	X	X	ACM: Full Ca: Full CVD: Full
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies%)	Varied	NR (12, 18, 20.9)	US	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than beta carotene

Abbreviations: ACM = All-cause mortality; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention BC =; Beta carotene; BL = Baseline; BMI = Body mass index; Ca = Calcium; CARET = The Beta-Carotene and Retinol Efficacy Trial; CVD = Cardiovascular disease; Curr. = Current; FUP = Followup; NA = Not applicable; NHS-I = Nurses' Health Study I; NR = Not reported; NSCPS = Nambour Skin Cancer Prevention Study; PHS-I = Physicians' Health Study-I; RAE = Retinol activity equivalents; SCPS = Skin Cancer Prevention Study; SKICAP = SKIn CAncer Prevention; Vit A = Vitamin A; Vit E = Vitamin E; WHS = Women's Health Study

Table 8. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin A Use (With or Without Beta-Carotene), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Moon, 1997 (SKICAP)[63] Fair	X	2297 (%)	Vit A: 7500 mcg RAE	3 (5, 5.1)	US	Cancer	Adults, age 21-85 years, with a history of more than 10 actinic keratoses and at most 2 squamous cell carcinoma or basal cell carcinoma skin cancers.	Mean age: 63 % Female: 30 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 12	NR	X	X	ACM: NR Ca: Full CVD: NA
Omenn, 1996 (CARET)[62] Good	X	18314 (100%)	Vit A: 7500 mcg RAE + 60000 mcg RAE beta-carotene	4 (3.7, 10, 11)	US	Cancer	Men age 45-69 years with a history of asbestos exposure or adults age 50-69 years with a history of at least 20 years of smoking	Mean age: 58 % Female: 34 % White: 93 % Black: 3 Mean BMI: NR % Curr. smoker: 60	NR	X	X	ACM: Full Ca: Full CVD: Full
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies)	Varied	<2 <3 ≥3 2-4 5-9 ≥10 (12, 18, 20.9)	US	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA
Lim, 2004 (IWHS)[141] Fair	X	34703 (82.95%)	Varied	9.5 ()	US	Other: Hip fracture	Women aged 55-69	Mean age: 62 % Female: 100 % White: 99 % Black: NR Mean BMI: 27.0 % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than Vitamin A

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Calcium; CARET = The Beta-Carotene and Retinol Efficacy Trial; Curr. = Current; CVD = Cardiovascular disease; FUP = Followup; IWHS = Iowa Women's Health Study; NA = Not applicable; NHS-I = Nurses' Health Study I; NR = Not reported; RAE = Retinol activity equivalents; RCT = Randomized controlled trial; SKICAP = SKIn CAncer Prevention; Vit A = Vitamin A

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Aloia, 2005[130] Fair		208 (71.2%)	1200 IU	3 (3)	USA	Other: Bone loss	Postmenopausal African American women	Mean age: 61 % Female: 100 % White: 0 % Black: 100 Mean BMI: 29.5 % Curr. smoker: 7	Vit D: 45.43 nmol/L	X	X	ACM: NR Ca: NA CVD: NA
Aloia, 2018 (PODA)[102] Fair		260 (71.1%)	3490 IU (average dose; titrated to maintain serum 25(OD)D >75 nmol/L)	3 (3)	USA	Other: Bone loss prevention	African American women age ≥60 years	Mean age: 68 % Female: 100 % White: 0 % Black: 100 Mean BMI: 30.0 % Curr. smoker: 73	Vit D: 54.66 nmol/L Calc: 2.38 mmol/L	X	X	ACM: NR Ca: NA CVD: NR
Avenell, 2012 (RECORD)[88] Good	X	5292 (100%)	IG1: 800 IU + 1000 mg Calcium IG2: 800 IU	3.75 (3.75, 6.2)	GBR	CVD, Cancer	Older adults age ≥70 years with a fragility fracture	Mean age: 77 % Female: 85 % White: 99 % Black: NR Mean BMI: NR % Curr. smoker: 12	NR	X	X	ACM: Full Ca: Full CVD: Full
Baeksgaard, 1998[124] Fair		240 (82.9%)	560 IU + 1000 mg Calcium	2 (2)	DNK	Other: Bone mineral density	Women aged 58-67 years	Mean age: 62 % Female: 100 % White: 100 % Black: 0 Mean BMI: NR % Curr. smoker: NR	NR Calc: 2.3 mmol/L	X	X	ACM: NR Ca: NA CVD: NA
Baron, 2015 (VCPPS)[90] Good		2259 (93.4%)	IG1: 1000 IU + 1200 mg Calcium IG2: 1000 IU	3.8 (3, 3.8)	USA	Other: Colorectal adenoma prevention	Age 45-75 years with recently diagnosed adenomas	Mean age: 58 % Female: 37 % White: 88 % Black: 8 Mean BMI: 29.0 % Curr. smoker: 10	Vit D: 61.4 nmol/L	X	X	ACM: NR Ca: Full CVD: Full

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Bischoff-Ferrari, 2020 (DO-HEALTH)[139] Good		2157 (88%)	2000 IU	3 (3)	AUT, FRA, DEU, PRT, CHE	Other : 6 primary outcomes (BP, Short Physical Performance Battery, Montreal Cognitive Assessment, nonvertebral fractures, infections)	Community dwelling adults 70 years or older	Mean age: 75 % Female: 62 Percent white: NR Mean BMI: NR % Curr. smoker: 6	Vit D: 55.91 nmol/L	X	X	ACM: Full Ca :NA CVD: NA
Brisson, 2017[94] Good		405 (96.5%)	IG1: 2000 IU IG2: 1000 IU IG3: 3000 IU	1 (1)	CAN	Other: Mammo-graphic breast density	Premenopausal women	Mean age: 43 % Female: 100 % White: 98 % Black: NR Mean BMI: 24.3 % Curr. smoker: NR	Vit D: 64.1 nmol/L		X	ACM: NA Ca: NA CVD: NA
Cooper, 2003[127] Fair		187 (81.8%)	1428.6 IU + 1000 mg Calcium	2 (2)	AUS	Other: Bone mineral density	Postmenopausal white women	Mean age: 56 % Female: 100 % White: 100 % Black: 0 Mean BMI: NR % Curr. smoker: 7	Vit D: 82.1 nmol/L Calc: 2.4 mmol/L	X	X	ACM: NR Ca: NA CVD: NA
Dawson-Hughes, 1991[110] Fair		276 (90.2%)	400 IU + 377 mg Calcium	1 (1)	USA	Other: Bone mineral density	White postmenopausal women	Mean age: 62 % Female: 100 % White: 100 % Black: 0 Mean BMI: NR % Curr. smoker: 8	NR	X	X	ACM: NR Ca: NA CVD: NA
Dawson-Hughes, 1997[123]		445 (87.4%)	700 IU + 500 mg Calcium	3 (3)	USA	Other: Bone mineral density	Adults aged 65 years or older	Mean age: 71 % Female: 55 % White: 97 % Black: 2 Mean BMI: NR % Curr. smoker: 6	NR		X	ACM: NA Ca: NA CVD: NA

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Dean, 2011[64] Good	X	128 (99.2%)	5000 IU	0.12 (0.12)	AUS	Other: Cognitive and emotional functioning	Adults, age ≥18 years	Mean age: 22 % Female: 57 % White: 38 % Black: NR Mean BMI: NR % Curr. smoker: NR	Vit D: 76.7 nmol/L		X	ACM: NA Ca: NA CVD: NA
Dukas, 2004[128] Fair		380 (84.5%)	40 IU	0.7 (0.7)	CHE	Other: Falls	Adults aged 70 and older	Mean age: 75 % Female: 52 % White: NR % Black: NR Mean BMI: 26.3 % Curr. smoker: NR	NR	X	X	ACM: NR Ca: NA CVD: NR
Fedirko, 2009[113] Fair		92 (92.4%)	IG1: 800 IU + 2000 mg Calcium IG2: 800 IU	0.5 (0.5)	USA	Other: Markers of apoptosis in colorectal mucosa	Adults aged 30-75 years with a history of colon or rectal adenoma	Mean age: 61 % Female: 30 % White: 71 % Black: NR Mean BMI: 30.1 % Curr. smoker: 3	Vit D: 54.91 nmol/L		X	ACM: NA Ca: NA CVD: NA
Gallagher, 2001 (STOP IT)[125] Fair		246 (86.6%)	20 IU	3 (3)	USA	Other: Bone mineral density	Women aged 65-77 years	Mean age: 71 % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	Vit D: 79.3 nmol/L	X	X	ACM: NR Ca: NR CVD: NR
Glendenning, 2012[116] Fair		686 (93.0%)	1666.7 IU (150,000 IU every 3 months)	0.75 (0.75)	AUS	Other: Falls, mobility	Women aged over 70 years	Mean age: 77 % Female: 100 % White: 96 % Black: 0 Mean BMI: 27.5 % Curr. smoker: NR	NR	X	X	ACM: NR Ca: Self-report CVD: Self-report
Grady, 1991[121] Fair		98 (98.0%)	20 IU	0.5 (0.5)	USA	Other: Muscle strength	Adults aged 70 years or older	Mean age: 79 % Female: 54 % White: 95 % Black: NR Mean BMI: NR % Curr. smoker: NR	Vit D: 63 nmol/L Calc: 2.3 mmol/L	X	X	ACM: Full Ca: Self-report CVD: Self-report

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Kenny, 2003[117] Fair		65 (92.3%)	1000 IU + 500 mg Calcium	0.5 (0.5)	USA	Other: Strength; physical function	Men, aged 65 years and older	Mean age: 76 % Female: 0 % White: NR % Black: NR Mean BMI: 27.8 % Curr. smoker: NR	Vit D: 62.4 nmol/L	X	X	ACM: Full Ca: NA CVD: NA
Komulainen, 1999 (KOS)[112] Fair		464 (94%)	300 IU + 93 mg Calcium	5 (5)	FIN	Other: Bone mineral density	Recently postmenopausal women, aged 47-56 years	Mean age: 53 % Female: 100 % White: NR % Black: NR Mean BMI: 26.8 % Curr. smoker: NR	NR	X		ACM: NR Ca: NR CVD: NR
Lappe, 2007[82] Fair	X	1180 (86.8%)	1000 IU + 1500 mg Calcium	4 (4)	USA	Cancer, Other: Skeletal status and calcium economy	Women age >55 years	Mean age: 67 % Female: 100 % White: 100 % Black: 0 Mean BMI: 29.0 % Curr. smoker: NR	Vit D: 71.8 nmol/L Calc: 2.33 mmol/L	X	X	ACM: NA Ca: Full CVD: NA
Lappe, 2017[92] Good		2303 (95.4%)	2000 IU + 1500 mg Calcium	4 (4)	USA	Cancer	Postmenopausal women age ≥55 years;	Mean age: 65 % Female: 100 % White: 100 % Black: NR Mean BMI: 30.0 % Curr. smoker: 6	Vit D: 81.87 nmol/L	X	X	ACM: Full Ca: Full CVD: NA
Lips, 1996[111] Fair		2578 (99.5%)	400 IU	3.5 (3.5)	NLD	Other: Fracture prevention	Adults 70 years of age or older	Mean age: 80 % Female: 74 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR	X		ACM: Full Ca: NA CVD: NA
Pittas, 2019 (D2d)[135] Good		2423 (99.1%)	4000 IU	3.5 (3.5)	US	Other: Diabetes incidence	Pre-diabetic adults aged 30 or over (25+ for AI/AN)	Mean age: 60 % Female: 45 % White: 67 Mean BMI: 32.1 % Curr. smoker: NR	Vit D: 69.89 mmol/L	X	X	ACM: NR Ca: NA CVD: NA
Manson, 2018 (VITAL)[93] Good		25871 (92.4%)	2000 IU	5.3 (5.3)	USA	CVD, Cancer	Men age ≥50 years and women ≥55 years, with no	Mean age: 67 % Female: 51 % White: 71 % Black: 20	Vit D: 76.88 nmol/L	X	X	ACM: Full Ca: Full CVD: Full

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
							history of cancer or CVD	Mean BMI: 28.1 % Curr. smoker: 7				
Murdoch, 2012[118] Good		322 (91%)	3333.3 IU (100,000 to 200,000 IU monthly)	1.5 (1.5)	NZL	Other: Upper respiratory tract infections	Healthy nonpregnant adults ≥ 18 years	Mean age: 47 % Female: 75 % White: 94 % Black: NR Mean BMI: 27.5 % Curr. smoker: 5	Vit D: 71.14 nmol/L Calc: 2.3 mmol/L	X	X	ACM: NA Ca: Self-report CVD: NA
Rake, 2020 (VIDAL)[138] Good		1615 (90.3%)	3333 IU (100,000 IU monthly)	2	GBR	Other: Feasibility for larger trial with ACM endpoint	Older adults aged 65–84 years	Mean age: 72 % Female: 47 Percent white: 99 Mean BMI: NR % Curr. smoker: NR	Vit D: 51.5 nmol/L	X	X	ACM: Full Ca: Full CVD: Full
Salovaara, 2010 [134] (OSTPRE-FPS) Fair		3432 (91.5%)	800 IU + 1000 mg Calcium	3.0 (3)	FIN	Other: Fracture	Women aged 65-71 years living in northern Savonia (latitude 62 to 64 North)	Mean age: 67 % Female: 100 % White: NR % Black: NR Mean BMI: 27.7 % Curr. smoker: 5	Vit D: 49.5 nmol/L	X		ACM: NR Ca: NA CVD: NA
Sanders, 2010 (Vital D)[115] Fair		2258 (90.0%)	1370 IU (500,000 IU annually)	5 (4)	AUS	Other: Falls and fractures	Women aged 70 years or older residing in southern Victoria, Australia (latitude 38 South) at higher risk of hip fracture	Mean age: 76 % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR	X	X	ACM: NR Ca: NR CVD: NR
Scragg, 2017 (ViDA)[91] Good		5110 (86.8%)	3333 IU (100,000 IU monthly after initial 200,000 IU dose)	3.3 (3.3)	NZL	CVD	Adults, age 50-84 years	Mean age: 66 % Female: 42 % White: 83 % Black: 0 Mean BMI: 28.4 % Curr. smoker: 6	Vit D: 63.4 nmol/L Calc: 2.3 mmol/L	X	X	ACM: Full Ca: Full CVD: Full
Toss, 2012[107] Fair		56 (80.4%)	1600 IU + 1000 mg Calcium	1 (1)	SWE	Other: Bone & mineral metabolism	Adults 55-85 years at 58 North latitude with circumstances	Mean age: 70 % Female: 71 % White: NR % Black: NR	Vit D: 48.9 nmol/L Calc: 1.25 mmol/L		X	ACM: NA Ca: NA CVD: NA

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
							suggesting a risk for vitamin D insufficiency (NOS)	Mean BMI: NR % Curr. smoker: NR				
Trivedi, 2003[87] Fair	X	2686 (100%)	1095.9 IU (100,000 IU every 4 months)	5 (5)	GBR	Other: Fractures and mortality	Age 65-85 years	Mean age: 75 % Female: 24 % White: NR % Black: NR Mean BMI: 24.4 % Curr. smoker: 4	NR	X	X	ACM: Full Ca: Self-report CVD: Self-report
Uusi-Rasi, 2015[120] Fair		409 (90.5%)	800 IU	2 (2)	FIN	Other: Falls prevention	Women aged 70-80 years with a previous fall	Mean age: 74 % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 3	Vit D: 67.14 nmol/L Calc: 2.35 mmol/L	X		ACM: NR Ca: NA CVD: NA
Wactawski-Wende, 2006 (WHI)[78] Good	X	36282 (93.1%)	400 IU + 1000 mg Calcium	7 (7, 9.8, 11.1, 11.9)	USA	CVD, Cancer, Other: Mortality, adverse events, risk of fractures,	Postmenopausal women aged 50-79 years	Mean age: 62 % Female: 100 % White: 83 % Black: 9 Mean BMI: 29.0 % Curr. smoker: 8	NR	X	X	ACM: Full Ca: Full CVD: Full
Witham, 2014[99] Fair		68 (89.7%)	1667 IU (100,000 IU bimonthly)	0.5 (0.50)	GBR	Other: Reduce blood pressure and left ventricular hypertrophy	Age ≥18 years with resistant hypertension	Mean age: 63 % Female: 35 % White: 100 % Black: NR Mean BMI: 31.7 % Curr. smoker: 6	Vit D: 41.5 nmol/L Calc: 2.3 mmol/L	X	X	ACM: NR Ca: NA CVD: Self-report
Wood, 2012[119] Fair		305 (96.1%)	IG1: 400 IU IG2: 1000 IU	1 (1)	GBR	Other: CVD risk factors	Caucasian postmenopausal women aged 60-70 years	Mean age: 64 % Female: 100 % White: 100 % Black: 0 Mean BMI: 26.7 % Curr. smoker: NR	Vit D: 33.8 nmol/L Calc: 2.35 mmol/L	X	X	ACM: NA Ca: NR CVD: NA
Zitterman, 2009[114] Fair		200 (82.5%)	3332 IU	1 (1)	DEU	Other: Weight loss, CVD risk factors	Adults aged 18-70 years with a BMI above 27	Mean age: 48 % Female: 67 % White: NR % Black: NR	NR	X		ACM: NA Ca: NR CVD: NA

Table 9. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin D Use (With or Without Calcium), Sorted by Study Design, Then Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
								Mean BMI: 33.3 % Curr. smoker: NR				
Cohort												
Ferraro, 2017 (NHS-II)[143] Fair		116430 (NR%)	Varied (a range of doses were examined)	NR (20)	USA	Other: Kidney stones	Female nurses aged 25 to 42 years	Mean age: NR % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies%)	Varied (a range of doses were examined)	NR (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA
Taylor, 2004 (HPFS)[144] Fair		51529 (NR%)	Varied (a range of doses were examined)	NR (14, 26)	USA	Other: Kidney stones	Male health professionals age 40 to 75 years	Mean age: NR % Female: 0 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than Vitamin D

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Cancer; Calc = Calcium; Curr = Current; CVD = Cardiovascular disease; FUP = Followup; IU = International units; mg = Milligrams; mmol/L = Millimoles per Liter; nmol/L = Nanomoles per liter; NA = not applicable; NOS = Not otherwise specified; NR = Not reported; RCT = Randomized controlled trial; Vit D = Vitamin D

Table 10. Cancer Mortality and Cancer Incidence Results for Vitamin D Trials Reporting Both Outcomes (KQ 3)

Study	Supplement (IU/day)	N	Followup, Years	Cancer mortality, OR (95% CI)	Cancer incidence, OR (95% CI)
Avenell, 2012 (RECORD)[88]	Vitamin D (800)	5,292	6.2	0.86 (0.63 to 1.20)	1.08 (0.92 to 1.27)
Trivedi, 2003[87]	Vitamin D (1095.9)	2,686	5	0.87 (0.61 to 1.23)	1.09 (0.86 to 1.39)
Manson 2018 (VITAL)[93]	Vitamin D (2000)	25,871	5.3	0.82 (0.66 to 1.02)	0.96 (0.87 to 1.06)
Rake, 2020 (VIDAL)[138]	Vitamin D (3333)	1,615	4	2.87 (1.03 to 8.01)	0.85 (0.47 to 1.53)
Scragg, 2017 (ViDA)[91]	Vitamin D (3333)	5,110	3.3	1.00 (0.60 to 1.66)	1.01 (0.81 to 1.26)
Wactawski-Wende, 2006 (WHI)[78]	Vitamin D (400) + Calcium	36,282	7	0.90 (0.77 to 1.04)	0.98 (0.9 to 1.06)

Abbreviations: CI = Confidence interval; IU = International units; OR = Odds ratio

Table 11. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin E Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
ATBC Study Group, 1994 (ATBC)[75] Good	X	29133 (100%)	111 IU	6.1 (6.1, 8, 11, 14, 22.1, 24.1)	FIN	Cancer	Male smokers age 50-69 years	Mean age: 57 % Female: 0 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 100	Vit E: 26.7 mcmol/L	X	X	ACM: Full Ca: Full CVD: Full
de Gaetano, 2001 (PPP)[103] Good		4495 (99.3%)	666 IU	4 (4)	ITA	CVD	Age ≥50 years with at least one CVD risk factor	Mean age: 64 % Female: 58 % White: NR % Black: NR Mean BMI: 27.6 % Curr. smoker: 15	NR	X	X	ACM: Full Ca: NA CVD: Full
Hodis, 2002 (VEAPS)[126] Fair		353 (73.1%)	400 IU	3 (3)	USA	Other: Subclinical atherosclerosis progression	Adults aged 40 years or older with LDL cholesterol ≥130 mg/dL	Mean age: 56 % Female: 52 % White: 75 % Black: NR Mean BMI: NR % Curr. smoker: 3	NR	X		ACM: NR Ca: Self-report CVD: Self-report
Lee, 2005 (WHS)[73] Good	X	39876 (99.4%)	300 IU	10 (10)	USA	CVD, Cancer	Adult females, aged ≥45 years, postmenopausal or not planning to become pregnant	Mean age: 55 % Female: 100 % White: 95 % Black: NR Mean BMI: 26.0 % Curr. smoker: 13	NR	X	X	ACM: Full Ca: Full CVD: Full
Lippman, 2009 (SELECT)[79] Good	X	34888 (92.1%)	IG1: 400 IU IG2: 400 IU + 200 mcg Selenium	5.5 (7.1)	USA, CAN	CVD, Cancer	African American men age ≥50 years and men of other races age ≥55 years	Mean age: 63 % Female: 0 % White: 79 % Black: 13 Mean BMI: NR % Curr. smoker: 8	NR	X	X	ACM: Full Ca: Full CVD: Full
Magliano, 2006 (MAVET)[131] Fair		409 (81.4%)	500 IU	4 (4)	AUS	Other: Carotid atherosclerosis progression	Caucasian smokers, aged 55 years or older	Mean age: 64 % Female: 54 % White: 100 % Black: NR Mean BMI: 26.0 % Curr. smoker: 100	NR	X		ACM: NR Ca: NR CVD: NR

Table 11. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin E Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
McNeil, 2004 (VECAT)[129] Good		1193 (87.4%)	500 IU	4 (4)	AUS	Other: Age-related cataracts	Adults aged 55-80 years with early or no cataract	Mean age: 66 % Female: 56 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 2	NR	X	X	ACM: Full Ca: NA CVD: NA
Salonen, 2000 (ASAP)[76] Fair	X	520 (88.1%)	IG1: 404 IU + 500 mg Vitamin C IG2: 404 IU	3 (3)	FIN	CVD, Other: Carotid atherosclerosis	Adults aged 46-70 years with hypercholesterol-aemia	Mean age: 60 % Female: 51 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 40	Vit E: 32.6 mcmol/L	X	X	ACM: NR Ca: NA CVD: NR
Sesso, 2008 (PHS-II)[80] Good	X	14641 (98.0%)	200 IU	8	USA	CVD, Cancer	US male physicians aged ≥ 50 years	Mean age: 64 % Female: 0 % White: NR % Black: NR Mean BMI: 26 % Curr. smoker: 4	NR	X	X	ACM: Full Ca: Full CVD: Full
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies%)	Unknown	<2 2-4 5-9 ≥10 (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA
Zheng Selin, 2013 (COSM)[142] Fair		27343 (100%)	Unknown	11 (8.4, 11)	SWE	Other: Harms (Cataracts)	Men age 45-79 years	Mean age: 58 % Female: 0 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 25	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than multivitamins

Abbreviations: ACM = All-cause mortality; BMI = Body mass index; Ca = Cancer; Calc = Calcium; Curr = Current; CVD = Cardiovascular disease; IU = International units; LDL = Low-density lipoprotein; mcmol/L = Micromole per liter; mg/dL = Milligram per deciliter; NA = Not applicable; NR = Not reported; Vit E = Vitamin E

Table 12. Table of Study, Intervention, and Population Characteristics for Studies of Folic Acid Use, Sorted by Author

Author, Year (Study) Quality	In previous	Study N (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertainment
RCT												
Cole, 2007 (AFPPS)[83] Fair	X	1021 (59.4%)	1000 mcg	6.2 (2.75, 6.2, 7)	USA	Cancer	Adults, age 21-80 years, with a history of adenomas	Mean age: 57 % Female: 36 Percent White: 86 Percent Black: 6 Mean BMI: 27.4 % Curr. smoker: 14	Fol: 23.8 nmol/L	X		ACM: NR Ca: Full CVD: Full
Durga, 2007 (FACIT)[132] Fair		819 (99.3%)	800 mcg	3 (3)	NLD	Other: Cognitive function	Adults aged 50-70 years with high homocysteine	Mean age: 60 % Female: 28 Percent White: NR Percent Black: NR Mean BMI: 26.5 % Curr. smoker: 20	Fol: 12 nmol/L	X	X	ACM: NR Ca: NA CVD: NA
Logan, 2008 (ukCAP)[108] Fair		939 (90.8%)	500 mcg	3 (3)	GBR, DNK	Other: Prevention of recurrent colorectal adenoma	Adults aged 75 years or younger with a recent history of colorectal adenoma	Mean age: 58 % Female: 43 Percent White: NR Percent Black: NR Mean BMI: NR % Curr. smoker: NR	NR	X	X	ACM: NR Ca: Self-report CVD: Self-report
van Wijngaarden, 2014 (B-PROOF)[96] Fair		2919 (82.7%)	400 mcg + 500 mcg Vitamin B12	2 (2, 6.5)	NLD	Other: Fractures	Age ≥65 years with elevated homocysteine concentrations	Mean age: 74 % Female: 50 Percent White: NR Percent Black: NR Mean BMI: 27.2 % Curr. smoker: 10	Fol: 18.8 nmol/L Vit B12: 286.6 pmol/L	X	X	ACM: Relative-report Ca: Full CVD: NA
Wu, 2009[109] Good		672 (100%)	1000 mcg	6.5 (6.5)	USA	Other: Colorectal adenoma	Adults aged 50-78 from NHS and HPFS cohorts with a history of colorectal adenoma	Mean age: 65 % Female: 62 Percent White: NR Percent Black: NR Mean BMI: 25.7 % Curr. smoker: 7	Fol: 21.5 nmol/L	X	X	ACM: Relative-report Ca: Full CVD: NA

Abbreviations: ACM = All-cause mortality; AFPPS = Aspirin/Folate Polyp Prevention Study; BL = Baseline; BMI = Body mass index; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; Ca = Cancer; CVD = Cardiovascular disease; Curr = Current; FACIT = Folic Acid and Carotid Intima-media Thickness; Fol = Folic acid; FUP = Followup; HPFS = Health Professionals Follow-Up Study; mcg = Microgram; NHS = Nurses' Health Study; NA = Not applicable; NR = Not reported; nmol/L = Nanomole per liter; pmol/L = Picomole per liter; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; Vit B12 = Vitamin B12

Table 13. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin B3 and B6 Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Chen, 2015 (ONTRAC)[101] Good		386 (91.2%)	Vit B3: 1000 mg	1 (1)	AUS	Cancer	Age ≥18 years with history of ≥2 nonmelanoma skin cancers	Mean age: 66 % Female: 37 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR	X	X	ACM: NR Ca: Self-report CVD: Self-report
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies%)	Vit B6: Unknown Vit B12: Unknown	NR (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than multivitamins

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index' Ca = Cancer; Curr = Current; CVD = Cardiovascular disease; NA = Not applicable; NHS-I = Nurses' Health Study; NR = Not reported; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer; RCT = Randomized controlled trial; Vit B3 = Vitamin B3; Vit B12 = Vitamin B12

Table 14. Table of Results for Vitamin B3 for Main Review Outcomes by Intervention Group; One Randomized, Controlled Trial With Aim to Prevent Non-Melanoma Skin Cancer in Persons at High Risk (KQ 3)

Outcome	Vitamin B3 n/N (%)	Placebo n/N (%)
All-cause mortality	2/193 (1.0)	1/193 (0.5)
MI	3/193 (1.6)	0/193 (0.0)
Stroke	0/193 (0.0)	1/193 (0.5)
Any cancer incidence	5/193 (2.6)	2/193 (1.0)
Colorectal cancer	1/193 (0.5)	0/193 (0.0)
Lung cancer	1/193 (0.5)	1/193 (0.5)
Prostate cancer	1/193 (0.5)	0/193 (0.0)

Abbreviations: MI = Myocardial infarction

Table 15. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin C Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Salonen, 2000 (ASAP)[76] Fair	X	520 (88.1%)	IG1: 500 mg + 404.04000 854 IU Vitamin E IG2: 500 mg	3 (3)	FIN	CVD, Other: Carotid atherosclerosis	Adults aged 46-70 years with hypercholesterol-aemia	Mean age: 60 % Female: 51 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 40	NR Vit C: 32.6 mcmol/L	X	X	ACM: NR Ca: NA CVD: NR
Sesso, 2008 (PHS-II)[80] Good	X	14641 (98.0%)	500 mg	8 ()	USA	CVD, Cancer	US male physicians aged ≥ 50 years	Mean age: 64 % Female: 0 % White: NR % Black: NR Mean BMI: 26 % Curr. smoker: 4	NR	X	X	ACM: Full Ca: Full CVD: Full
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies)	Unknown	<2 2-4 5-9 ≥10 (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA
Rautiainen, 2010 (SMC)[145] Fair		38984 (63.1%)	1000 mg	8.2 (8.2)	SWE	Other: Cataract	Women aged 49-83 years	Mean age: 61 % Female: 100 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: 25	NR		X	ACM: NA Ca: NA CVD: NA
Taylor, 2004 (HPFS)[144] Fair		51529 (NR%)	Unknown	NR (14, 26)	USA	Other: Kidney stones	Male health professionals age 40 to 75 years	Mean age: NR % Female: 0 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA
Zheng Selin, 2013 (COSM)[142]		27343 (100%)	Unknown	11 (8.4, 11)	SWE	Other: Harms (Cataracts)	Men age 45-79 years	Mean age: 58 % Female: 0 % White: NR % Black: NR	NR		X	ACM: NA Ca: NA CVD: NA

Table 15. Table of Study, Intervention, and Population Characteristics for Studies of Vitamin C Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Fair								Mean BMI: NR % Curr. smoker: 25				

*Includes participants randomized to all intervention groups, including for supplements other than multivitamins

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Cancer; CVD = Cardiovascular disease; Curr = Current; FUP = Followup; mcmol/L = Micromoles per liter; mg = Milligram; NA = Not applicable; NR = Not reported; Vit C = Vitamin C; Randomized controlled trial

Table 16. Table of Study, Intervention, and Population Characteristics for Studies of Calcium Use (Without Vitamin D), Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Avenell, 2012 (RECORD)[88] Fair	X	5292 (100%)	1000 mg	3.75 (3.75, 6.2)	GBR	CVD, Cancer	Older adults age ≥70 years with a fragility fracture	Mean age: 77 % Female: 85 % White: 99 % Black: NR Mean BMI: NR % Curr. smoker: 12	NR	X	X	ACM: Full Ca: Full CVD: Full
Baron, 2005 (CPPS)[84] Fair	X	930 (89.5%)	1200 mg	4 (4, 6, 10.3)	USA	Other: Colorectal adenoma prevention	Adults age <80 years with ≥1 histologically confirmed large-bowel adenoma removed in past 3 months	Mean age: 61 % Female: 28 % White: NR % Black: 5 Mean BMI: NR % Curr. smoker: NR	NR	X	X	ACM: NR Ca: Full CVD: NA
Baron, 2015 (VCPPS)[90] Good		2259 (93.4%)	1200 mg	3.8 (3, 3.8)	USA	Other: Colorectal adenoma prevention	Age 45-75 years with recently diagnosed adenomas	Mean age: 58 % Female: 37 % White: 88 % Black: 8 Mean BMI: 29.0 % Curr. smoker: 10	NR	X	X	ACM: NR Ca: Full CVD: Full
Bolland, 2008 (ACS)[81] Fair	X	1471 (100%)	1000 mg	60 (5)	NZL	Other: Bone density and fracture incidence	Postmenopausal women age >55 years	Mean age: 75 % Female: 100 % White: NR % Black: NR Mean BMI: 26.4 % Curr. smoker: 3	2.31 mmol/L	X	X	ACM: Full Ca: NA CVD: Full
Fedirko, 2009[113] Fair		92 (92.4%)	2000 mg	0.5 (0.5)	USA	Other: Markers of apoptosis in colorectal mucosa	Adults aged 30-75 years with a history of colon or rectal adenoma	Mean age: 61 % Female: 30 % White: 71 % Black: NR Mean BMI: 30.1 % Curr. smoker: 3	NR		X	ACM: NA Ca: NA CVD: NA
Lappe, 2007[82] Fair	X	1180 (86.8%)	1500 mg	4 (4)	USA	Cancer, Other: Skeletal status and calcium economy	Women age >55 years	Mean age: 67 % Female: 100 % White: 100 % Black: 0 Mean BMI: 29.0 % Curr. smoker: NR	2.33 mmol/L	X	X	ACM: NA Ca: Full CVD: NA

Table 16. Table of Study, Intervention, and Population Characteristics for Studies of Calcium Use (Without Vitamin D), Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
Lewis, 2011 (CAIFOS)[104] Good		1460 (84.1%)	1200 mg	5 (5, 9.5)	AUS	Other: Fractures	Women age >70 years	Mean age: 75 % Female: 100 % White: NR % Black: NR Mean BMI: 27.2 % Curr. smoker: NR	NR	X	X	ACM: Full Ca: NA CVD: Full
Reid, 2008[105] Fair		323 (96.6%)	IG1: 1200 mg IG2: 600 mg	2 (2)	NZL	Other: Bone density	Men age ≥40 years	Mean age: 56 % Female: 0 % White: NR % Black: NR Mean BMI: 26.6 % Curr. smoker: 27	NR	X	X	ACM: NR Ca: NA CVD: Self-report
Cohort												
Feskanich, 2002 (NHS-I)[140] Fair	X	121700 (Varies)	Varied	NR (12, 18, 20.9)	USA	Other: Hip fractures, kidney stones, cataracts	Postmenopausal registered nurses age 30-55 years	Mean age: 58 % Female: 100 % White: NR % Black: NR Mean BMI: 26.0 % Curr. smoker: 26	NR		X	ACM: NA Ca: NA CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than multivitamins

Abbreviations: ACM = All-cause mortality; ACS = Auckland calcium study; BL = Baseline; BMI = Body mass index; Ca = Cancer; CAIFOS = Calcium Intake Fracture Outcome Study; CPPS = Calcium Polyp Prevention Study; CVD = Cardiovascular disease; Curr. = Current; FUP = Followup; mg = Milligrams; mmol/L = Millimoles per liter; NA = Not applicable; NHS – I = Nurses' Health Study; NR = Not reported; RECORD = Randomized Evaluation of Calcium OR vitamin D; RCT = Randomized controlled trial; VCPPS = Vitamin D/Calcium Polyp Prevention Study; WHI = Women's Health Initiative

Table 17. Table of Study, Intervention, and Population Characteristics for Studies of Selenium Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N* (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Clark, 1996 (NPC)[77] Fair	X	1312 (100%)	200 mcg	4.4 (6.3, 7.4, 7.6)	USA	Cancer	Adults with a history of 2 or more past-year basal cell or squamous cell carcinomas of the skin	Mean age: 63 % Female: 25 % White: NR % Black: NR Mean BMI: 25.6 % Curr. smoker: 28	Se: 1.45 mcmol/L	X	X	ACM: Full Ca: Full CVD: NA
Lippman, 2009 (SELECT)[79] Good	X	34888 (92.1%)	IG1: 200 mcg IG2: 200 mcg + 400 IU Vitamin E	5.5 (7.1)	USA, CAN	CVD, Cancer	African American men age ≥50 years and men of other races age ≥55 years	Mean age: 63 % Female: 0 % White: 79 % Black: 13 Mean BMI: NR % Curr. smoker: 8	NR	X	X	ACM: Full Ca: Full CVD: Full
Rayman, 2012 (UK-PRECISE)[89] Fair	X	501 (93.2%)	IG1: 300 mcg IG2: 100 mcg IG3: 200 mcg	0.5 (0.5)	GBR	Cancer	Adults, aged 60-74 years	Mean age: 68 % Female: 47 % White: NR % Black: NR Mean BMI: 27.5 % Curr. smoker: 10	Se: 1.12 mcmol/L		X	ACM: NA Ca: NA CVD: NA
Rayman, 2018 (DK-PRECISE)[97] Fair		491 (78.0%)	IG1: 300 mcg IG2: 100 mcg IG3: 200 mcg	5 (5, 15.9)	DNK	Cancer	Age 60 to 74 years	Mean age: 66 % Female: 48 % White: NR % Black: NR Mean BMI: 26.8 % Curr. smoker: 30	Se: 1.1 mcmol/L	X	X	ACM: Full Ca: Full CVD: NA
Thompson, 2016 (Sel/Cel)[98] Fair		1621 (84.8%)	200 mcg	2.8 (3)	USA	Other: Colorectal adenoma	Adults aged 40-80 years with a recent colorectal adenoma	Mean age: 63 % Female: 35 % White: 94 % Black: 3 Mean BMI: 29.2 % Curr. smoker: 10	Se: 1.72 mcmol/L	X	X	ACM: NR Ca: NR CVD: NA

*Includes participants randomized to all intervention groups, including for supplements other than selenium

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Cancer; CVD = Cardiovascular disease; Curr. = Current; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; FUP = Followup; IU = International units; mcg = Microgram; mcmol/L = Micromoles per liter; NPC = Nutritional Prevention of Cancer; Se = Selenium; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial; UK-PRECISE = United Kingdom PREvention of Cancer by Intervention with Selenium

Table 18. Table of Study, Intervention, and Population Characteristics for Studies of Zinc Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Hemila, 2020[137] Fair		87 (100)	78 mg	0.03 (10 days)	FIN	Other: Treatment of common cold	Adults aged 18 and older with a self-report that they usually have had ≥1 colds per winter	Mean age: 47 % Female: 89.7 % White: NR % Black: NR Mean BMI: NR % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Cancer; CVD = Cardiovascular disease; Curr. = Current; FUP = Followup; mg = Milligram; NA = Not applicable; NR = Not reported

Table 19. Table of Study, Intervention, and Population Characteristics for Studies of Magnesium Use, Sorted by Author (KQs 3 and 4)

Author, Year (Study) Quality	In previous	Study N (% FUP)	Daily dose	Years used (FUP)	Country	Study aim (CVD, Cancer, Other)	Brief population description	Demographics	Mean BL serum level	KQ3	KQ4	Ascertain-ment
RCT												
Alonso, 2020[136] Fair		59 (88.1)	400 mg	0.19 (0.19)	USA	Other: Atrial fibrillation	Adults, aged 55 years and older	Mean age: 62 % Female: 73.1 % White: 94.2 % Black: NR Mean BMI: 28.1 % Curr. smoker: NR	NR		X	ACM: NA Ca: NA CVD: NA

Abbreviations: ACM = All-cause mortality; BL = Baseline; BMI = Body mass index; Ca = Cancer; CVD = Cardiovascular disease; Curr. = Current; FUP = Followup; mg = Milligram; NA = Not applicable; NR = Not reported

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Multivitamin 9 RCTs, 3 prospective cohort studies (n=218,610)	KQ1 (benefits) 8 RCTs (n=30,503)	Evidence suggested no benefit for all-cause mortality, CVD, and cancer incidence. Pooled results reflected the findings of two large good-quality trials with CVD and cancer aims that provided most of the evidence. Pooled results included: • All-cause mortality: OR 0.94 (95% CI, 0.85 to 1.03; 8 RCTs [n=30,108]). • CVD mortality: OR 0.95 (95% CI, 0.83 to 1.09; 3 RCTs [n=15,958]) • Any cancer: OR 0.92 (0.84 to 0.1.01; 3 RCTs [n=27,417])	All-cause mortality: Reasonably consistent, reasonably precise CVD mortality: Reasonably consistent, reasonably precise Other CVD outcomes: consistency NA, reasonably precise. Cancer mortality and site-specific cancers: Reasonably consistent (or NA for most site-specific cancers), imprecise Any cancer incidence: Reasonably consistent, reasonably precise	Specific formulations differed widely and included both broad spectrum and antioxidant-focused supplements. One of the main trials had a number of background interventions in a 2x2x2x2 study design.	All-cause mortality: Low no benefit CVD: Low no benefit Cancer: Low for no benefit	Most studies were conducted outside the US, including one of the two main trials. The other main trial was limited to male physicians.

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Multivitamin 9 RCTs, 3 prospective cohort studies (n=218,610)	KQ2 (harms) 8 RCTs (n=30,172) 3 prospective cohort studies (n=188,027)	No evidence of increased risk of serious adverse events, but few events. Small increases in cataracts reported by cohort studies were not statistically significant and were not examined in any of the trials. A large trial found small increased risk of skin rash and epistaxis.	Cataracts: Consistent, imprecise Other serious: Consistency NA, imprecise Skin rash and epistaxis: Consistency NA, reasonably precise.	Cataracts, hip fractures: evidence limited to observational studies, supplement use was self-reported.	Low for increased risk of skin rash, epistaxis, insufficient for other harms.	Most studies were conducted outside the US, including one of the two main trials. The other main trial was limited to male physicians.
Beta-carotene 6 RCTs, 1 prospective cohort (n=278,653) Vitamin A 2 RCTs, 2 prospective cohorts (n=177,014)	KQ3 (benefits) Beta-carotene 6 RCTs (n=112,820) Vitamin A 2 RCTs (n=20,611)	Pooled estimates for several outcomes showed statistically significant paradoxical harm associated with beta-carotene use, for example: • All-cause mortality: OR 1.06 (95% CI, 1.00 to 1.12; 6 RCTs [n=112,820]) • All-cause mortality including vitamin A study (SKICAP): OR 1.06 (95% CI, 1.01 to 1.12); 7 RCTs [n=115,117]) • CVD mortality: OR 1.10 (1.02 to 1.19); 5 RCTs [n=95,506]) • Lung cancer: 1.20 (95% CI, 1.01 to 1.42); 4 RCTs [n=94,830]) Pooled estimates for all cancer mortality, any cancer incidence, colorectal, breast, and prostate cancer showed no statistically significant differences in risk associated with beta-carotene	All-cause mortality: reasonably consistent, precise for increased risk for beta-carotene with or without vitamin A CVD mortality: reasonably consistent, precise for increased risk for beta-carotene Cancer: Lung cancer: Reasonably consistent, precise for increased risk Any cancers and other site-specific cancers: Consistent and imprecise for no difference	Variation in study dose and duration. Combined supplement use in CARET and varied background interventions in almost all other trials. Multiple comparisons and outcomes examined in a body of literature with different primary aims.	All-cause mortality: Moderate for small increased risk for beta-carotene with or without vitamin A Low for no increased risk with vitamin A alone CVD mortality: Moderate for a small increased risk for beta-carotene CVD events: Low for no association for beta-carotene	Most studies of beta-carotene and vitamin A conducted in the US, but participants were primarily white. Included general risk samples as well as those limited to persons at increased risk for lung cancer due to smoking status or asbestos exposure. Vitamin A doses above the current upper limit in all trials evaluating vitamin A.

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		use. There were no differences in composite CVD events in 2 reporting trials. Vitamin A had no impact on all-cause mortality.			Cancer: Lung cancer: moderate for an increased risk for beta-carotene Any cancer and other site-specific cancers: Low for no difference for beta-carotene	
Beta-carotene 6 RCTs, 1 prospective cohort (n=278,653) Vitamin A 2 RCTs, 2 prospective cohorts (n=177,014)	KQ4 (harms) Beta-carotene 6 RCTs (n=112,820), 1 prospective cohort (n=121,700) Vitamin A 2 RCTs (n=20,611), 2 prospective cohorts (n=156,403)	The most substantial serious harms are the paradoxical harms of increased all-cause mortality, CVD mortality, and lung cancer (see KQ3). Trials generally showed no statistically significant findings for other adverse events other than hypercarotenodermia (4 trials, ORs ranging from 1.10 to 24.75), and GI symptoms in the one trial reporting this outcome. Two cohort studies in women found an elevated but not statistically significantly increased risk of hip fracture associated with vitamin A supplementation.	(excluding paradoxical harms above) Consistent, precise for beta-carotene and increased risk of hyper-carotenodermia Consistent and imprecise for vitamin A and increased risk of hip fracture Consistent and imprecise for other nonserious harms for beta-carotene and vitamin A	Variation in study dose and duration. Combined supplement use in CARET and varied background interventions in almost all other trials. Supplement use in cohort study was self-reported	(excluding paradoxical harms above) Hyper-carotenodermia: Moderate for increased risk with beta-carotene Hip fractures: Low for increased risk for vitamin A Cataracts: Low for no increased risk for vitamin A	Most studies of beta-carotene and vitamin A conducted in the US, but participants were primarily white. Evidence Included general risk samples as well as those limited to persons at increased risk for lung cancer due to smoking status or asbestos exposure. Vitamin A doses were above the current upper limit in all trials evaluating vitamin A. Data suggesting a possible increased hip fracture risk with vitamin A are from cohort studies of

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
						primarily white women.
Vitamin D (with or without calcium) 35 RCTs, 3 prospective cohort studies (n=390,565)	KQ3 (benefits) 30 RCTs (n=99,095)	Evidence suggested a small benefit for all-cause and cancer mortality but no benefit for the incidence of cancer or CVD events. For example, pooled ORs included: • All-cause mortality: 0.94 (95% CI, 0.89 to 1.00; 24 RCTs [n=93,003]) • Cancer mortality: 0.89 (95% CI, 0.80 to 0.99; k=6 [n=74,237]) • CVD events: 1.00 (95% CI, 0.95 to 1.05; 6 RCTs [n=72,430]) • Any cancer: 0.97 (95% CI, 0.92 to 1.03; 17 RCTs [n=82,019) Findings were consistent across different pooling methods, robustness of outcome ascertainment, and whether vitamin D was taken alone or with calcium.	All-cause mortality, cancer mortality, CVD events: Consistent, precise CVD mortality, any cancer incidence: Reasonably consistent, precise Site-specific cancers: Reasonably consistent, imprecise	Most studies had primary aims related to bone density, fractures, or falls (however there were two very large good-quality trials plus additional smaller trials with cancer and CVD as primary aims). Few large studies reported most site-specific cancers.	ACM: Moderate for small benefit CVD: CVD mortality: Moderate for no benefit CVD events: High for no benefit Cancer: Cancer mortality: Moderate for benefit Any cancer, site-specific incidence: Low for no benefit	Primarily white older adults.
Vitamin D (with or without calcium) 35 RCTs, 3 prospective cohort studies (n=390,565)	KQ4 (harms) 30 RCTs (n=93,296), 3 prospective cohort studies (n=289,659)	Both trial and cohort evidence suggested an increased risk of kidney stone with 1000 IU/day or more of vitamin D over 7 or more years. Most evidence supported no increased risk of GI-related symptoms. Other non-serious symptoms also generally found no group differences, and other serious	Kidney stones: inconsistent, imprecise GI symptoms: consistent, precise Other AE: inconsistent, imprecise	Most studies had primary aims related to bone density, fractures, or falls. Supplement use in cohort studies was self-reported	Kidney stones: Low for small increased risk GI: Moderate for no increased risk Other AE: Low for no increased risk	Primarily white older adults.

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		harms had too few events to draw conclusions.				
Vitamin E 9 RCTs, 2 prospective cohort studies (N= 265,511)	KQ3 (benefits) 9 RCTs (n=116,468)	Most evidence indicated that vitamin E had no benefit for mortality, CVD, or cancer. For example, pooled ORs included: • All-cause mortality: 1.02 (5% CI, 0.97 to 1.07; 9 RCTs [n=107,772]) • CVD events: 0.96 (95% CI, 0.90 to 1.04; 4 RCTs [n=62,136]) • Any cancer: 1.02 (95% CI, 0.98 to 1.08; 5 RCTs [n=76,777])	All-cause mortality: Reasonably consistent, precise CVD: Consistent, imprecise Cancer: Inconsistent, imprecise for prostate cancer; Consistent, imprecise for other cancer outcomes	Few studies for most outcomes other than all-cause mortality, several studies underpowered for the main outcomes of this review (but all main outcomes for the review also include some studies powered for CVD and/or cancer outcomes).	All-cause mortality: High for no benefit CVD, other than hemorrhagic stroke: Moderate for small to no benefit Hemorrhagic stroke: Low for increased risk Cancer: Low for prostate for small to no benefit; Moderate for small to no benefit for other cancer outcomes	Most included participants were white American or European adults age 45 and older. Included general risk samples as well as those limited to persons at increased risk for cancer or CVD due to smoking or CVD risk factors.
Vitamin E 9 RCTs, 2 prospective cohort studies (N= 265,511)	KQ4 (harms) 7 RCTs (n=115,576) 2 prospective cohort studies (N= 149,043)	Although data on specific outcomes were sparse, no clear increased risk of serious harm was identified, but effects were wide-ranging and included findings in the direction of benefit and harm across all review outcomes, including 2 trials we increased risk of hemorrhagic stroke; one cohort study with a single assessment	Inconsistent, imprecise	Supplement use in cohort studies was self-reported	(other than paradoxical harm for hemorrhagic stroke above) Cataracts, hospitalization from pneumonia, other non-	Most included participants were white American or European adults age 45 and older. Included general risk samples as well as those limited to persons at increased risk for cancer or

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		of vitamin E use found an increased risk of cataracts, but a higher quality cohort study with biennial reporting of vitamin E use showed no increased risk of cataracts.			serious: Low for no increased risk	CVD due to smoking or CVD risk factors.
Folic acid 5 RCTs (N=6,370)	KQ3 (benefits) 5 RCTs (N=6,370)	Most evidence indicated that folic acid increased the risk of cancer and had no benefit for mortality. The pooled ORs included: • All-cause mortality: 0.71 (95% CI 0.49 to 1.03; 5 RCTs [n=6,370]) • Any cancer: 1.42 (95% CI 1.10 to 1.84; 3 RCTs [n=4,612]) There were too few events to draw conclusions for CVD, or single-site cancers. One study found an increased risk of prostate cancer, however there were only 34 events total and another trial found no increased risk.	All-cause mortality: Reasonably consistent, imprecise CVD: Reasonably consistent, imprecise Cancer: Inconsistent and reasonably precise for any cancer incidence. Inconsistent and imprecise for site-specific cancers.	Trials were often underpowered for the main outcomes. None of the trials had CVD prevention as a primary aim.	All-cause mortality: Low for no benefit CVD: Insufficient Cancer: Any cancer: Low for increased risk. Site-specific: Insufficient	Three trials recruited participants with a history of colorectal adenomas. Other two trials recruited participants with an elevated homocysteine. Participants were from the US, the Netherlands, Great Britain, and Denmark with the mean age ranging from 57 to 74 years.
Folic acid 5 RCTs (N=6,370)	KQ4 (harms) 4 RCTs (N=5,854)	Trial evidence suggests no serious or non-serious harms with folic acid use.	Withdrawals due to AE: reasonably consistent, imprecise Other: Consistency NA, imprecise	Trials were often underpowered for the main outcomes. None of the trials had CVD prevention as a primary aim.	Low for no serious harms other than increased cancer risk.	Three trials recruited participants with a history of colorectal adenomas. Other two trials recruited participants with an elevated homocysteine. Participants were from the US, the Netherlands, Great Britain, and Denmark

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
						with the mean age ranging from 57 to 74 years.
Vitamin B3 (evaluated as nicotinamide) 1 RCT (n=386)	KQ3 (benefits) 1 RCT (n=386)	Insufficient evidence to determine the effect on mortality, CVD, or cancer. Only a very small number of events was reported.	All-cause mortality: Consistency NA, imprecise CVD: Consistency NA, imprecise Cancer: Consistency NA, imprecise	Only one RCT, which was underpowered for the outcomes of interest.	All-cause mortality: Insufficient CVD: Insufficient Cancer: Insufficient	Included participants were Australian men and women aged 30–91 years with a history of two or more nonmelanoma skin cancers.
Vitamin B3 (evaluated as nicotinamide) 1 RCT (n=386)	KQ4 (harms) 1 RCT (n=386)	Only a very small number of adverse events reported with no difference between the groups.	Consistency NA, imprecise	Only one RCT, which was underpowered for serious harms.	Insufficient	Included participants were Australian men and women aged 30–91 years with a history of two or more nonmelanoma skin cancers.
Vitamin B6 1 Prospective cohort study (n=75,864)	KQ3 (benefits)	No evidence found.	NA	NA	NA	NA
Vitamin B6 1 Prospective cohort study (N=75,864)	KQ4 (harms) 1 Prospective cohort study (N=75,864)	The increased risk for hip fracture was associated with a high cumulative intake (food and supplements) of vitamin B6 and vitamin B6 from supplements only.	Consistency NA, reasonably precise	Only one cohort study. All data on vitamin B6 intake, potential confounders, hip fractures were self-reported by questioners. Supplement use	All-cause mortality: NA CVD: NA Cancer: NA Harms: Low for increased risk	All participants were preliminarily white postmenopausal female registered nurses in the United States.

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
				in was self-reported		
Vitamin C 2 RCTs, 4 prospective cohorts (N=254,587)	KQ3 (benefits) 2 RCTs (n=15,031)	One large (n=14,641) good quality trial found that vitamin C had no benefit for mortality, CVD, or cancer. HRs include: • All-cause mortality: 1.07 (95% CI, 0.97 to 1.18) • CVD events: 0.99 (95% CI, 0.89 to 1.11) • Any cancer: 1.01 (95% CI, 0.92 to 1.10) The other RCT was small and not powered to evaluate mortality. One death occurred in each group; all deaths were CVD-related.	All-cause mortality: Consistent, reasonably precise CVD: Consistent, reasonably precise Cancer: Consistency NA, reasonably precise	Evidence is primarily from one very large trial in men only; the other trial was not powered to evaluate health outcomes. Multiple and varied background interventions in context of 2x2x2x2 trial.	All-cause mortality: Low for no benefit CVD: Low for no benefit Cancer: Low for no benefit	Most trial data were in men with high socioeconomic status who were predominately white.
Vitamin C 2 RCTs, 4 prospective cohorts (N=254,587)	KQ4 (harms) 2 RCTs (n=15,031), 4 prospective cohorts (N=239,556)	Trial evidence suggested no serious or nonserious harms and no statistically significant paradoxical findings. Cohort studies had conflicting results for cataracts with possible increased risk of cataracts which was not confirmed in a large trial. 2 large cohorts show evidence for increased risk of kidney stones in men.	Cataracts: Inconsistent and reasonably precise Other serious and non-serious: Consistent and reasonably precise	Supplement use in cohort studies was self-reported and collected at one time only in two cohorts.	Kidney stones: Low for increased risk Cataract: Low for no increased risk Other harms: Low for no increased risk	Most trial data were in men with high socioeconomic status who were predominately white. All cohort evidence for kidney stones was in men only.
Calcium 8 RCTs, 1 prospective cohort (n=134,707)	KQ3 (benefits) 7 RCTs (n=11,884)	Most evidence indicated no benefit for mortality, CVD, or cancer after up to 6 years of calcium use. However, one smaller study suggested a possible reduction in prostate cancer, among persons with a recent adenoma. Pooled ORs for other outcomes include:	All-cause mortality: Reasonably consistent, Reasonably precise CVD: Inconsistent, imprecise	Primary outcomes were often underpowered, since half of studies had primary aims irrelevant to this review.	ACM: Moderate for no benefit CVD: Low for no benefit Cancer: Low for no benefit	Best evidence limited to white adults age 70 years and older with fragility fractures. Other studies also primarily in adults age 40 and older, white, and mostly female.

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		• All-cause mortality: 1.05 (95% CI, 0.92 to 1.21; 6 RCTs [n=8,394]) • CVD events: 1.11 (95% CI, 0.90 to 1.36; 4 RCTs [n=4,076]) • Any cancer: 0.94 (95% CI, 0.41 to 2.14; 3 RCTs [n=5,051])	Cancer: Inconsistent or NA (for site-specific cancers), imprecise			
Calcium 8 RCTs, 1 prospective cohort (n=134,707)	KQ4 (harms) 8 RCTs (n=11,930), 1 prospective cohort (n=121,700)	Findings suggested an increased risk of constipation and gastrointestinal complaints, and possibly kidney stones.	Gastrointestinal complaints: Consistent, reasonably precise Kidney stones: Reasonably consistent and imprecise	Reporting of any, any serious, and withdrawal due to adverse effects sparely reported; kidney stone evidence primarily limited to observational data in women only, where supplement use was measured by self-report	GI-related complaints: Moderate for increased risk Kidney stones: Low for increased risk	Best evidence limited to white adults age 70 years and older with fragility fractures. Other studies also primarily in adults age 40 and older, white, and mostly female.
Selenium 5 RCTs (n=29,909)	KQ3 (benefits) 4 RCTs (n=29,408)	Most evidence suggested that approximately 6 months to 5.5 years of selenium use had no benefit for mortality, CVD, or cancer at followup ranging from 6 months to 15.9 years. The pooled OR for all-cause mortality was 0.94 (0.83 to 1.07; 4 RCTs [n=20,832]). Effect sizes for any CVD event ranged from HRs of 0.97 (95% CI, 0.86 to 1.09) to 1.04 (95% CI, 0.73 to 1.49). Cancer incidence effects were highly	All-cause mortality: Inconsistent, imprecise CVD: Reasonably consistent, imprecise Cancer: Inconsistent, imprecise	Few studies, females not well-represented, most studies did not have CVD prevention as a primary aim.	All-cause mortality: Low for no benefit CVD: Low for no benefit Cancer: Low for no benefit	The largest, best-quality trial was conducted in the US and Canada but limited to males. Across the body of evidence, participants were predominantly white race and age 50 years and older (mean age in the 60s for all studies).

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		variable and rarely differed between groups, although one smaller study of persons with a history of basal or squamous cell cancer (75% male) found a reduction in cancer incidence (HR, 0.75 (95% CI 0.58 to 0.97), despite no impact on the recurrence of skin cancer.				
Selenium 5 RCTs (N=29,909)	KQ4 (harms) 5 RCTs (N=29,909)	No clear increased risk of serious harm. The smallest study (n=491) found increased risk of all-cause mortality, but all others found no association, and no other increased risk of serious harm was identified in any study.	Reasonably consistent, imprecise	Few studies, females not well-represented, most studies did not have CVD prevention as a primary aim.	Low for no serious harm	The largest, best-quality trial was conducted in the US and Canada but limited to males. Across the body of evidence, participants were predominantly white race and age 50 years and older (mean age in the 60s for all studies).
Zinc 1 RCT (N=87)	KQ3 (benefits)	No evidence found.	NA	NA	NA	NA

Table 20. Summary of Evidence

Supplement No. of Studies by study design (No. of observations)	Key question No. of Studies by study design (No. of observations)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Zinc 1 RCT (N=87)	KQ4 (harms)	Increased risk of having any adverse events, including stomachache, taste problems, teeth and mouth roughness or dryness, and aching in the mouth	Consistency NA, imprecise	One a single small study, 5-day use only	Insufficient	General US adult population age 18 and older.
Magnesium 1 RCT (N=59)	KQ3 (benefits)	No evidence found.	NA	NA	NA	NA
Magnesium 1 RCT (N=59)	KQ4 (harms)	Increased risk of gastrointestinal symptoms	Consistency NA, imprecise	One a single small study, short-term (12-week) use only	Insufficient	General US adult population age 55 and older.

Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword
tu = Therapeutic Use
py = publication year
lim = limit
mj = major
ajd = adjacent
PDAT = publication date

MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 29, 2019>
Search Strategy:
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1 Calcium, dietary/ or Calcium Carbonate/
2 Calcium Compounds/tu [Therapeutic Use]
3 calcium citrate/tu
4 (dietary calcium or calcium supplement$ or calcium monotherapy).ti,ab.
5 folic acid/
6 (folic acid or folate).ti,ab.
7 (methyltetrahydrofolic or methyltetrahydrofolate or methyl tetrahydrofolic or methyl tetrahydrofolate or mthf).ti,ab.
8 (Vitamin B 9 or Vitamin B9).ti,ab.
9 exp Thiamine/
10 (Thiamine or Thiamin or Vitamin B 1 or Vitamin B1 or Aneurin).ti,ab.
11 Riboflavin/
12 (Riboflavin or Vitamin B 2 or Vitamin B2).ti,ab.
13 exp Vitamin B 6/
14 (Vitamin B 6 or Vitamin B6 or Pyridoxin$).ti,ab.
15 exp Vitamin B 12/
16 (Vitamin B 12 or Vitamin B12).ti,ab.
17 (Cobalamin or Cyanocobalamin or Cobamides or Hydroxocobalamin).ti,ab.
18 Vitamin D/
19 Vitamin D.ti,ab.
20 Cholecalciferol/
21 Cholecalciferol.ti,ab.
22 Dihydroxycholecalciferols/
23 Dihydroxycholecalciferol$.ti,ab.
24 Calcitriol/

25 Calcitriol.ti,ab.
26 Ergocalciferols/
27 Ergocalciferol$.ti,ab.
28 exp Vitamin E/
29 (Vitamin E or Tocopherol$ or Tocotrienol$).ti,ab.
30 exp Ascorbic acid/
31 (Ascorbic acid or Vitamin C or ascorbate or Dehydroascorbate).ti,ab.
32 Vitamin A/
33 Vitamin A.ti,ab.
34 beta carotene/
35 (beta carotene or Betacarotene).ti,ab.
36 Retinol.ti,ab.
37 retinoids/
38 iron, dietary/
39 (iron adj5 dietary).ti,ab.
40 (iron adj5 supplement$).ti,ab.
41 zinc/
42 (zinc adj5 dietary).ti,ab.
43 (zinc adj5 supplement$).ti,ab.
44 Magnesium/ or Magnesium Compounds/
45 (magnesium adj5 dietary).ti,ab.
46 (magnesium adj5 supplement$).ti,ab.
47 Niacin/
48 Niacin.ti,ab.
49 Nicotinic acids/
50 nicotinic acid$.ti,ab.
51 Selenium/
52 Selenium compounds/
53 Selenium.ti,ab.
54 Vitamins/
55 Minerals/
56 (Vitamin$ adj5 dietary).ti,ab.
57 (Vitamin$ adj5 supplement$).ti,ab.
58 (mineral$ adj5 dietary).ti,ab.
59 (mineral$ adj5 supplement$).ti,ab.
60 (Multivitamin$ or Multi-vitamin$).ti,ab.
61 (multimineral$ or multi-mineral$).ti,ab.
62 or/1-61
63 exp Cardiovascular Diseases/
64 (cardi$ disease$ or heart disease$).ti,ab.
65 cardiomyopath$.ti,ab.
66 myocardial infarction.ti,ab.
67 (heart arrest or heart attack$).ti,ab.
68 (coronary arter$ disease or coronary heart disease).ti,ab.
69 isch?emi$.ti,ab.
70 arrhythmia$.ti,ab.
71 ((heart or myocardial or cardiac or systolic or diastolic or ventricular) adj1 (failure$ or dysfunction)).ti,ab.

72 angina.ti,ab.
73 vascular disease$.ti,ab.
74 (cerebrovascular disease$ or cerebrovascular disorder$).ti,ab.
75 aneurysm.ti,ab.
76 arterial occlusive disease.ti,ab.
77 stroke.ti,ab.
78 cerebrovascular accident$.ti,ab.
79 (diabetic angiopath$ or diabetic foot or diabetic retinopathy$).ti,ab.
80 (hypertensi$ or high blood pressure).ti,ab.
81 prehypertensi$.ti,ab.
82 hypotension/
83 (hypotens$ or low blood pressure).ti,ab.
84 carotid artery disease$.ti,ab.
85 ((thromb$ or embolic or emboli or embolism$ or embolus) adj1 (vein or veins or venous or venules or pulmonary or lung)).ti,ab.
86 peripheral arter$ disease$.ti,ab.
87 atherosclero$.ti,ab.
88 exp Hyperlipidemias/
89 hyperlipid?emia$.ti,ab.
90 (hypercholesterol$ or high cholesterol or elevated cholesterol).ti,ab.
91 exp Neoplasms/
92 (neoplas$ or cancer$ or tumor or tumors or tumour or tumours or malignan$ or carcinoma$ or adenocarcinoma$ or blastoma$ or squamous or metastatic or meta-static or sarcoma$ or myeloma$ or adenoma$ or glioblastoma$ or lymphoma$ or schwannoma$ or Leukemia$ or Leukaemia$ or Hepatoma$ or Metastas$ or oncology or glioma$ or carcinogen$ or cholangiocarcinoma$ or Neurofibroma$ or Osteosarcoma$ or Teratoma$ or melanoma$).ti,ab.
93 or/63-92
94 safety/
95 safety.ti,ab.
96 adverse$.ti,ab.
97 adverse effects.fs.
98 side effect$.ti,ab.
99 product surveillance, postmarketing/
100 Long Term Adverse Effects/
101 Adverse Drug Reaction Reporting Systems/
102 drug toxicity/
103 drug toxicity.ti,ab.
104 harm$.ti,ab.
105 exp Sarcoidosis/
106 (sarcoid$ or neurosarcoidosis or besnier or schaumann syndrome).ti,ab.
107 exp Urolithiasis/ or exp Cholelithiasis/
108 (stone or stones).ti,ab.
109 (lithiasis or nephrolithiasis or cholelithiasis or urolithiasis or choledocholithiasis or hepatolithiasis or calculus or calculi).ti,ab.
110 exp Hemorrhage/
111 (bleeding or h?emorrhage).ti,ab.
112 or/94-111

113 (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or (randomized or randomised or placebo or randomly).ti,ab. or trial.ti.
114 (RCT or placebo or sham or dummy or single blind$ or double blind$ or allocated or allocation or triple blind$ or treble blind$ or random$).ti,ab. not medline.st.
115 113 or 114
116 62 and 93 and 115
117 case-control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or Cross-Sectional Studies/
118 (case control$ or cohort or longitudinal or follow up or followup or prospective$ or retrospective$ or comparison group$ or control group$ or observational or nonrandom$ or database$ or population$ or cross sectional).ti,ab.
119 117 or 118
120 115 or 119
121 62 and 112 and 120
122 116 or 121
123 limit 122 to (english language and yr="2013 -Current")
124 123 not (animals/ not humans/)
125 124 not ((infant/ or child/ or adolescence/) not (adult/ or aged/ or middle aged/))
126 meta analysis.pt. or (metaanaly$ or meta analy$).ti,ab.
127 (62 and 93) or (62 and 112)
128 126 and 127
129 limit 127 to systematic reviews
130 128 or 129
131 limit 130 to (english language and yr="2013 -Current")
132 125 or 131

PUBMED- [publisher supplied references only]

RCTs:

(dietary calcium[tiab] OR calcium supplement*[tiab] OR calcium monotherapy[tiab] OR folic acid[tiab] OR folate[tiab] OR methyltetrahydrofolic[tiab] OR methyltetrahydrofolate[tiab] OR methyl tetrahydrofolic[tiab] OR methyl tetrahydrofolate[tiab] OR mthf[tiab] OR Vitamin B 9[tiab] OR Vitamin B9[tiab] OR Thiamine[tiab] OR Thiamin[tiab] OR Vitamin B 1[tiab] OR Vitamin B1[tiab] OR Aneurin[tiab] OR Riboflavin[tiab] OR Vitamin B 2[tiab] OR Vitamin B2[tiab] OR Vitamin B 6[tiab] OR Vitamin B6[tiab] OR Pyridoxin*[tiab] OR Vitamin B 12[tiab] OR Vitamin B12[tiab] OR Cobalamin[tiab] OR Cyanocobalamin[tiab] OR Cobamides[tiab] OR Hydroxocobalamin[tiab] OR Vitamin D[tiab] OR Cholecalciferol[tiab] OR Dihydroxycholecalciferol*[tiab] OR Calcitriol[tiab] OR Ergocalciferol*[tiab] OR Vitamin E[tiab] OR Tocopherol*[tiab] OR Tocotrienol*[tiab] OR Ascorbic acid[tiab] OR Vitamin C[tiab] OR ascorbate[tiab] OR Dehydroascorbate[tiab] OR Vitamin A[tiab] OR beta carotene[tiab] OR Betacarotene[tiab] OR Retinol[tiab] OR Niacin[tiab] OR nicotinic acid*[tiab] OR Selenium[tiab] OR Multivitamin*[tiab] OR Multi-vitamin*[tiab] OR multimineral*[tiab] OR multi-mineral*[tiab] OR ((Iron[tiab] OR zinc[tiab] OR magnesium[tiab] OR Vitamin*[tiab] OR mineral*[tiab]) AND (dietary[tiab] OR supplement*[tiab])))
AND publisher[sb]
AND (RCT[tiab] OR placebo[tiab] OR sham[tiab] OR dummy[tiab] OR single blind*[tiab] OR double blind*[tiab] OR allocated[tiab] OR allocation[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR random*[tiab])
AND (cardiovascular disease*[tiab] OR heart disease*[tiab] OR cardiomyopath*[tiab] OR myocardial infarction[tiab] OR heart arrest[tiab] OR heart attack*[tiab] OR coronary artery disease[tiab] OR

coronary heart disease[tiab] OR ischemi*[tiab] OR ischaemi*[tiab] OR arrhythmia*[tiab] OR ((heart[tiab] OR myocardial[tiab] OR cardiac[tiab] OR systolic[tiab] OR diastolic[tiab] OR ventricular[tiab]) AND (failure*[tiab] OR dysfunction[tiab])) OR angina[tiab] OR vascular disease*[tiab] OR cerebrovascular disease*[tiab] OR cerebrovascular disorder*[tiab] OR aneurysm[tiab] OR arterial occlusive disease[tiab] OR stroke[tiab] OR cerebrovascular accident*[tiab] OR diabetic angiopath*[tiab] OR diabetic foot[tiab] OR diabetic retinopathy*[tiab] OR hypertensi*[tiab] OR high blood pressure[tiab] OR prehypertensi*[tiab] OR hypotens*[tiab] OR low blood pressure[tiab] OR carotid artery disease*[tiab] OR ((thromb*[tiab] OR embolic[tiab] OR emboli[tiab] OR embolism*[tiab] OR embolus[tiab]) AND (vein[tiab] OR veins[tiab] OR venous[tiab] OR venules[tiab] OR pulmonary[tiab] OR lung[tiab])) OR peripheral artery disease*[tiab] OR atherosclero*[tiab] OR hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR hypercholesterol*[tiab] OR high cholesterol[tiab] OR elevated cholesterol[tiab] OR neoplas*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR blastoma*[tiab] OR squamous[tiab] OR metastatic[tiab] OR meta-static[tiab] OR sarcoma*[tiab] OR myeloma*[tiab] OR adenoma*[tiab] OR glioblastoma*[tiab] OR lymphoma*[tiab] OR schwannoma*[tiab] OR Leukemia*[tiab] OR Leukaemia*[tiab] OR Hepatoma*[tiab] OR Metastas*[tiab] OR oncology[tiab] OR glioma*[tiab] OR carcinogen*[tiab] OR cholangiocarcinoma*[tiab] OR Neurofibroma*[tiab] OR Osteosarcoma*[tiab] OR Teratoma*[tiab] OR melanoma*[tiab])
AND ("2013/01/01"[PDAT] : "3000/12/31"[PDAT])
AND English

Harms:
(dietary calcium[tiab] OR calcium supplement*[tiab] OR calcium monotherapy[tiab] OR folic acid[tiab] OR folate[tiab] OR methyltetrahydrofolic[tiab] OR methyltetrahydrofolate[tiab] OR methyl tetrahydrofolic[tiab] OR methyl tetrahydrofolate[tiab] OR mthf[tiab] OR Vitamin B 9[tiab] OR Vitamin B9[tiab] OR Thiamine[tiab] OR Thiamin[tiab] OR Vitamin B 1[tiab] OR Vitamin B1[tiab] OR Aneurin[tiab] OR Riboflavin[tiab] OR Vitamin B 2[tiab] OR Vitamin B2[tiab] OR Vitamin B 6[tiab] OR Vitamin B6[tiab] OR Pyridoxin*[tiab] OR Vitamin B 12[tiab] OR Vitamin B12[tiab] OR Cobalamin[tiab] OR Cyanocobalamin[tiab] OR Cobamides[tiab] OR Hydroxocobalamin[tiab] OR Vitamin D[tiab] OR Cholecalciferol[tiab] OR Dihydroxycholecalciferol*[tiab] OR Calcitriol[tiab] OR Ergocalciferol*[tiab] OR Vitamin E[tiab] OR Tocopherol*[tiab] OR Tocotrienol*[tiab] OR Ascorbic acid[tiab] OR Vitamin C[tiab] OR ascorbate[tiab] OR Dehydroascorbate[tiab] OR Vitamin A[tiab] OR beta carotene[tiab] OR Betacarotene[tiab] OR Retinol[tiab] OR Niacin[tiab] OR nicotinic acid*[tiab] OR Selenium[tiab] OR Multivitamin*[tiab] OR Multi-vitamin*[tiab] OR multimineral*[tiab] OR multi-mineral*[tiab] OR ((Iron[tiab] OR zinc[tiab] OR magnesium[tiab] OR Vitamin*[tiab] OR mineral*[tiab]) AND (dietary[tiab] OR supplement*[tiab])))
AND publisher[sb]
AND ((RCT[tiab] OR placebo[tiab] OR sham[tiab] OR dummy[tiab] OR single blind*[tiab] OR double blind*[tiab] OR allocated[tiab] OR allocation[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR random*[tiab]) OR (case control*[tiab] OR cohort[tiab] OR longitudinal[tiab] OR follow up[tiab] OR followup[tiab] OR prospective*[tiab] OR retrospective*[tiab] OR comparison group*[tiab] OR control group*[tiab] OR observational[tiab] OR nonrandom*[tiab] OR database*[tiab] OR population*[tiab] OR cross sectional[tiab]))
AND (safety[tiab] OR adverse*[tiab] OR side effect*[tiab] OR drug toxicity[tiab] OR harm*[tiab] OR sarcoid*[tiab] OR neurosarcoidosis[tiab] OR besnier[tiab] OR schaumann syndrome[tiab] OR stone[tiab] OR stones[tiab] OR lithiasis[tiab] OR nephrolithiasis[tiab] OR cholelithiasis[tiab] OR urolithiasis[tiab] OR choledocholithiasis[tiab] OR hepatolithiasis[tiab] OR calculus[tiab] OR calculi[tiab] OR bleeding[tiab] OR hemorrhage[tiab] OR haemorrhage[tiab])

AND ("2013/01/01"[PDAT] : "3000/12/31"[PDAT])
AND English

Cochrane Central Register of Controlled Clinical Trials (CENTRAL) and Systematic Reviews

#1 "cardiovascular disease".ti,ab,kw
#2 "cardiovascular diseases":ti,ab,kw
#3 "heart disease":ti,ab,kw
#4 "heart diseases":ti,ab,kw
#5 Arrhythmia*:ti,ab,kw
#6 Cardiomyopath*:ti,ab,kw
#7 "Heart Arrest":ti,ab,kw
#8 ((heart or myocardial or cardiac or systolic or diastolic or ventricular) NEAR/1 (failure* or dysfunction)):ti,ab,kw
#9 Isch*emi*:ti,ab,kw
#10 "myocardial infarction":ti,ab,kw
#11 ("coronary artery disease" or "coronary heart disease"):ti,ab,kw
#12 "heart attack":ti,ab,kw
#13 "heart attacks":ti,ab,kw
#14 "Vascular Diseases":ti,ab,kw
#15 "Vascular Disease":ti,ab,kw
#16 Aneurysm*:ti,ab,kw
#17 "Arterial Occlusive":ti,ab,kw
#18 Cerebrovascular:ti,ab,kw
#19 "Carotid Artery":ti,ab,kw
#20 stroke:ti,ab,kw
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#23 "diabetic foot":ti,ab,kw
#24 "diabetic retinopathy":ti,ab,kw
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#27 hypotensi*:ti,ab,kw
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#34 Hyperlipid*emia*:ti,ab,kw
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#37 "elevated cholesterol":ti,ab,kw
#38 atherosclero*:ti,ab,kw
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Hepatoma* or Metastas* or oncology or glioma* or carcinogen* or cholangiocarcinoma* or Neurofibroma* or Osteosarcoma* or Teratoma* or melanoma*):ti,ab,kw
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#47 calcium monotherapy:ti,ab,kw
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#71 Calcitriol:ti,ab,kw
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#74 Tocopherol*:ti,ab,kw
#75 Tocotrienol*:ti,ab,kw
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#92 (Multimineral* or multi-mineral* or "multi mineral" or "multi minerals"):ti,ab,kw
#93 {OR #45-#92}
#94 #44 and #93 with Publication Year from 2013 to 2019, in Trials
#95 #44 and #93 with Cochrane Library publication date Between Jan 2013 and Aug 2019, in Cochrane Reviews

Embase (via embase.com)

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#47 'neoplasm'/exp/mj
#48 neoplas*:ti,ab OR cancer*:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumour:ti,ab OR tumours:ti,ab OR malignan*:ti,ab OR carcinoma*:ti,ab OR adenocarcinoma*:ti,ab OR blastoma*:ti,ab OR squamous:ti,ab OR metastatic:ti,ab OR 'meta static':ti,ab OR sarcoma*:ti,ab OR myeloma*:ti,ab OR adenoma*:ti,ab OR glioblastoma*:ti,ab OR lymphoma*:ti,ab OR schwannoma*:ti,ab OR leukemia*:ti,ab OR leukaemia*:ti,ab OR hepatoma*:ti,ab OR metastas*:ti,ab OR oncology:ti,ab OR glioma*:ti,ab OR carcinogen*:ti,ab OR cholangiocarcinoma*:ti,ab OR neurofibroma*:ti,ab OR osteosarcoma*:ti,ab OR teratoma*:ti,ab OR melanoma*:ti,ab
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#51 harm*:ti,ab OR advers*:ti,ab OR 'side effect*':ti,ab OR 'drug toxicity':ti,ab
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#53 sarcoid*:ti,ab OR neurosarcoidosis:ti,ab OR besnier:ti,ab OR 'schaumann syndrome':ti,ab
#54 'stone formation'/exp/mj

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#66 #64 OR #65
#67 #61 OR #66
#68 #41 AND #58 AND #67
#69 #41 AND #58 AND #67 AND [2013-2019]/py
#70 #63 OR #69
#71 (#63 OR #69) AND [english]/lim NOT (('animal'/exp OR 'nonhuman'/de) NOT 'human'/exp)
#72 #71 NOT (([adolescent]/lim OR [child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim) NOT ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim))

Appendix A. Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Populations	**KQs 1, 3:** Community-dwelling adults (age ≥18 years), including those: • Without chronic disease and without nutritional deficiencies • With high blood pressure or abnormal lipid levels without known cardiovascular disease (e.g., coronary, cerebrovascular, or peripheral artery disease) or type 2 diabetes mellitus **KQs 2, 4:** Community-dwelling adults without chronic disease	Populations that only include pregnant women, infants, persons with chronic diseases other than overweight or obesity (e.g., cancer, cardiovascular disease, type 2 diabetes mellitus, HIV, end-stage renal disease, tuberculosis, arthritis, or chronic pain), persons with known clinical nutritional deficiencies, persons taking prescribed medications, persons who had intestinal or stomach surgery or have known malabsorption syndromes that may influence nutritional absorption or status, or persons who are institutionalized or hospitalized Studies will be excluded if ≥50% of patients have known nutritional deficiencies, cardiovascular disease, type 2 diabetes mellitus, personal history of cancer (other than nonmelanoma skin cancer) or are taking prescription medications that may influence nutritional absorption or status
Setting	Trials conducted in countries rated as "very high" on the 2017 Human Development Index (as defined by the United Nations Development Programme)	Trials conducted in countries not categorized as "very high" on the 2017 Human Development Index, as there is concern for nutritional deficiencies in developing countries
Interventions	**KQs 1, 2:** Supplementation with multivitamins/minerals, defined as three or more vitamins, minerals, or combinations of both without added herbs, hormones, or drugs, each at a dose less than the tolerable upper intake level, as determined by the Food and Nutrition Board **KQs 3, 4:** Supplementation with single nutrients and functionally related pairs (i.e., calcium; folic acid; vitamins B1, B2, B6, B12, D, E, C, and A; iron; zinc; magnesium; niacin; calcium/vitamin D; calcium/magnesium; folic acid/vitamin B12; selenium; beta-carotene; and folic acid/vitamin B6), each at a dose less than the tolerable upper intake level, as determined by the Food and Nutrition Board	Supplementation with other types of dietary supplements (e.g., herbal supplements, omega-3 fatty acids, amino acids, enzymes, proprietary products, fiber, garlic, or turmeric), or vitamin-derived agents with dermatologic indication (i.e., tretinoin, isotretinoin); interventions to increase dietary intake of a single nutrient (e.g., iron)
Comparisons	Placebo, no intervention, or usual diet	Supplementation with other vitamins or minerals

Appendix A. Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Outcomes	**KQs 1, 3:** • Cancer incidence (any cancer or site-specific). • Cardiovascular disease incidence (including coronary heart, peripheral artery, and cerebrovascular disease) • Cardiovascular disease events (myocardial infarction and ischemic and hemorrhagic stroke), heart failure • Mortality (all-cause, cardiovascular disease–related, or cancer-related) **KQs 2, 4:** • Serious adverse events (as defined by the study, or those likely requiring medical attention, such as kidney stones, sarcoidosis, and hip fracture) • Withdrawals due to adverse events • Nonserious adverse events based on self-report or objective measurements, reported by at least 5% of the study sample taking the supplement • Paradoxical effects on main outcomes (from trial evidence included for KQs 1 and 3)	**KQs 1, 3:** Intermediate measures of cardiovascular disease risk factors (i.e., systolic and diastolic blood pressure, lipid measures, and glucose measures), precancerous lesions Nonmelanoma skin cancer will not be considered in studies that target populations with a history of previous skin cancer KQs 2, 4: Intermediate or laboratory measures (e.g., hypercalciuria)
Timing	**All-cause mortality:** Minimum of 1 year of followup **All other outcomes:** No minimum followup	Less than 1 year of followup (all-cause mortality only)
Study Designs	**KQs 1, 3:** Randomized, controlled trials **KQs 2, 4:** Randomized, controlled trials or, for serious harms only, large (n ≥1,000) comparative observational studies (cohort or case-control) or postmarket surveillance data Only randomized, controlled trials will be considered for studies showing paradoxical harmful effects on main outcomes (cancer incidence and cardiovascular disease incidence or events)	All other study designs

Appendix A. Table 2. Single Screening Terms

Single Screening Terms	No. (%)*
Adolesc	1056 (7.45)
Allele	228 (1.61)
Animal	976 (6.88)
Arthrit	250 (1.76)
Braz	99 (0.70)
Child	1373 (9.68)
Chin	665 (4.69)
Fiber	198 (1.40)
Garlic	32 (0.23)
Hepati	361 (2.55)
Herbal	149 (1.05)
HIV	203 (1.43)
India	219 (1.54)
Infant	700 (4.94)
Infect	895 (6.31)
Iran	170 (1.20)
Isotretinoin	40 (0.28)
Mexic	36 (0.25)
Mice	157 (1.11)
Neonat	335 (2.36)
Niger	30 (0.21)
Peru	5 (0.04)
Polymorphism	515 (3.63)
Preg	1519 (10.71)
Rats	183 (1.29)
Rheum	177 (1.25)
Russ	21 (0.15)
South Africa	29 (0.20)
Transplant	339 (2.39)
Tretinoin	66 (0.47)
Turk	43 (0.30)
Turmeric	67(0.04)

*Counts are not mutually exclusive

Appendix A Table 3. Recommended Dietary Allowance (RDA) and Upper Intake Levels for Included Micronutrients[146, 195]

Vitamin or mineral	Other Names	Group	Age (years)	RDA	UL
Vitamin A (mcg/d)* Conversion factor 1IU supplemental beta-carotene=0.3 mcg RAE	Vitamin A Retinol, Retinal	Males	9-13	600 mcg/d RAE	1700 mcg/d RAE (5,667 IU)
			14-18	900 mcg/d RAE	2800 mcg/d RAE (9,333 IU)
			≥19	900 mcg/d RAE	3000 mcg/d RAE (10,000 IU)
		Females	9-13	600 mcg/d RAE	1700 mcg/d RAE (5,667 IU)
			14-18	700 mcg/d RAE	2800 mcg/d RAE (9,333 IU)
			≥19	700 mcg/d RAE	3000 mcg/d RAE (10,000 IU)
Vitamin B_1 (mg/d)	Thiamine, thiamin, aneurine	Males	9-13	0.9	ND
			≥14	1.2	ND
		Females	9-13	0.9	ND
			14-18	1.0	ND
			≥19	1.1	ND
Vitamin B_2 (mg/d)	Riboflavin	Males	9-13	0.9	ND
			≥14	1.3	ND
		Females	9-13	0.9	ND
			14-18	1.0	ND
			≥19	1.1	ND
Vitamin B_6 (mg/d)	None	Males	9-13	1.0	60
			14-18	1.3	80
			19-50	1.3	100
			≥51	1.7	100
		Females	9-13	1.0	60
			14-18	1.2	80
			19-50	1.3	100
			≥51	1.5	100
Vitamin B_{12} (mcg/d)	Cobalamin	Males	9-13	1.8	ND
			≥14	2.4	ND
		Females	9-13	1.8	ND
			≥14	2.4	ND
Vitamin C (mg/d)	L-ascorbic acid, ascorbate, Dehydroascorbic acid (DHA)	Males	9-13	45	1200
			14-18	75	1800
			≥19	90	2000
		Females	4-8	75	1200
			9-18	65	1800
			≥19	75	2000
Vitamin D (mcg/d (IU))	Calciferol, cholecalciferol (Vit D3), Calcitriol (synthetic Vit D3) Alfacalcidol (Vit D3) Ergocalciferol (Vit D2)	Males	9-70	15 mcg/d	100 mcg/d (4000 IU/d)
			>70	20 mcg/d	100 mcg/d (4000 IU/d)
		Females	9-70	15 mcg/d	100 mcg/d (4000 IU/d)
			>70	20 mcg/d	100 mcg/d (4000 IU/d)
Vitamin E (mg/d)	α-tocopherol	Males	9-13	11	600
			14-18	15	800
			≥19	15	1000
		Females	9-13	11	600
			14-18	15	800

Appendix A Table 3. Recommended Dietary Allowance (RDA) and Upper Intake Levels for Included Micronutrients[146, 195]

Vitamin or mineral	Other Names	Group	Age (years)	RDA	UL
			≥19	15	1000
Calcium (mg/d)	*calcium* carbonate, *calcium* gluconate, *calcium* citrate	Males	9-13	1300	3000
			19-30	1000	2500
			51-70	1000	2000
			≥71	1200	2000
		Females	9-13	1300	3000
			19-30	1000	2500
			≥51	1200	2000
Folic acid (mcg/d)	Vitamin M, vitamin B_9, vitamin B_c, folacin, pteroyl-L-glutamic acid, pteroyl-L-glutamate, and pteroylmonoglutamic acid, folate	Males	9-13	300	600
			14-18	400	800
			≥19	400	1000
		Females	9-13	300	600
			14-18	400	800
			≥19	400	1000
Iron (mg/d)	None	Males	9-13	8	40
			14-18	11	45
			≥19	8	45
		Females	9-13	8	40
			14-18	15	45
			19-30	18	45
			31-50	15	45
			≥51	8	45
Magnesium (mg/d)	Magnesia, Magnesia Carbonica, Magnesia Muriatica, Magnesium Gluconate, Milk of Magnesia	Males	9-13	240	350
			14-18	410	350
			19-30	400	350
			≥31	420	350
		Females	9-13	240	350
			14-18	360	350
			19-30	310	350
			≥31	320	350
Niacin (mg/d)	Vitamin B3, nicotinic acid, Nicotinamide, vitamin PP	Males	9-13	12	20
			14-18	16	30
			≥19	16	35
		Females	9-13	12	20
			14-18	14	30
			≥19	14	35
Selenium (mcg/d)	High-*selenium* yeast, selenized yeast, chelated *selenium*	Males	9-13	40	280
			≥14	55	400
		Females	9-13	40	280
			≥14	55	400
Zinc (mg/d)	*Zinc* acetate	Males	9-13	8	23
			14-18	11	34
			≥19	11	40
		Females	9-13	8	23
			14-18	9	34
			≥19	8	40

*Beta-carotene is a provitamin A carotenoid, meaning the body converts it to Vit A. Beta-carotene is thought to not cause toxicity and has no designated upper limit.

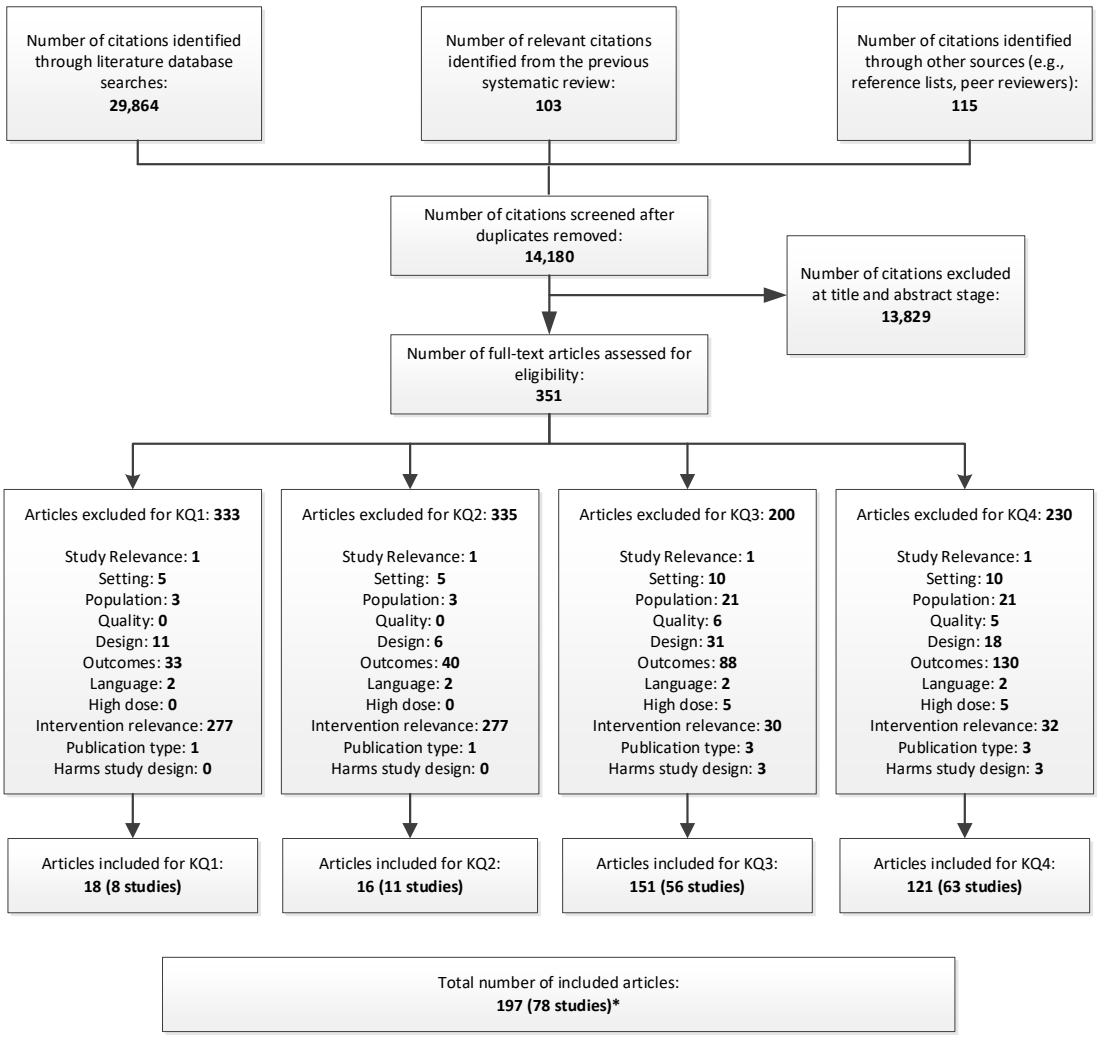
Abbreviations: IU = International unit; RAE = Retinol activity equivalents; RDA = Recommended daily allowance (Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals, often used to plan nutritionally adequate diets for individuals); UL= Tolerable upper intake level (Maximum daily intake unlikely to cause adverse health effects)

Appendix A. Table 4. Study Design-Specific Quality Rating Criteria

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[46]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer

Appendix A Figure 1. Literature Flow Diagram



*Studies may appear in more than one Key Question

Below is a list of included studies and their ancillary publications (indented below main results publication):

Aloia, J, Fazzari, M, et al. Vitamin D Supplementation in Elderly Black Women Does Not Prevent Bone Loss: a Randomized Controlled Trial. J Bone Miner Res. 33(11): 1916-1922. 2018. PMID: 29905969. https://dx.doi.org/10.1002/jbmr.3521

> Owusu, JE, Islam, S, et al. Cognition and Vitamin D in Older African-American Women-Physical performance and Osteoporosis prevention with vitamin D in older African Americans Trial and Dementia. J Am Geriatr Soc. 67(1): 81-86. 2019. PMID: 30359476. https://dx.doi.org/10.1111/jgs.15607

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Appendix C. Excluded Studies

Reason for Exclusion*
E1. Study relevance
E2. Setting
E3. Population
E4. Study quality
E5. Study design
E5a. Comparative effectiveness
E6. Outcomes – No relevant outcomes
E6a. No CVD or cancer outcome
E7. Precedes search period
E8. Non-English publication
E9. Source document only
E10. Non-RCT harms on CVD or cancer
E11. High dose > upper limit
E12. No relevant intervention/agent
E13. Publication type (i.e., conference abstract)
E14. Short-terms harms-only trial for agent with no evidence of benefit (KQ1 or KQ3 outcomes)

*Assigned at full-text phase

Abbreviations: E = exclude

Appendix C. Excluded Studies

1. Adebamowo, SN, Feskanich, D, et al. Multivitamin use and risk of stroke incidence and mortality amongst women. European Journal of Neurology. 24(10): 1266-1273. 2017. PMID: 28758316. https://dx.doi.org/10.1111/ene.13358 **KQ1E5, KQ2E6, KQ3E12, KQ4E12**

2. Age-Related Eye Disease Study Research, Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 119(10): 1417-36. 2001. PMID: 11594942. https://dx.doi.org/10.1001/archopht.119.10.1417 **KQ1E6, KQ2E6, KQ3E11, KQ4E11**

3. Age-Related Eye Disease Study Research, Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Control Clin Trials. 20(6): 573-600. 1999. PMID: 10588299. https://dx.doi.org/10.1016/s0197-2456(99)00031-8 **KQ1E6, KQ2E6, KQ3E11, KQ4E11**

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6. Ambrosini, GL, Bremner, AP, et al. No dose-dependent increase in fracture risk after long-term exposure to high doses of retinol or beta-carotene. Osteoporos Int. 24(4): 1285-93. 2013. PMID: 22986930. https://dx.doi.org/10.1007/s00198-012-2131-6 **KQ1E12, KQ2E12, KQ3E5a, KQ4E5a**

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8. Anderson, JJ, Kruszka, B, et al. Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 5(10): 11. 2016. PMID: 27729333. **KQ1E12, KQ2E12, KQ3E5, KQ4E6**

9. Araghi, SO, Jong, JCK, et al. Long-term Effect of Folic Acid and Vitamin B12 Supplementation on Fracture Risk and Cardiovascular Disease: Follow-up Study of B-PROOF Trial (P24-031-19). Current Developments in Nutrition. 3(Suppl 1). 2019. PMID: 31223693. https://dx.doi.org/10.1093/cdn/nzz044.P24-031-19 **KQ1E12, KQ2E12, KQ3E13, KQ4E13**

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11. Barrington, WE, Schenk, JM, et al. Difference in Association of Obesity With Prostate Cancer Risk Between US African American and Non-Hispanic White Men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA Oncology. 1(3): 342-9. 2015. PMID: 26181184. https://dx.doi.org/10.1001/jamaoncol.2015.0513 **KQ1E1, KQ2E1, KQ3E1, KQ4E1**

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13. Bolland, MJ, Barber, A, et al. Differences between self-reported and verified adverse cardiovascular events in a randomised clinical trial. BMJ Open. 3(3): 18. 2013. PMID: 23512838. https://dx.doi.org/10.1136/bmjopen-2012-002334 **KQ1E12, KQ2E12, KQ3E6, KQ4E6**

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20. Cangussu, LM, Nahas-Neto, J, et al. Effect of vitamin D supplementation alone on muscle function in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. Osteoporos Int. 26(10): 2413-21. 2015. PMID: 25956283. https://dx.doi.org/10.1007/s00198-015-3151-9 **KQ1E12, KQ2E12, KQ3E2, KQ4E2**

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Appendix D. Contextual Question

Contextual question: What is the effect of vitamin and mineral supplementation on cardiovascular disease risk factors (e.g., high blood pressure, abnormal lipid levels, metabolic syndrome, atrial fibrillation, renal disease, or type 2 diabetes mellitus) and precancerous outcomes (e.g., adenoma or cervical dysplasia)?

Cardiovascular Disease Risk Factors

Blood Pressure

A very large body of trial evidence evaluates the effect of vitamin and mineral supplementation on blood pressure. The strongest signals for benefit are for vitamin C, magnesium, calcium, and multivitamins. For these supplements, pooled effects were on the order of 1 to 4 mm Hg SBP and 1 to 2 mm Hg DBP. However, evidence of benefit is from short-term trials with wide variations in doses and pooled effects often have high statistical heterogeneity. The largest body of evidence is for vitamin D with or without calcium which showed no effect. Few studies have been conducted for vitamin K supplementation and similarly showed no effect. Evidence is insufficient for selenium.

Vitamin C. An umbrella review of systematic reviews identified one systematic review of 29 RCTs (N=1,407), finding that vitamin C is associated with moderate blood pressure reduction.[196, 197] This review found a statistically significant pooled effect of -3.84/-1.48 mm Hg, but with high statistical heterogeneity (SBP -3.84 mm Hg [95 CI%, -5.29 to -2.38], I^2=69%; DBP -1.48 mm Hg [95% CI, -2.86 to -0.10], I^2=81%). Included trials were primarily short-term (median 8 weeks) and had a median vitamin C dose of 500 mg/day. Participants had a wide range of baseline blood pressures.

Magnesium. A meta-analysis of 34 trials (N=2,028) of adults with and without hypertension found that magnesium supplementation was associated with small statistically significant reductions blood pressure (SBP -2 mm Hg [95% CI, -3.58 to -0.43], I^2=62%; DBP -1.78 mm Hg [95% CI, -2.82 to -0.73 to]; I^2=64%).[198] The median dose was 368 mg/d with a median treatment duration of 3 months. A more narrowly scoped meta-analysis of magnesium supplementation in adults with diabetes or diabetes risk factors (k=19, N=NR) by Verma and Garg[199] found a statistically significant moderate benefit for SBP [-3.06 mm Hg (95% CI, -5.51, to -0.60); I^2=59%) but no statistically significant association with DBP [-1.40 mm Hg (95% CI, -3.02 to 0.29); I^2= 65%]. Trial duration ranged from 4 to 24 weeks and most doses of elemental calcium were between 360 and 394 mg/d.

Calcium. A systematic review of 16 studies of normotensive individuals (N=3,048) found that calcium supplementation was associated with a very small but statistically significant reduction in blood pressure of -1.43/-0.98 mm Hg (SBP -1.43 mm Hg [95% CI, -2.15 to -0.72], I^2=0%; DBP -0.98 mm Hg [95% CI, -1.46 to -0.50], I^2=49%).[200] The dose of calcium in these studies was most commonly 1,000 to 2,000 mg/day and the median followup was 3.5 months. Subgroup analyses suggested larger blood pressure reduction with higher calcium doses and in younger participants.

Multivitamin. One systematic review of 8 RCTs (N=2,011) found that multivitamins were associated with a very small statistically significant reduction in continuous blood pressure of 1.31/0.71 mm Hg and that reductions were greater in those with chronic conditions, including hypertension, obesity, or gastrointestinal disease (SBP -1.31 mm Hg [95% CI, -2.48 to -0.14], I^2=28%; DBP: -0.71 mm Hg [95% CI, -1.43 to 0.00]; I^2=31%).[201] Followup in these studies

ranged widely, from 1 to 86 months. In 4 RCTs of adults without hypertension (N=22,852), multivitamins were not associated with a reduced risk of incident hypertension [OR 0.92 (95% CI, 0.80 to 1.05); I^2=67%].

Vitamin D with or without calcium. A large body of evidence from trial-level and individual patient-level meta-analyses shows that supplementation with vitamin D alone or with calcium does not reduce continuous measures of blood pressure.[202-207] Meta-analyses of vitamin D supplementation alone include data from more than 46 RCTs and over 4,700 participants and represent a heterogeneous body of literature where populations had varied baseline 25(OH)D concentrations, and interventions were of varied dose and duration. The most reliable data for exploration of subgroup effects—individual patient data meta-analyses—show no baseline factors associated with more favorable blood pressure outcomes.[202, 203] One meta-analysis of 39 trials (N=NR) that restricted inclusion to studies with 3 months minimum duration showed a statistically significant but exceedingly small benefit for blood pressure reduction of SBP/DBP -0.102/-0.07 mm Hg (SBP -0.102 mm Hg [95% CI, -0.20 to -0.03], I^2=NR; DBP -0.07 mm Hg [95% CI, -0.14 to -0.006], I^2=NR).[208] Vitamin D administered jointly with calcium similarly showed no effect on blood pressure. A meta-analysis of eight trials (N=36,806) found a non-statistically significant pooled effect of +0.61/-0.22 mm Hg with study followup ranging from 15 weeks to 7 years.[206] This meta-analysis includes results from the very large (N=36,282) Women's Health Initiative (WHI) trial which evaluated a calcium dose of 1000 mg/d plus 400 IU/day of vitamin D. In WHI, the mean change in blood pressure showed no statistically significant change over median 7 years followup between the intervention and placebo groups (SBP: 0.22 mm Hg [95% CI, -0.05 to 0.49]; DBP: 0.11 mm Hg [95% CI, -0.04 to 0.27).[209] Similarly, there was no statistically significant change in the risk of incident hypertension in the 17,122 nonhypertensive participants at baseline over median 7 years followup (HR 1.01 [95% CI, 0.96 to 1.06]).

Vitamin K. A 2019 systematic review of vitamin K supplementation found no effect on blood pressure outcomes in a meta-analysis of 4 studies (N=590).[210] These trials evaluated interventions of various vitamin K doses and formulations of ranging from 24 to 156 weeks.

Selenium. There is sparse evidence about the effect of selenium on blood pressure. A systematic review by Kuruppu and colleagues[211] identified no RCTs of selenium supplementation alone that report blood pressure outcomes. Similarly, a systematic review by Rees and colleagues[189] identified only one short term study of selenium on blood pressure. The focus of this study was on high protein diets for weight loss, where the intervention group receive chicken breasts enriched with selenium; no blood pressure effect was found.

Lipids

A number of systematic reviews have examined the effect of vitamin and mineral supplementation on lipids. The strongest signal for benefit is from magnesium which showed both an LDL reduction (pooled MD -10.67 [95% CI, -19.11 to -2.23]) and an HDL increase (pooled MD 3.2 mg/dL [95% CI, 1.46 to 4.94]). LDL reductions are also seen for zinc, vitamin D, and possibly selenium. Similar to the blood pressure literature, evidence of benefit is typically from short-term trials with wide variations in doses and pooled effects often have high statistical heterogeneity. There is also a wide variation of baseline serum levels of the vitamin or mineral

of interest suggesting clinical heterogeneity. Synthesized evidence for vitamin D plus calcium, vitamin K, and vitamin C suggest no benefit for any lipid outcome.

Magnesium. A systematic review of 21 studies (N=NR) reporting lipid outcomes associated with magnesium supplementation showed a substantial benefit.[199] Pooled estimates showed statistically significant HDL increases of 3.2 mg/dL (95% CI, 1.46 to 4.94, I^2=67%) and LDL decreases of -10.67 (95% CI, -19.11 to -2.23, I^2=71). Statistical heterogeneity was somewhat high for both outcomes. Studies were of 4 to 24 weeks duration and doses ranged from 300 to 729 mg elemental calcium per day.

Zinc. A large systematic review of zinc supplementation including 24 trials and 14,515 people suggests a large benefit for LDL (-6.87 mg/dL [95% CI, -11.16 to -2.58], I^2=31%) but no statistically significant HDL benefit.[212] This body of evidence encompasses a wide range of patients, including many with obesity and/or diabetes in addition to healthy adults. A small number of studies were conducted in individuals with kidney disease, heart disease, or cancer. Study duration ranged from 1 month to 7.5 years and the dose range was highly variable at 15 to 240 mg zinc per day. A newer systematic review of zinc supplementation that included a slightly smaller number of studies (k=20) confirmed findings of statistically significant reductions in some lipid measures.[213]

Vitamin D. Several systematic reviews, comprising over 40 RCTs and 3,000 people, consistently show that vitamin D is associated with a small to moderate statistically significant reduction in LDL on the order of about 3 to 4 mg/dL.[203, 208, 214] This synthesized literature has shown mixed findings for HDL benefit. These studies represent somewhat heterogeneous interventions in terms of dose and duration where the median study duration was 6 months and the median dose was 2800 to 2900 mg/day; the baseline levels of 25(OH)D also varied widely in these studies.

Selenium. A systematic review of 12 trials (N=NR) showed generally no lipid benefit for selenium supplementation.[189] While one contributing trial of 6 months, UK PRECISE, showed a statistically significant benefit for non-HDL when results for intervention arms of various doses were combined (-7.73 mg/dL [95% CI, -15.85 to 0], I^2=NR), no other pooled estimates for lipid parameters were statistically significant in the systematic review.

Vitamin D+calcium. Fewer studies evaluated the combined supplementation of calcium and vitamin D and reported lipid change.[215] These studies generally showed no benefit for lipid reduction, including 5-year results from the large WHI trial which tested 1,000 mg calcium + 400 IU vitamin D per day.[216]

Vitamin K. One systematic review of 7 RCTs (N=676) evaluating vitamin K supplementation found no benefit for LDL, HDL, or TC.[210] Studies were of 4 to 152 weeks duration with most being less than 24 weeks. A large range of doses and formulations were tested in these studies.

Vitamin C. A large systematic review of vitamin C supplementation (k=40; N=1981) showed no benefit for any lipid parameter in overall analyses of a wide range of participants.[217] Subgroup analyses indicated potential benefit in some population subgroups for some lipid outcomes, but these results were not consistent across lipid outcomes. Trials tested a wide range of vitamin C dose (125 to 4500 mg/d) and durations ranged from 2 to 240 weeks.

Diabetes Incidence

Overall, relatively little trial evidence has accrued evaluating the association of vitamin or mineral supplementation with incident diabetes. The largest body of evidence is for selenium which shows a statistically significant harm in a recent meta-analysis of 5 trials. The effect of vitamin D supplementation on incident diabetes has been tested in several recent trials of adults with prediabetes and these trials consistently show that vitamin D is likely not associated with any benefit, but no pooled analyses are available. For zinc, very limited evidence from just one trial of adults with prediabetes in a setting not relevant to the US suggests benefit.

Selenium. Two systematic reviews show a small but consistent association between selenium supplementation and increased risk for incident diabetes.[189, 190] The systematic review by Vinceti and colleagues includes the same 4 RCTs as the systematic review by Rees and colleagues and adds one newer trial. Pooled analyses of 5 RCTs (N=22,265) of selenium supplementation of 200 mcg/d was associated with a statistically significant 11 percent increase in risk for new diabetes with median followup from 3 to 7.9 years (1.11 [95% CI 1.01 to 1.22]; I^2=0%).[190] Most of the evidence is from the SELECT trial which only recruited men; diabetes incidence was a prespecified secondary outcome in this study.

Vitamin D. Three recent trials of varying vitamin D doses and formulations suggest that vitamin D supplementation is likely not associated with a meaningful reduction in incident diabetes in populations with prediabetes.[135, 218, 219] The largest of these trials, D2d, was a US study of 2,434 adults with prediabetes who were randomized to 4,000 IU vitamin D per day over a median followup of 2.5 years.[135] D2d had no baseline serum 25-hydroxyvitamin D eligibility criterion and a high percentage of participants were considered to have adequate levels at baseline. The hazard ratio for incident diabetes was 0.88 (95% CI, 0.75 to 1.04). A smaller Norwegian trial of 511 participants with prediabetes and generally with adequate vitamin D status showed similar results over five years followup (HR 0.90 [95% CI, 0.69 to 1.18]).[218] In this study, participants in the intervention group received weekly doses of a vitamin D 20,000 capsule. Finally, a Japanese trial of 1,256 participants with impaired glucose tolerance and a range of baseline vitamin D levels reported a hazard ratio of 0.87 (95% CI, 0.68 to 1.09) for incident diabetes over 2.6 years followup.[219] This trial evaluated a daily dose of 0.75 mcg eldecalcitol which is an active form of vitamin D analog.

Zinc. Very limited RCT evidence from one Sri Lankan trial of 200 people suggests that zinc supplementation may delay progression to diabetes in those with prediabetes.[220] This trial randomized adults with prediabetes to 20 mg elemental zinc daily or placebo for one year and found a substantial reduction in diabetes incidence in those taking zinc (OR 0.28 [95 CI, 0.13 to 0.64]). Diabetes was a secondary outcome in this trial with 36 incident events (11 in the zinc group and 25 in the placebo group). Additional evidence from more relevant settings to the US is needed to confirm this finding.

Atrial Fibrillation

Virtually all of the evidence for supplementation for atrial fibrillation is in the context of hospitalized or post-surgical patients.[221, 222] Only limited RCT evidence is available to assess the association of supplementation with prevention of atrial fibrillation in generally healthy adults. This evidence is focused on vitamin D with or without calcium and suggests no benefit.

Vitamin D+calcium. A secondary analysis of 16,801 postmenopausal women from the Women's Health Initiative trial found no association of vitamin D and calcium supplementation with new atrial fibrillation over an average followup of 4.5 years (HR 1.02 [95% CI, 0.92 to 1.13]).[223] The supplementation intervention consisted of 1,000 mg/d of elemental calcium and 400 IU/d of vitamin D3.

Vitamin D. Two recent trials of vitamin D show no association between supplementation and incident atrial fibrillation or arrhythimas. A substudy of VITAL, the VITAL Rhythm Study (N=25,119), evaluated new diagnoses of atrial fibrillation on annual followup questionnaires over a mean duration of 5.3 years and found no association between 2,000 IU/day of vitamin D3 and clinically-detected incident atrial fibrillation (HR 1.09 [95% CI 0.96 to 1.24]; 900 total confirmed atrial fibrillation diagnoses).[224] The ViDA trial of 5,108 adults in New Zealand evaluated the effect of monthly doses of 100,000 IU vitamin D3 on CVD events over a median followup of 3.3 years.[91] ViDA found no association between vitamin D supplementation and arrhythmias, but this outcome was not restricted to atrial fibrillation (HR 0.93 [95% CI, 0.62 to 1.39]).

Renal Outcomes

Relatively little evidence is available regarding the effect of supplementation to maintain or improve renal function in generally healthy adults. Most of the evidence on supplementation is available in patients with established CKD or diabetic nephropathy, which suggests some potential benefit for reduced proteinuria or albuminuria.[225, 226] The sparse evidence available in relevant general healthy populations is in the context of monitoring renal function as potential harm of supplementation. A few of these studies suggest there may be a small increase in blood or serum creatinine in individuals randomized to calcium. However, these are intermediate measures of kidney function with an unknown clinical significance of small increases. Studies of vitamin D supplementation generally show no association with renal measures in healthy populations or individuals with type 2 diabetes.

Calcium and vitamin D. The Vitamin D/Calcium Polyp Prevention Study—an included study in our review—tested 1,000 IU/day vitamin D, 1,000 mg/d calcium, or both for preventing recurrent colorectal adenoma.[90] Blood creatinine concentration was measured as a prespecified interim outcome for safety to assess potential renal effects. In the 1,675 participants in the full factorial trial, creatinine values were slightly higher at 1 year in the calcium group than in the control group (mean 0.013 (0.006 SE) mg/dL, p=0.03) but were not different in the vitamin D group compared to control.[227] No other measures of renal function were measured in this trial and the clinical significance of a small increase at one year is unknown. Similarly, a 2 year trial of 1,000 mg/day or 2,000 mg/day calcium for bone loss prevention found a statistically significant increase in serum creatinine ($p < 0.01$) in both calcium groups compared to control.[228] In contrast, a US-based RCT of 438 adults age 60 years or older evaluated 750 mg calcium or 15 mcg vitamin D3 for the primary aim of bone loss prevention and measured serum creatinine as a safety outcome.[229] No significant differences in serum creatinine were found between the calcium, vitamin D and placebo groups at 4 years. Finally, VITAL conducted a substudy (VITAL-DKD) to evaluate vitamin D for the prevention and treatment of CKD in trial participants with type 2 diabetes at baseline (N=1,312).[230] Over 5 years of followup, vitamin D was not

associated with a statistically significant difference in estimated eGFR compared to placebo (0.9 mL/min/1.73^2 [95% CI, -0.7 to 2.6]).

Precancerous Outcomes

Colorectal Adenomas

There is a small and disparate body of evidence for single or multivitamins to prevent colorectal adenomas. These trials are typically conducted in populations with a history of prior adenoma. The number of studies for any one supplement or supplement combination is relatively small and editorials have noted that the follow-up periods of 3 to 5 years may not be adequate to detect an effect.[231] Calcium appears to be the most promising supplement, suggesting at best a modest benefit, and there is a possible signal that multivitamins may have some benefit.

Calcium. A systematic review of 5 trials (N=2,234) of calcium 1200 to 2000 mg/day found a statistically significant 17 percent reduction in recurrent colorectal adenoma (RR 0.83 [95% CI, 0.75 to 0.93] with low heterogeneity [I^2=8.5%]).[232] However, results showed no association with the likelihood for recurrent adenomas that were advanced (RR 1.01 [95% CI, 0.74 to 1.38], I^2=17.5%). This systematic review included two studies of 1200 mg/d calcium by the same investigator group that were conducted 16 years apart and showed conflicting results. The earlier 1999 trial, the Calcium Polyp Prevention Study[233] showed a significant benefit for recurrent colorectal adenoma (RR 0.81 [95% CI, 0.67 to 0.99] that was not replicated in the later 2015 trial, the Vitamin D/Calcium Polyp Prevention Study (VCPPS) (0.95 [95% CI, 0.85 to 1.06]).[90] Barry and colleagues hypothesized that effect modification by BMI present in both trials, which showed risk reduction in those with normal BMI and no effect or risk increase in those with overweight or obesity, might explain the conflicting results, with higher BMI in the later trial which is consistent with US trends.[234]

Multivitamins. The body of evidence for multivitamins to prevent new or recurrent colorectal adenoma is mixed, with results ranging from substantial statistically significant benefit to suggestion of harm. A pooled analysis of eight trials of multivitamins (containing various combinations of beta carotene, vitamin A, vitamin C, vitamin E, and selenium) for a duration of 1 to 6.3 years (N=17,620) did not rule out a potential benefit for a combined outcome of new or recurrent colorectal adenoma (RR 0.82 [95% CI, 0.60 to 1.1]).[235] However, statistical and methodologic heterogeneity in this body of literature was high and authors reported that estimated effect seemed to depend on the risk of bias of the contributing trials, with low risk of bias studies suggesting potential harm. Only two of eight contributing studies found statistically significant benefit, and these had sample sizes of less than 150 participants each. On the other hand, an Italian trial (N=411) of a multivitamin comprised of vitamin A, vitamin C, vitamin E, zinc and selenium not included in this meta-analysis because of a later publication date showed a statistically significant 39 percent reduction in recurrent colorectal adenoma (HR 0.61 (95% CI, [0.41 to 0.92]), although the 50 percent reduction in advanced recurrent colorectal adenoma was not statistically significant (HR 0.50 [95% CI, 0.24 to 1.01]).[95]

Folic acid. A small body of evidence evaluating folic acid for the prevention of primary or recurrent colorectal adenoma shows mixed results, although the most relevant studies suggest no benefit. The Aspirin/Folate Polyp Prevention Study (AFPPS), conducted in the US and Canada, found no benefit for 1 mg/d folic acid over 3 to 5 years on recurrent colorectal

adenoma or advanced recurrent adenoma in a 2x2 trial also evaluating aspirin (RR 1.04 [95% CI, 0.90 to 1.20] and RR 1.32 [95% CI, 0.90 to 1.92], respectively).[83] The ukCAP trial, conducted in the United Kingdom, showed similar results for 0.5 mg/d folic acid over 3 years (RR 1.07 [95% CI, 0.85 to 1.34] for recurrent adenoma and RR 1.32 [95% CI, 0.90 to 1.92]) for advanced recurrent adenoma.[108] A secondary study of participants from the NHS and HPFS with some design limitations also found no suggestion of benefit for 1 mg/d folic acid for 3 to 6.5 years (RR 0.82 [95% CI, 0.59 to 1.13] for recurrent adenoma and RR 1.08 [95% CI, 0.54 to 2.16]) for advanced recurrent adenoma).[109] In contrast, a 2013 Chinese trial showed substantial benefit for folic acid supplementation for primary prevention of colorectal adenoma and advanced colorectal adenoma (RR 0.74 [95% CI, 0.65 to 0.85] and RR 0.67 [95% CI, 0.58 to 0.76]); however, the lack of folate-fortified foods available in China could explain differences in results compared with the North American-based AFPPS.[236] A very small US trial of 93 participants conducted in one VA Medical Center reported that adenoma recurrence was twice that in the placebo group compared to the folic acid group, but data are not shown; this trial used a 5 mg/d dose of folic acid and participants were almost exclusively men.[237] Fortification of the food supply with folate became mandatory in the US in 1998 to increase maternal folate levels during pregnancy to protect against neural tube defects; most studies were accruing followup after this time.[238]

Selenium. A small number of trials have investigated selenium for the prevention of new or recurrent colorectal adenoma. A 2016 US trial of 1,824 participants found no effect for 200 mcg/d selenium over 33 month followup for recurrent colorectal adenoma or advanced recurrent adenomas (RR 1.03 [95% CI, 0.91 to 1.16] and RR 1.02 [95% CI, 0.74 to 1.43], respectively).[98] A substudy from SELECT in a primary prevention population similarly showed no effect, although analyses were limited to men reporting that they underwent endoscopy during the trial which only included 18.4 percent of the overall population.[239]

Vitamin E. Two primary prevention studies of vitamin E, each with design limitations, show mixed results of either no effect or harm for colorectal adenomas. The SELECT substudy which also evaluated selenium, found no effect for their vitamin E arm.[239] Another secondary analysis in a primary prevention population, this of the ATBC study, found that vitamin E was associated with an increased risk of colorectal adenoma (RR 1.66 [95% CI, 1.19 to 2.32]).[179] This analysis is likely subject to detection bias as there was no systematic CRC screening; cases were identified through pathology labs in study areas and symptoms which may have led to colonoscopy referrals were more common in those randomized to vitamin E.

Beta-carotene. One secondary analysis of the primary prevention ATBC study found no effect of beta-carotene on colorectal adenomas (RR 0.98 [95% CI, 0.71 to 1.35]).[179] This analysis may be subject to detection bias as there was no systematic CRC screening.

Vitamin D. Evidence from two trials suggests that vitamin D is not associated with incident or recurrent colorectal adenomas over 3 to 5 years followup. VITAL included a prespecified ancillary study of the association of 2,000 IU/day of vitamin D with colorectal adenomas (N=25,871).[240] Over a median followup of 5.3 years, there was no association between vitamin D supplementation and adenomas (OR 1.08 [95% CI, 0.92 to 1.27]). The much smaller VCPPS trial (N=2,259) evaluated the effect of 1000 IU/day vitamin D on recurrent colorectal adenoma in a 2x2 factorial design. No benefit was seen for vitamin D for either recurrent colorectal adenoma over 3 to 5 years followup (RR 0.99 [95% CI, 0.89 to 1.09]) or advanced recurrent colorectal adenoma (RR 0.99 [95% CI, 0.75 to 1.29]).[90]

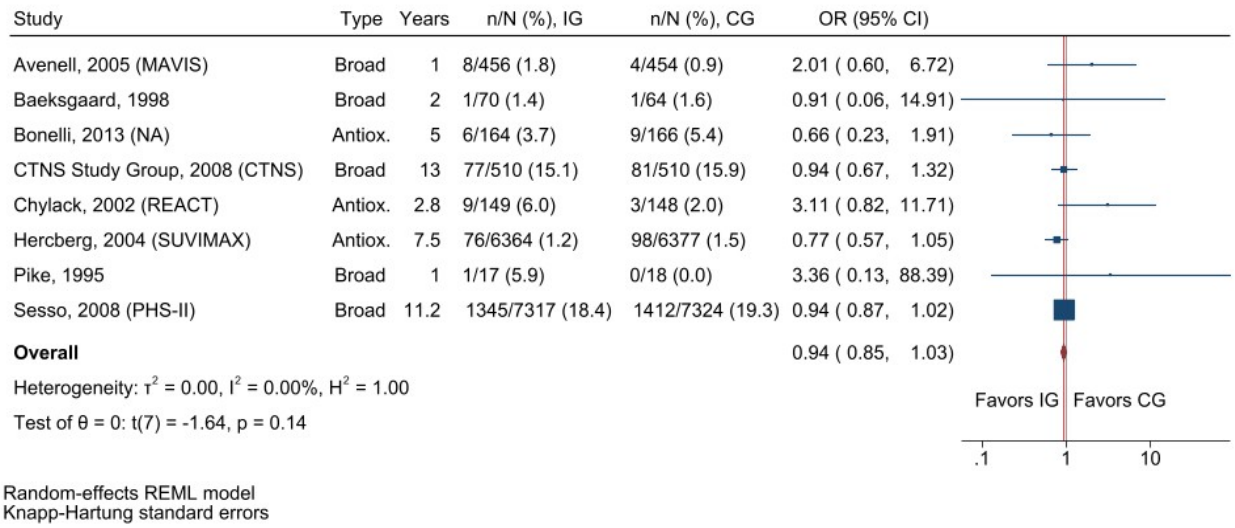
Mammographic Breast Density

A very small number of RCTs evaluate whether supplementation can reduce mammographic breast density which is a strong risk factor for breast cancer. These studies investigated vitamin D with or without calcium and findings were not promising. A Canadian study of 405 premenopausal women tested three doses of vitamin D (1,000 IU/day; 2,000 IU/day; 3,000 IU/day) compared to placebo over one year.[94] No differences in mammographic breast density were found between the 1,000 IU/day and 2,000 IU/day doses compared to placebo, and the 3,000 IU/day dose showed significantly less density decline compared to placebo, but the difference was judged not to be clinically significant. Likewise, an ancillary study to WHI found no effect of 1,000 mg/day calcium plus 400 IU/day VitD over one year on mammographic breast density.[241]

Cervical Intraepithelial Neoplasia

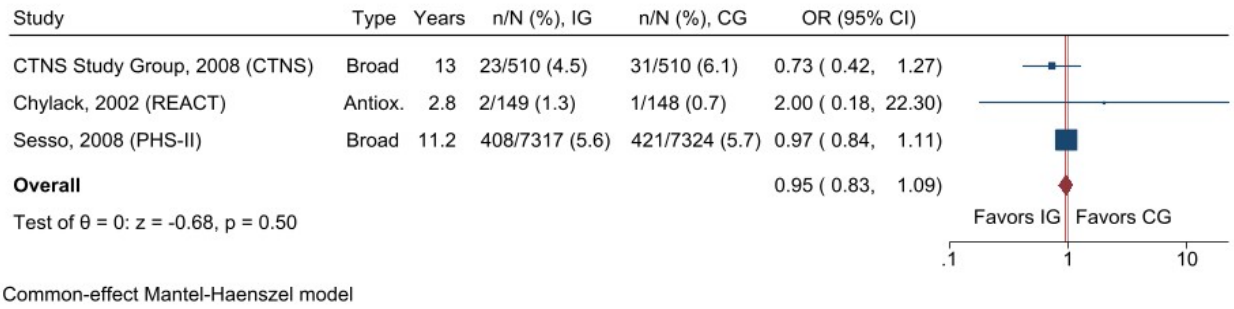
Extremely limited RCT evidence is available regarding the use of supplements for the regression or prevention of recurrent cervical intraepithelial neoplasia (CIN), a precursor lesion for cervical cancer. While promising, these studies are very small and have not been replicated by different investigator groups. Two Iranian studies of 58 women each evaluated 50,000 IU vitamin D every 2 weeks for 6 months in women with various histories of CIN. A 2017 study of women with CIN1 found that 84.6 percent of those in the vitamin D group showed CIN1 regression compared to 53.8 percent in the placebo group (p=0.01).[242] A 2018 study by the same investigator group in women with CIN 2/3 treated with loop electrical excision found that recurrence of CIN1/2/3 was lower in those in the vitamin D group compared with placebo (18.5% vs 48.1%, p=0.02) but the difference between groups for CIN2/3 recurrence was not statistically significant (3.7% vs 14.8%, p=0.15).[243] Another Iranian study of the same size found that folate supplementation of 5 mg/day reduced CIN1 regression compared to placebo (83.3% vs 52.0%, p=0.019).[244] The clinical significance of these findings are unknown given high rates of spontaneous regression.[244] These data can only be considered exploratory, given the very small number of participants (174 women total across all 3 studies), short time frame (6 months each), and the lack of independent replication.

Appendix E Figure 1. Forest Plot Showing Odds Ratios of All-Cause Mortality for Multivitamins



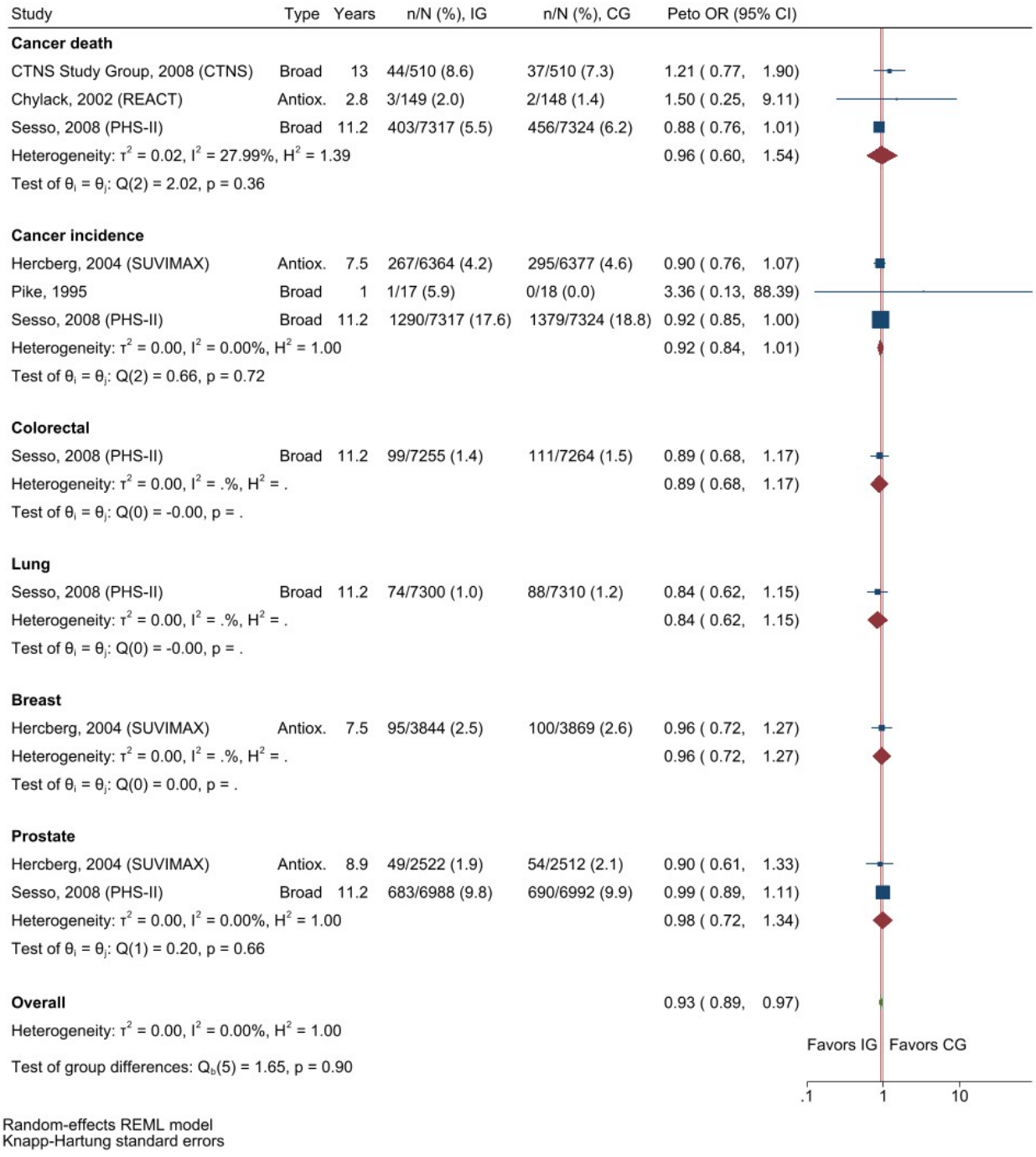
Abbreviations: CG = Control group; CI = Confidence interval; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; IG = Intervention group; MAVIS = Mineral and Vitamin Intervention Trial; OR = Odds ratio; PHS-II = Physicians' Health Study; REACT = Roche European American Cataract Trial; REML = Random effects restricted maximum likelihood model; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants

Appendix E Figure 2. Forest Plot Showing Odds Ratios of CVD Mortality for Multivitamins



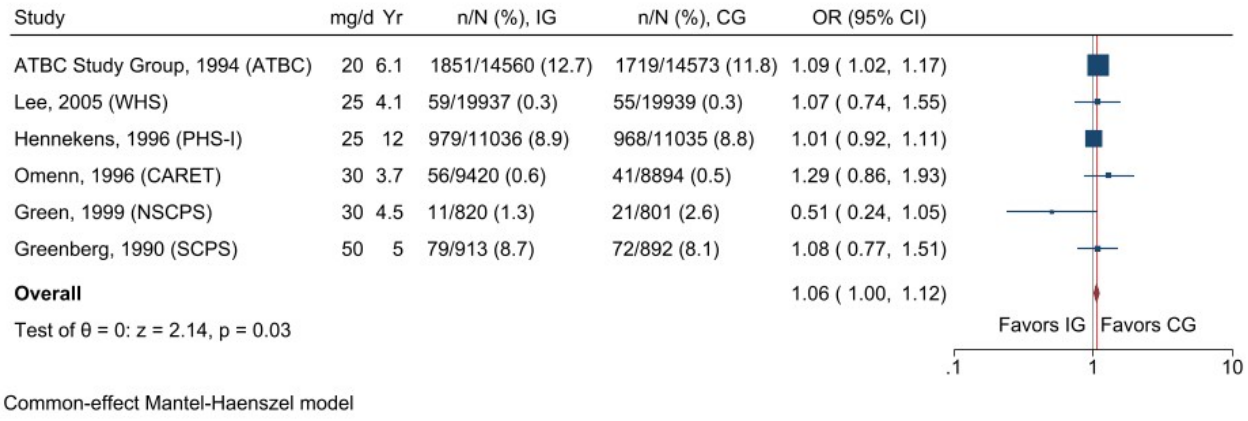
Abbreviations: CG = Control group; CI = Confidence interval; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; IG = Intervention group; PHS-II = Physicians' Health Study; REACT = Roche European American Cataract Trial

Appendix E Figure 3. Forest Plot Showing Odds Ratios of Primary Cancer Outcomes for Multivitamins



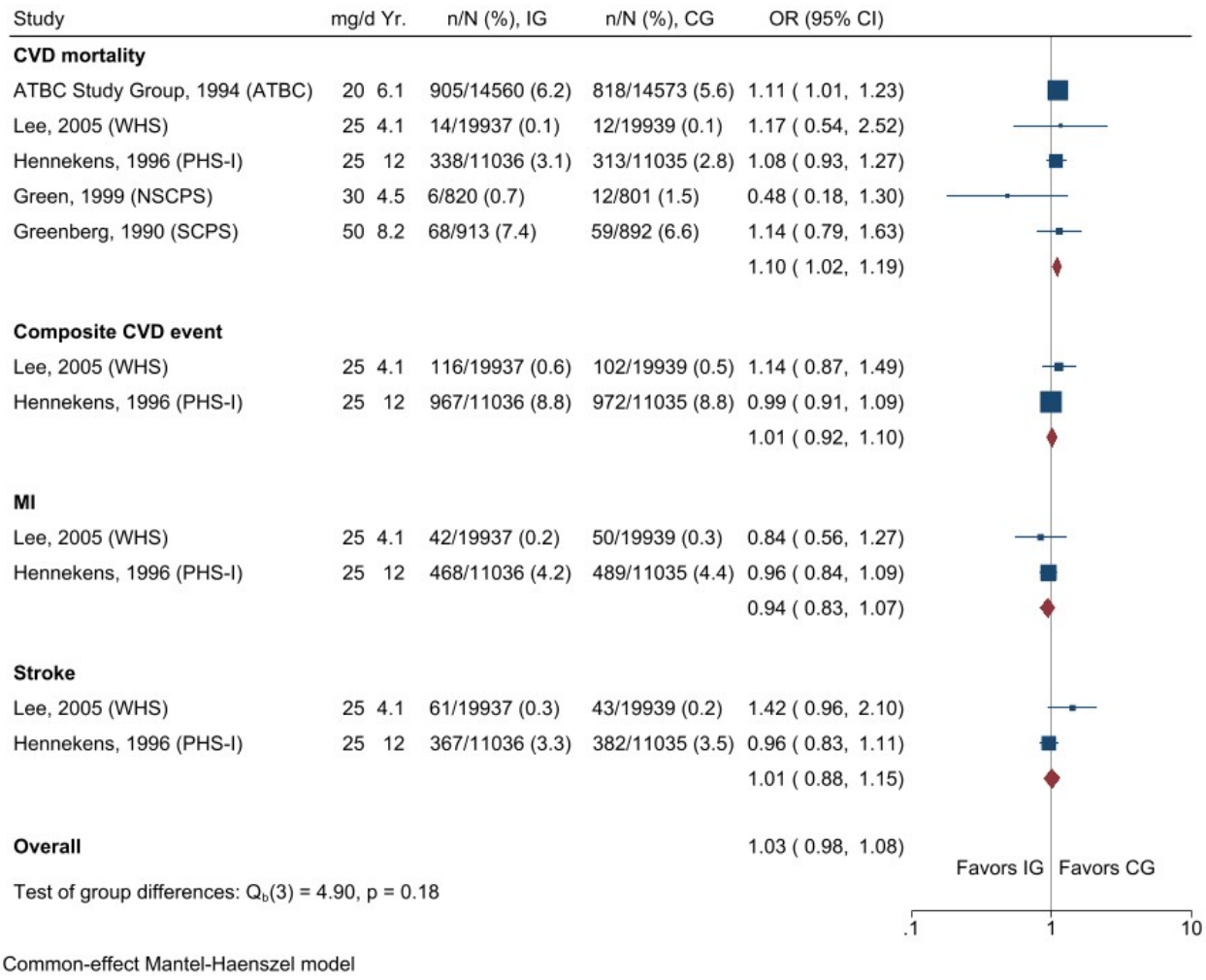
Abbreviations: CG = Control group; CI = Confidence interval; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; IG = Intervention group; OR = Odds ratio; PHS-II = Physicians' Health Study; REACT = Roche European American Cataract Trial; REML = Random effects restricted maximum likelihood model; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants

Appendix E Figure 4. Forest Plot Showing Odds Ratios of All-Cause Mortality for Beta-Carotene



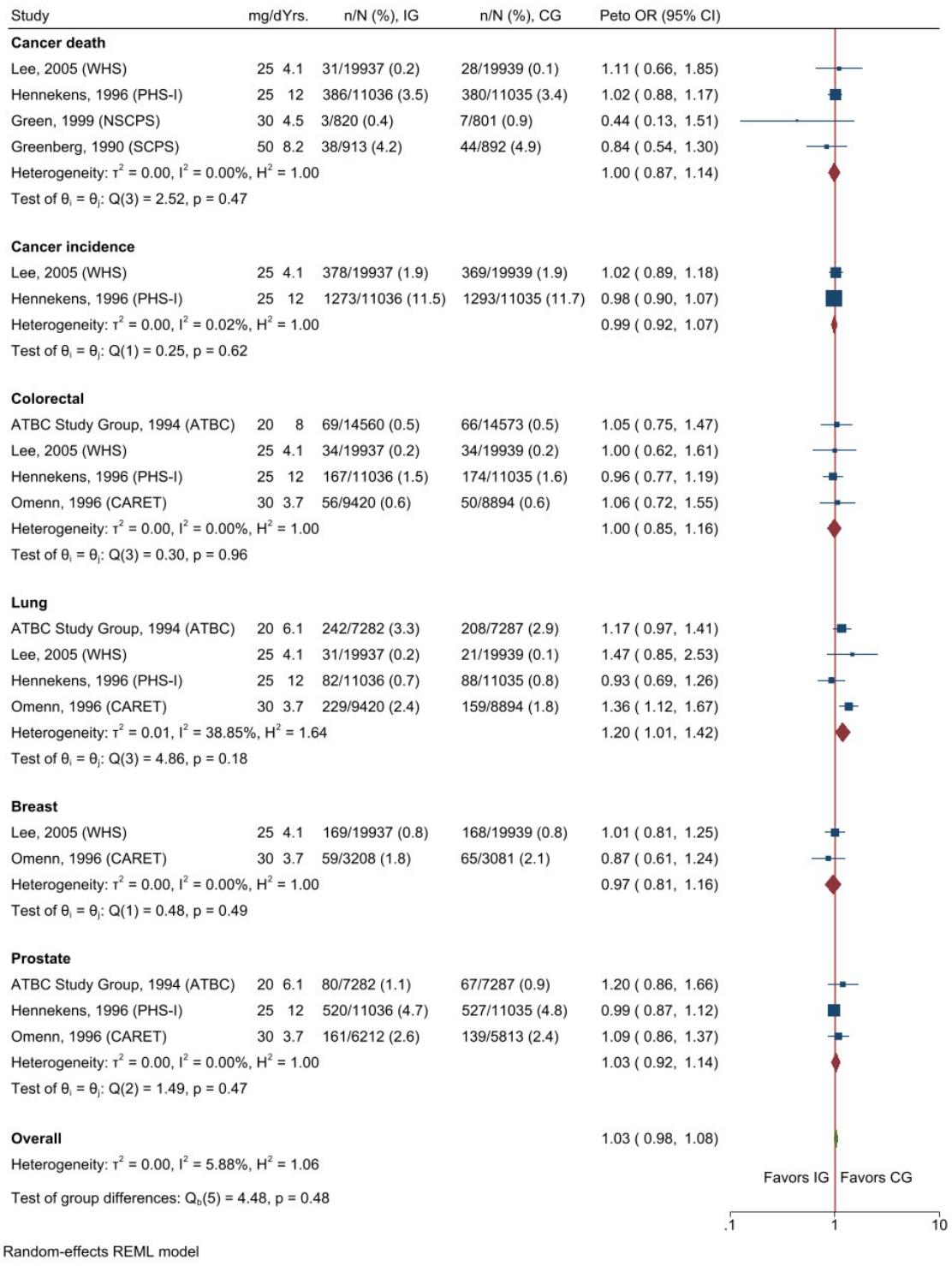
Abbreviations: ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CG = Control group; CI = Confidence interval; IG = Intervention group; mg/d = Milligram per day; NSCPS = Nambour Skin Cancer Prevention Study; OR = Odds ratio; PHS-I = Physicians' Health Study-I; SCPS = Skin Cancer Prevention Study; WHS = Women's Health Study; Yr = Year

Appendix E Figure 5. Forest Plot Showing Odds Ratios of Primary Cardiovascular Outcomes for Beta-Carotene



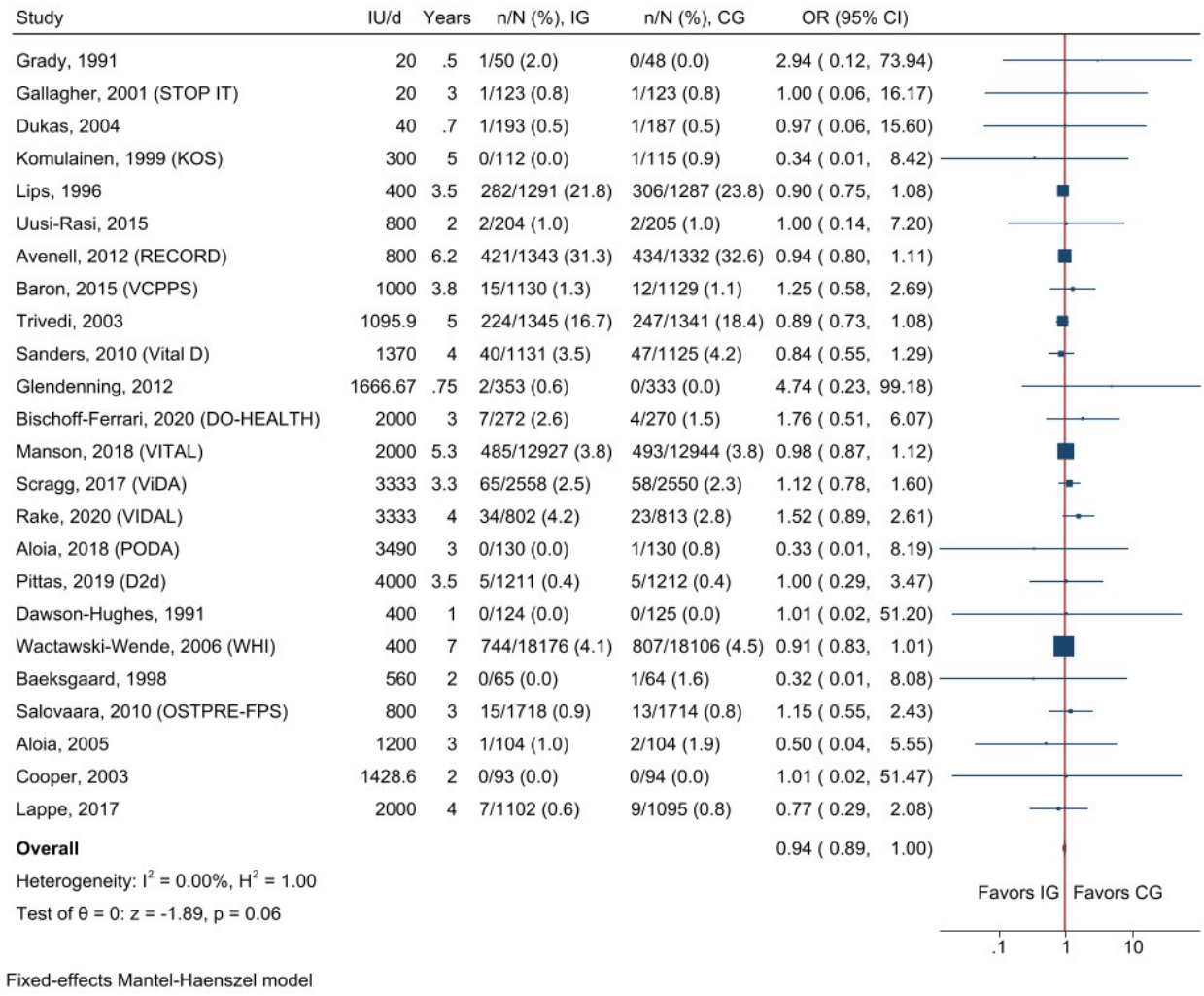
Abbreviations: ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; mg/d = Milligram per day; MI = Myocardial infarction; NSCPS = Nambour Skin Cancer Prevention Study; OR = Odds ratio; PHS-I = Physicians' Health Study-I; SCPS = Skin Cancer Prevention Study; WHS = Women's Health Study; Yr = Year

Appendix E Figure 6. Forest Plot Showing Odds Ratios of Primary Cancer Outcomes for Beta-Carotene



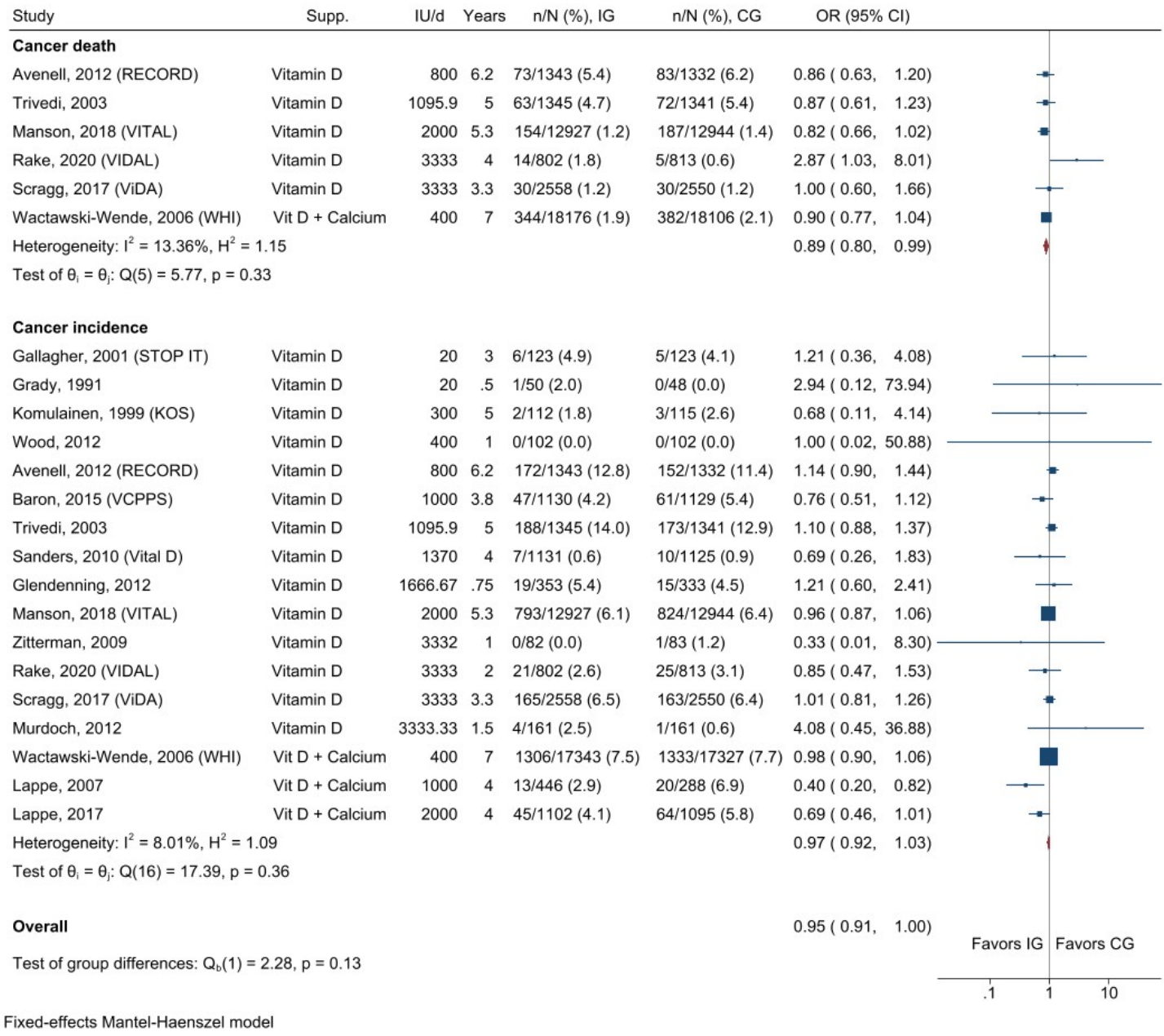
Abbreviations: ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CG = Control group; CI = Confidence interval; IG = Intervention group; mg/d = Milligram per day; NSCPS = Nambour Skin Cancer Prevention Study; OR = Odds ratio; PHS-I = Physicians' Health Study-I; SCPS = Skin Cancer Prevention Study; WHS = Women's Health Study; Yrs = Years

Appendix E Figure 7. Forest Plot Showing Odds Ratios of All-Cause Mortality for Vitamin D, With or Without Calcium



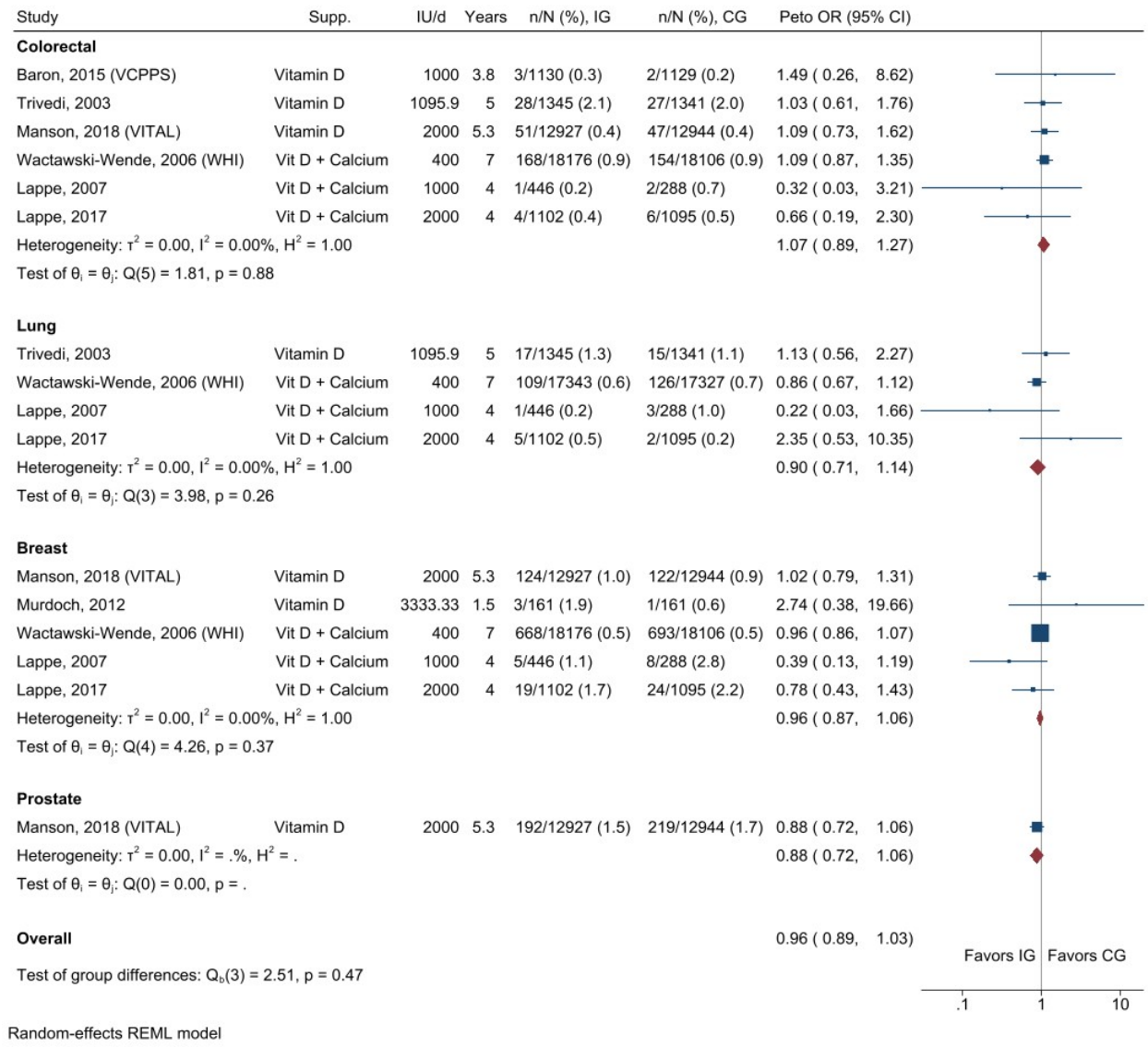
Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; IU/d =International units per day; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; OR = Odds ratio; OSTPRE-FPS = Osteoporosis Risk Factor and Prevention Fracture Prevention Study; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; RECORD = Randomised evaluation of calcium or vitamin D; VCPPS = Vitamin D/Calcium Polyp Prevention Study; VITAL = VITamin D and OmegA-3 TriaL; ViDa = Vitamin D Assessment Study; WHI = Women's Health Initiative

Appendix E Figure 8. Forest Plot Showing Odds Ratios of Cancer Mortality and Cancer Incidence for Vitamin D, With or Without Calcium



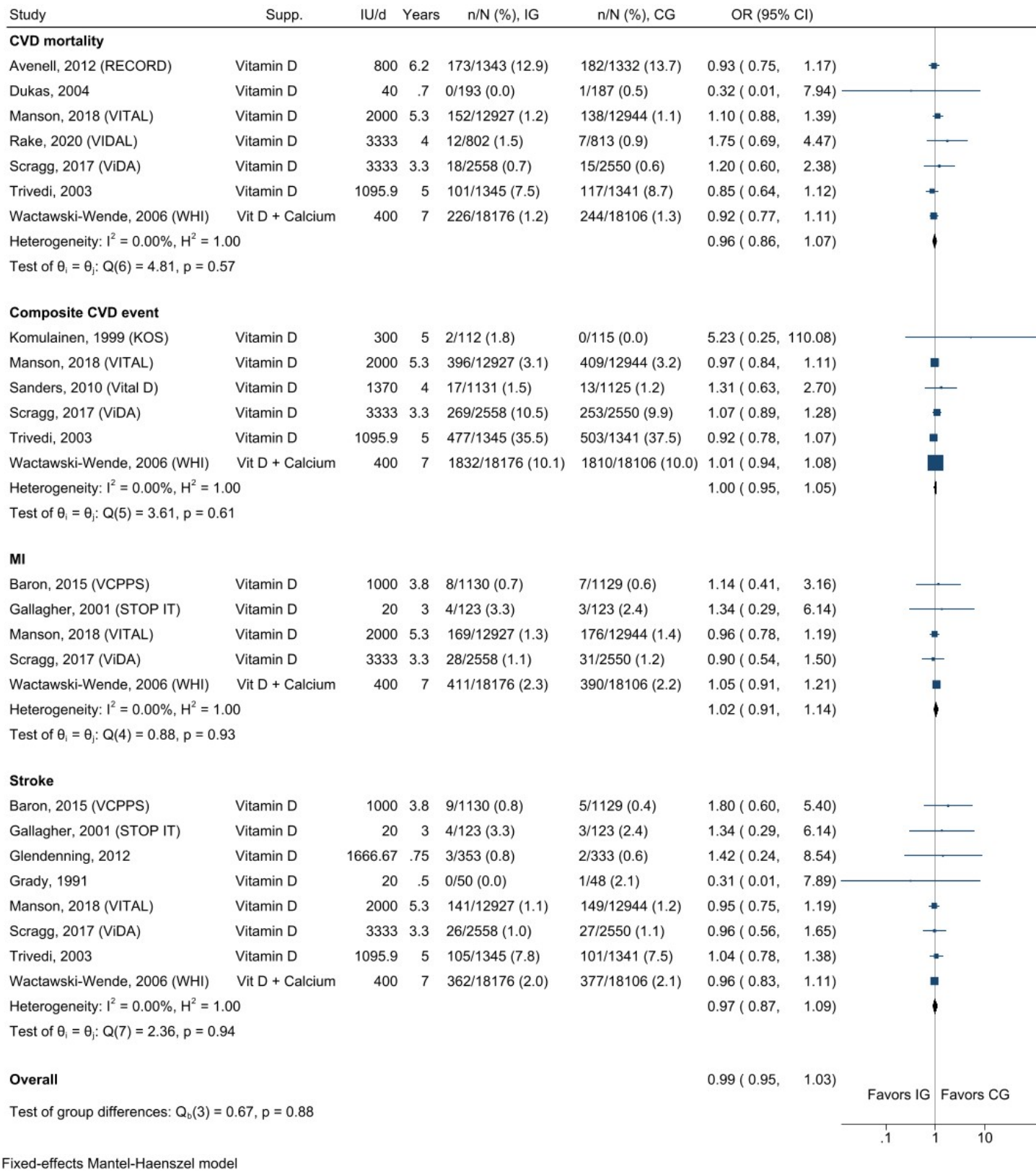
Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; IU/day = International units per day; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; OR = Odds ratio; RECORD = Randomised evaluation of calcium or vitamin D; VCPPS = Vitamin D/Calcium Polyp Prevention Study; VITAL = VITamin D and OmegA-3 TriaL; ViDa = Vitamin D Assessment Study; WHI = Women's Health Initiative

Appendix E Figure 9. Forest Plot Showing Odds Ratios of Site-Specific Cancer Incidence for Vitamin D, With or Without Calcium



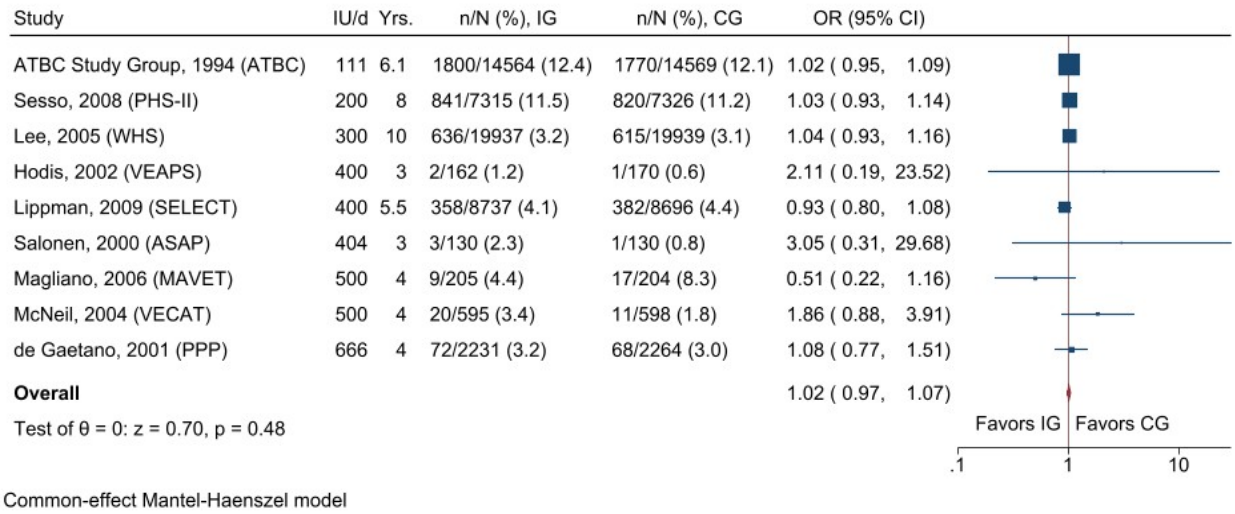
Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; IU/d = Internatioinal units per day; OR = Odds ratio; REML = Random effects restricted maximum likelihood model; VCPPS = Vitamin D/Calcium Polyp Prevention Study; VITAL = VITamin D and OmegA-3 TriaL; WHI = Women's Health Initiative

Appendix E Figure 10. Forest Plot Showing Odds Ratios of Primary Cardiovascular Outcomes for Vitamin D, With or Without Calcium



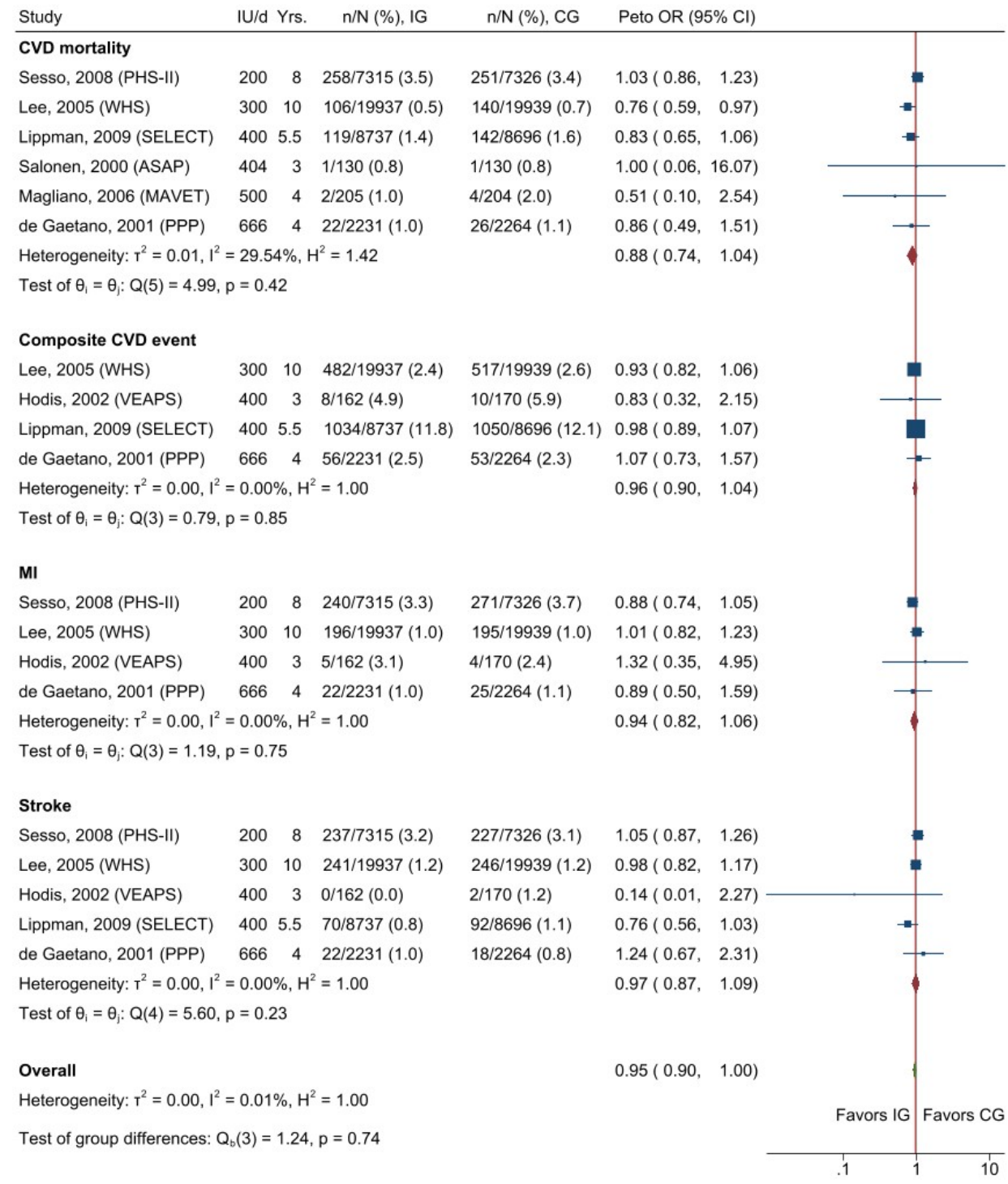
Abbreviations: CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; IU/d = International units per day; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; MI = Myocardial infarction; OR = Odds ratio; RECORD = Randomised evaluation of calcium or vitamin D; VCPPS = Vitamin D/Calcium Polyp Prevention Study; VITAL = VITamin D and OmegA-3 TriaL; ViDa = Vitamin D Assessment Study; WHI = Women's Health Initiative

Appendix E Figure 11. Forest Plot Showing Odds Ratios of All-Cause Mortality for Vitamin E



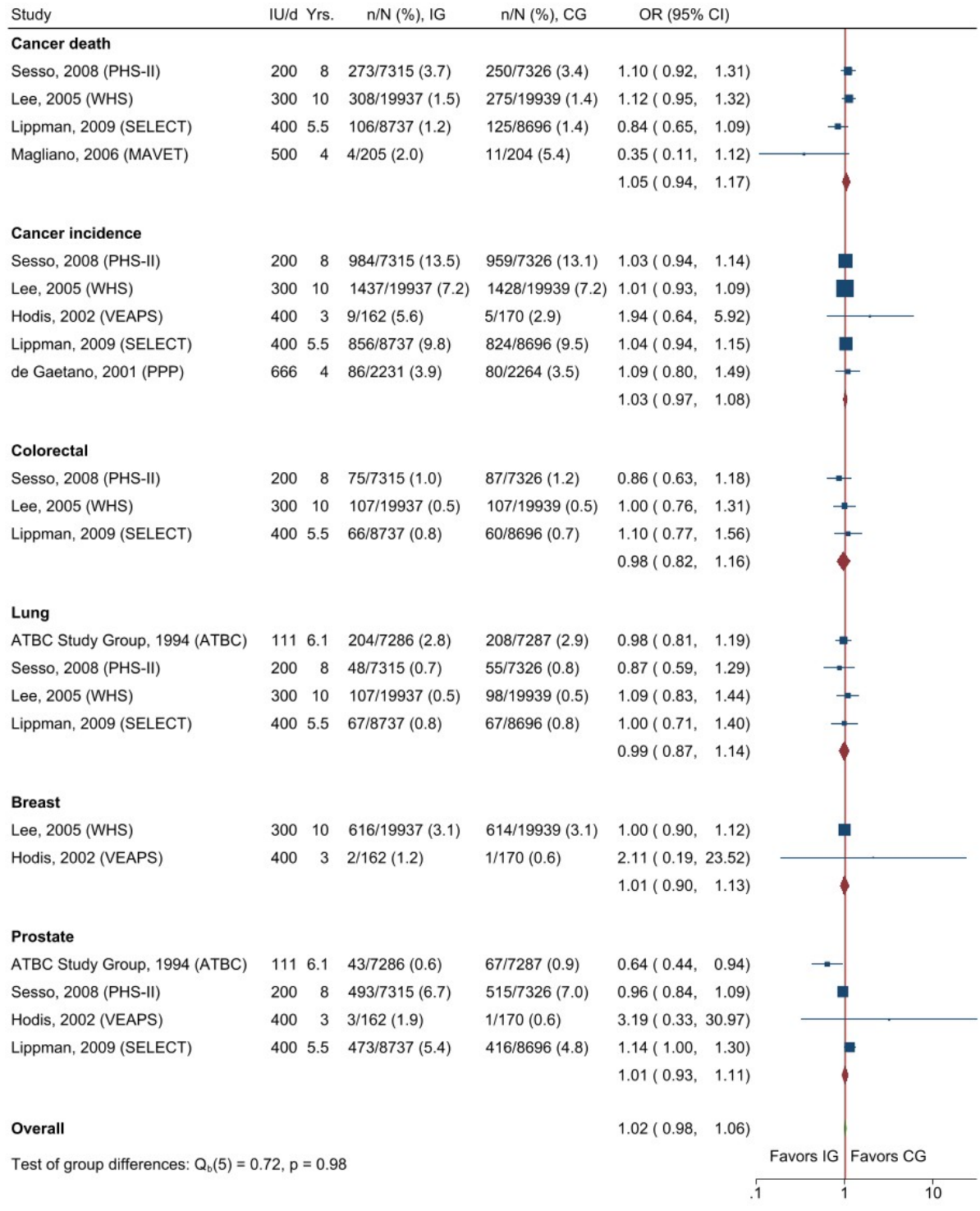
Abbreviations: ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; CI = Confidence interval; IG = Interval group; IU/d = International units per day; MAVET = Melbourne Atherosclerosis Vitamin E Trial; OR = Odds ratio; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; VECAT = Vitamin E, Cataract and Age-related Maculopathy Trial; WHS = Women's Health Study

Appendix E Figure 12. Forest Plot Showing Odds Ratios of Primary Cardiovascular Outcomes for Vitamin E



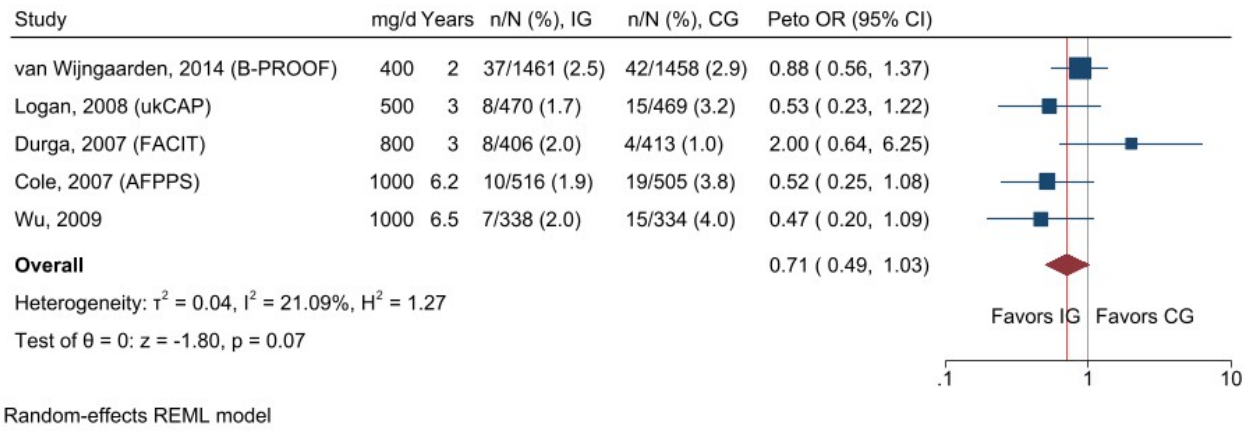
Abbreviations: ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; IG = Intervention group; IU/day = International units per day; MAVET = Melbourne Atherosclerosis Vitamin E Trial; MI = Myocardial infarction; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; WHS = Women's Health Study

Appendix E Figure 13. Forest Plot Showing Odds Ratios of Primary Cancer Outcomes for Vitamin E



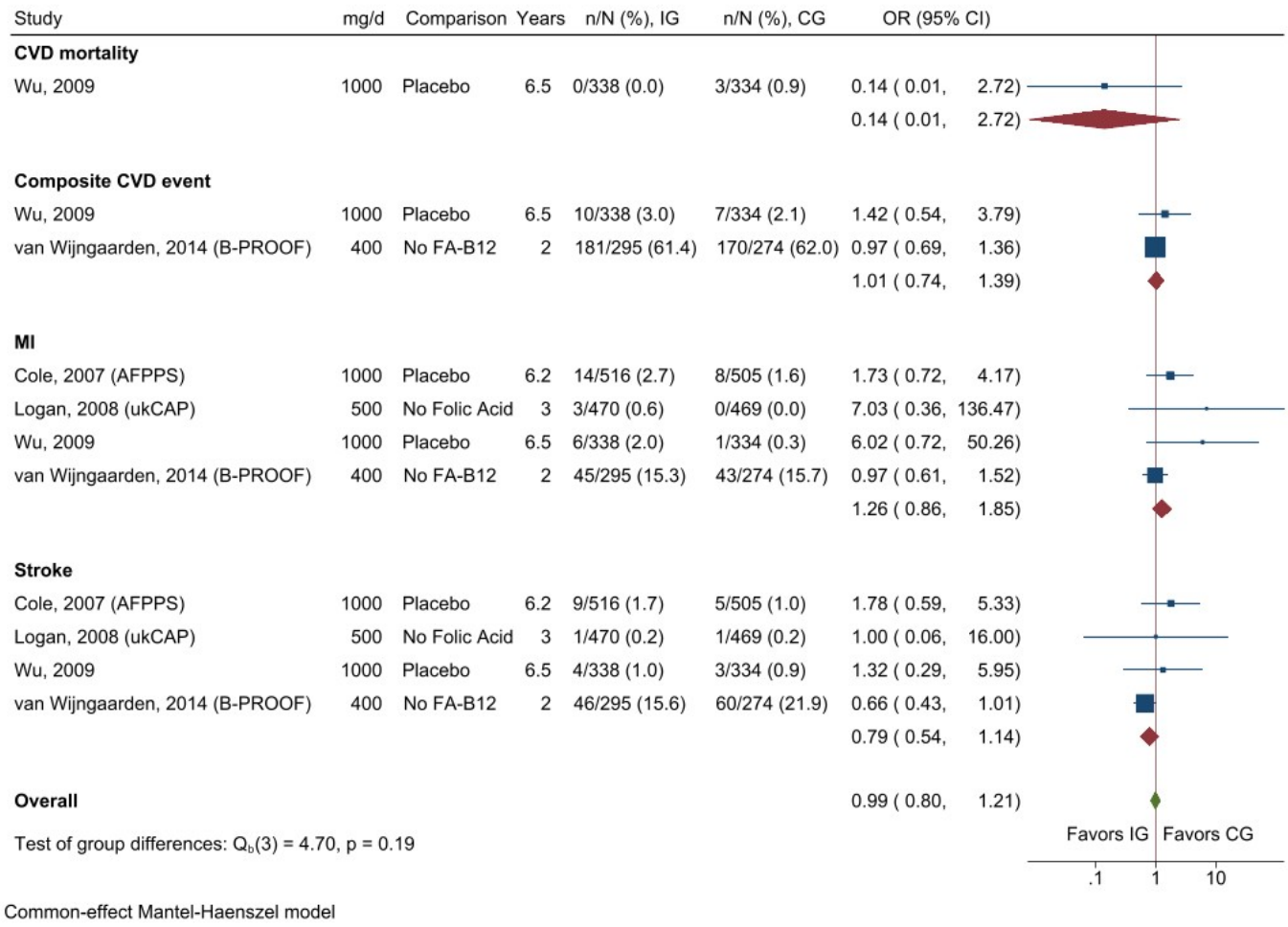
Abbreviations: ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; CI = Confidence interval; IG = Intervention group; IU/d = International units per day; MAVET = Melbourne Atherosclerosis Vitamin E Trial; OR = Odds ratio; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; WHS = Women's Health Study

Appendix E Figure 14. Forest Plot Showing Odds Ratios of All-Cause Mortality for Folic Acid



Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; CG = Control group; CI = Confidence interval; FACIT = Folic Acid and Carotid Intima-media Thickness; HPFS = Health Professionals Follow-Up Study; IG = Intervention group; mg/d = Milligrams per day; OR = Odds ratio; REML = Random effects restricted maximum likelihood model; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

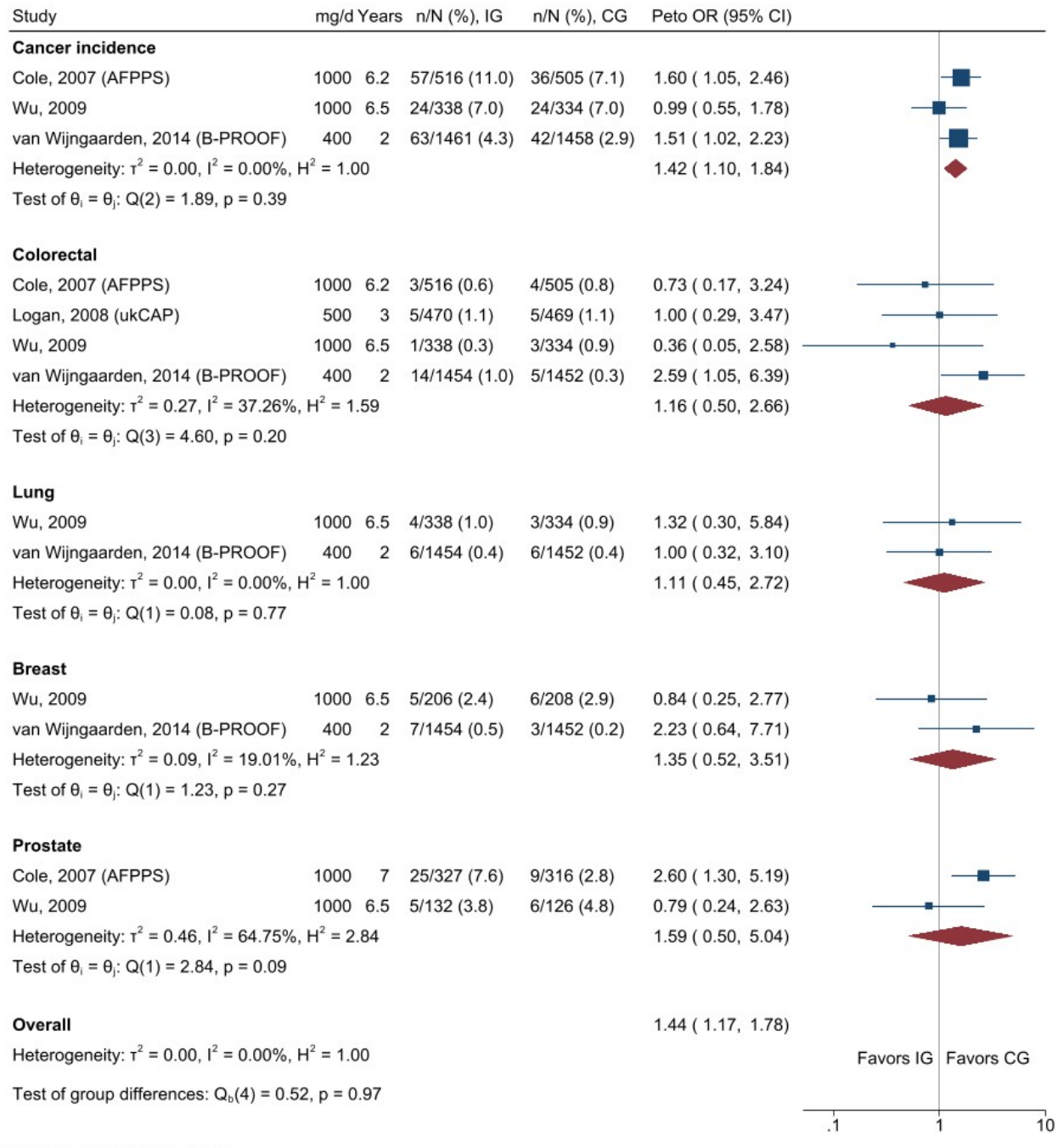
Appendix E Figure 15. Forest Plot Showing Odds Ratios of Cardiovascular Outcomes for Folic Acid (Without Pooling)*



*van Wijngaarden, 2014 (B-PROOF) administered 500 mcg/day vitamin B12 in combination with folic acid

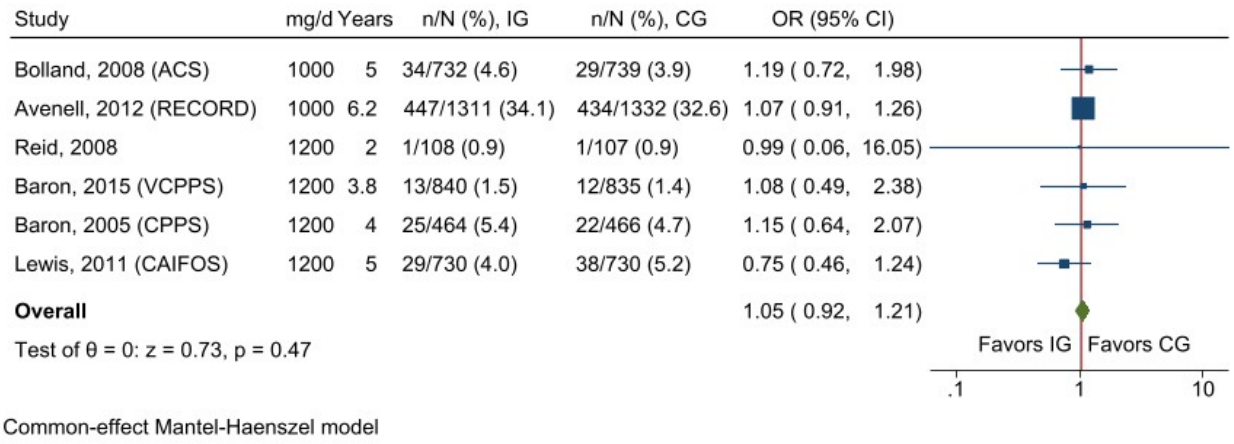
Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; calcOR = Calculated odds ratio; CG = Control group; CI = Confidence interval; CVD = Cardiovascular disease; FA-B12 = Folic acid given with Vitamin B-12; IG = Intervention group; mg/d = Milligrams per day; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix E Figure 16. Forest Plot Showing Odds Ratios of Cancer Incidence and Colorectal Cancer Outcomes for Folic Acid



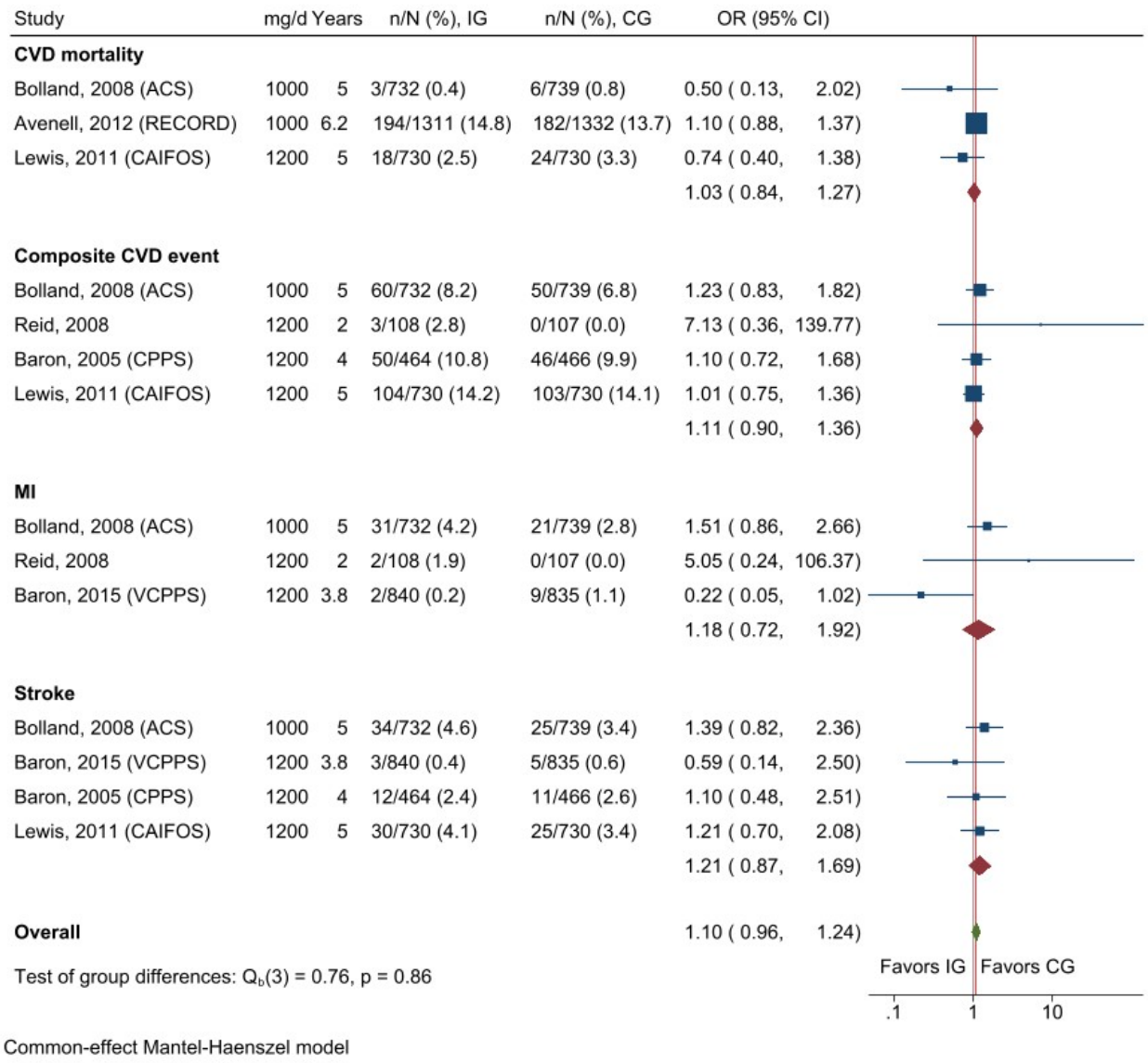
Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; CG = Control group; CI = Confidence interval; IG = Intervention group; mg/d = Milligrams per day; NHS = Nurses' Health Study; OR = Odds ratio; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix E Figure 17. Forest Plot Showing Odds Ratios of All-Cause Mortality for Calcium



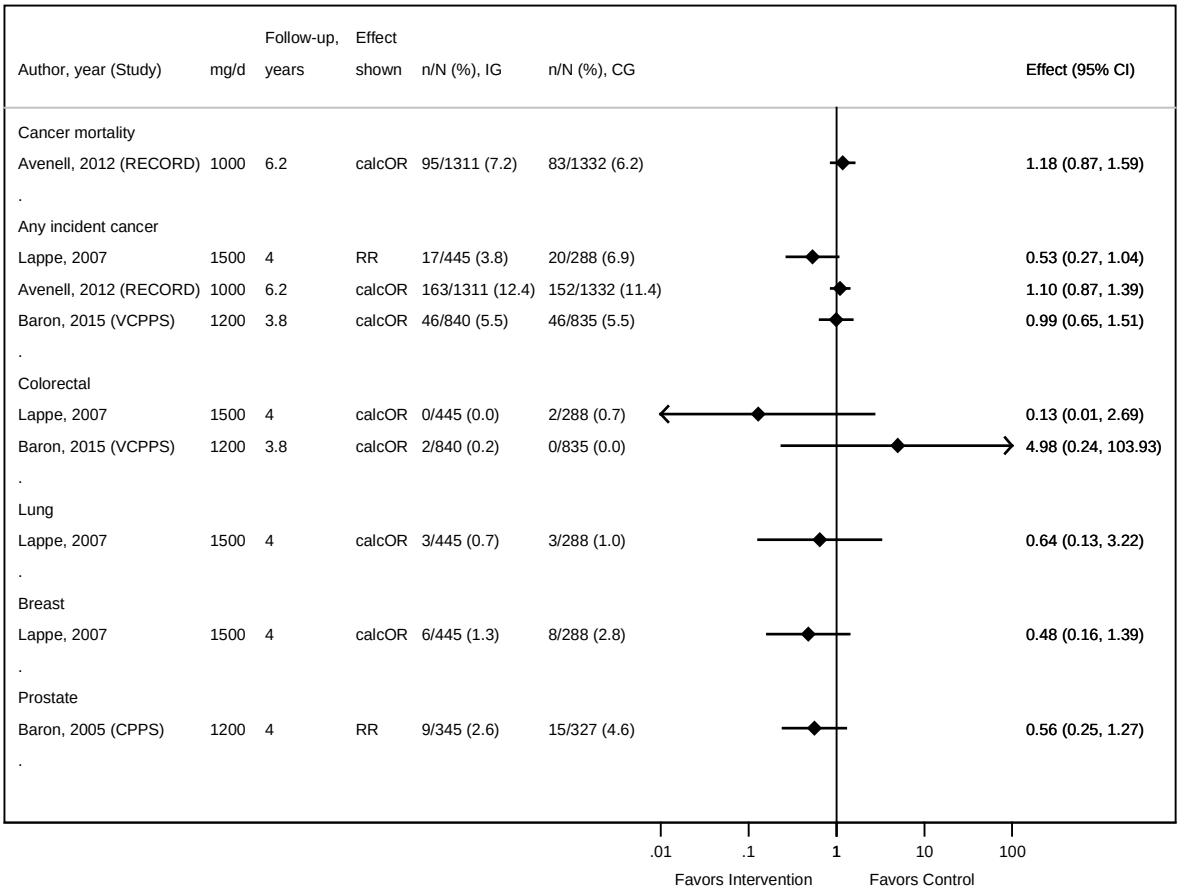
Abbreviations: ACS = Auckland calcium study; CAIFOS = Calcium Intake Fracture Outcome Study; CG = Control group; CI = Confidence interval; CPPS = Calcium Polyp Prevention Study; IG = Intervention group; mg/d = Milligrams per day; OR = Odds ratio; RECORD = Randomized Evaluation of Calcium OR vitamin D; VCPPS = Vitamin D/Calcium Polyp Prevention Study

Appendix E Figure 18. Forest Plot Showing Odds Ratios of Primary Cardiovascular Outcomes for Calcium



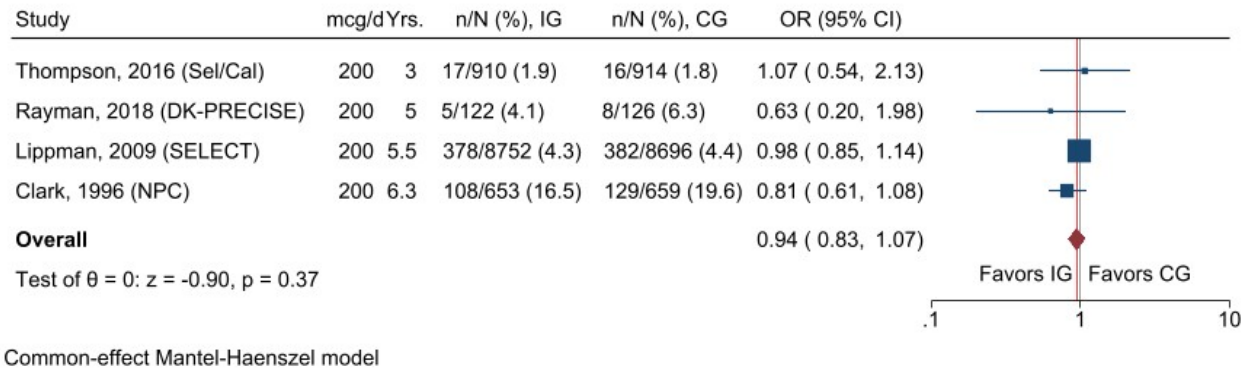
Abbreviations: ACS = Auckland calcium study; CAIFOS = Calcium Intake Fracture Outcome Study; CG = Control group; CI = Confidence interval; CPPS = Calcium Polyp Prevention Study; CVD = Cardiovascular disease; IG = Intervention group; mg/d = Milligrams per day; OR = Odds ratio; RECORD = Randomized Evaluation of Calcium OR vitamin D; VCPPS = Vitamin D/Calcium Polyp Prevention Study

Appendix E Figure 19. Forest Plot Showing Odds Ratios of Primary Cancer Outcomes for Calcium (Without Pooling)



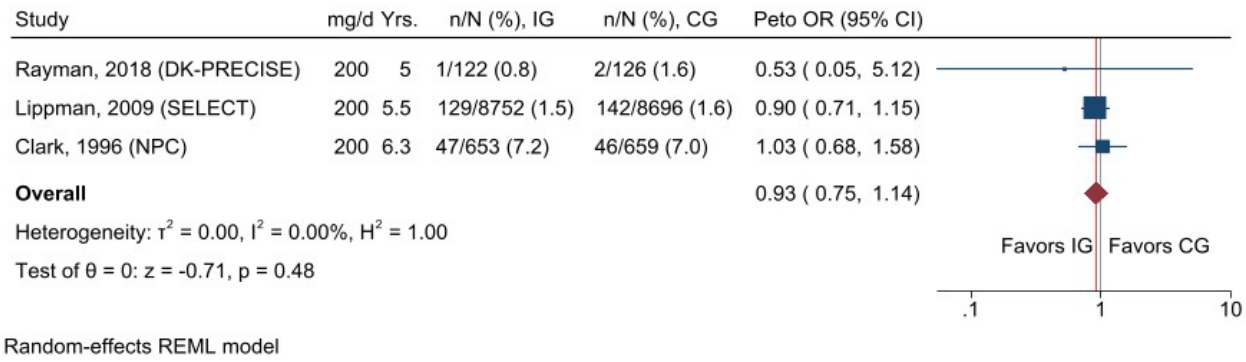
Abbreviations: calcOR = Calculated odds ratio, based on raw event rates in each group; CG = Control group; CI = Confidence interval; CPPS = Calcium Polyp Prevention Study; mg/d = Milligrams per day; RECORD = Randomized Evaluation of Calcium OR vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study; WD = Withdrawal; WHI = Women's Health Initiative

Appendix E Figure 20. Forest Plot Showing Odds Ratios of All-Cause Mortality for Selenium



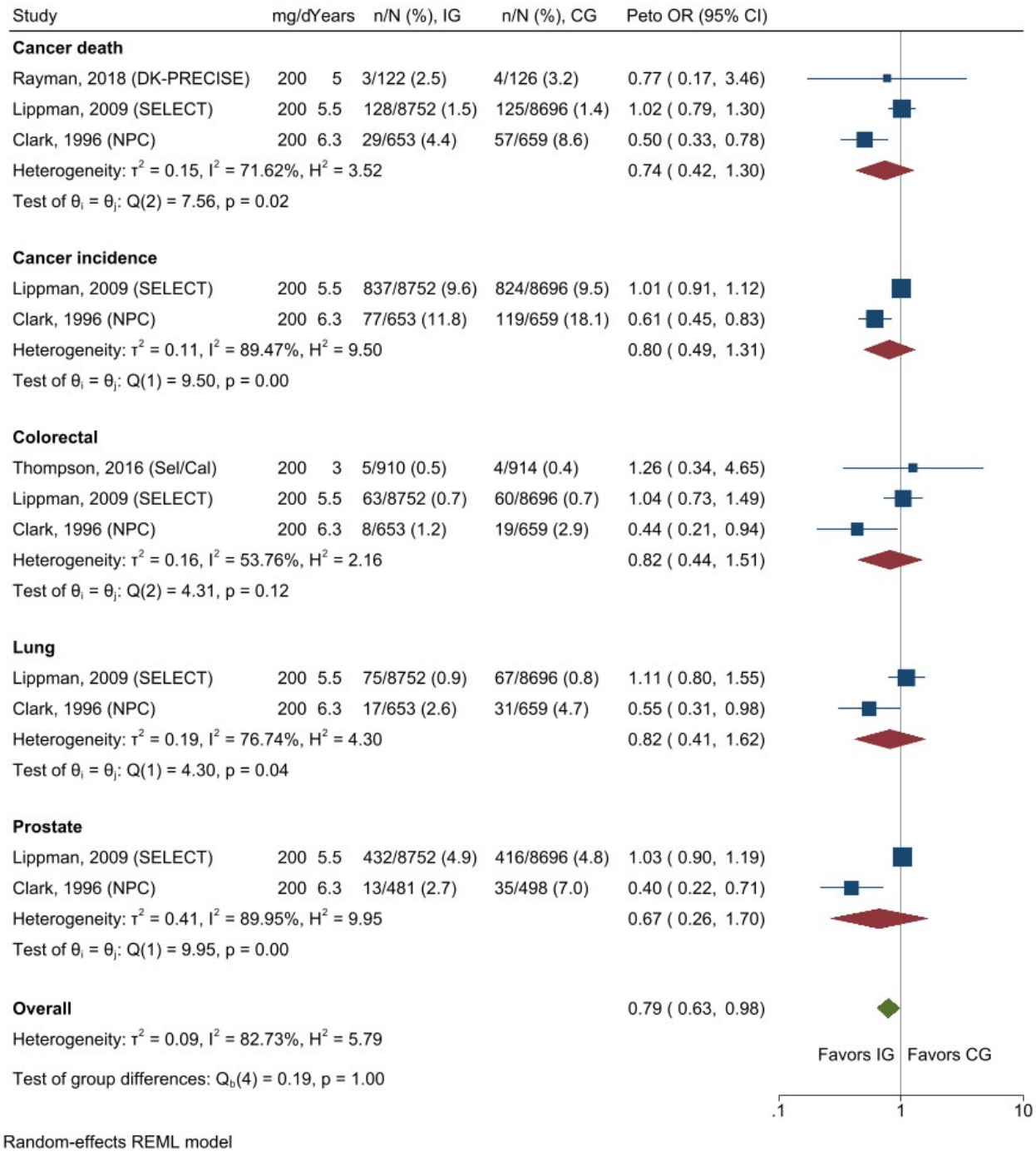
Abbreviations: CG = Control group; CI = Confidence interval; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; mcg/d = Micrograms per day; NPC = Nutritional Prevention of Cancer; OR = Odds ratio; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial, Yrs. = Years

Appendix E Figure 21. Forest Plot Showing Odds Ratios of Cardiovascular Mortality for Selenium



Abbreviations: CG = Control group; CI = Confidence interval; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; IG = Intervention group; mcg/d = Micrograms per day; NPC = Nutritional Prevention of Cancer; OR = Odds ratio; REML = Random effects restricted maximum likelihood model; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial

Appendix E Figure 22. Forest Plot Showing Odds Ratios of Primary Cancer Outcomes for Selenium



Abbreviations: ACM = All-cause mortality; AE = Adverse events; CVD = Cardiovascular disease; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; mcg = Micrograms; mg/d = Milligrams per deciliter; NPC = Nutritional Prevention of Cancer; NR = Not reported; RCT = Randomized controlled trial; Sel = Selenium; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial; UK-PRECISE = United Kingdom PREvention of Cancer by Intervention with Selenium; WD = Withdrawal

Appendix F Table 1. Summary of Results for Studies of Multivitamin Use

Author, Year (Study)	Quality Rating	Study Design	Study N*	Multivitamin Type (No. of specific micronutrients)	ACM	CVD	Cancer	Harms
Avenell, 2005 (MAVIS)[106]	Fair	RCT	910	Broad (16)	?	NR	NR	↔ Any AE
Baeksgaard, 1998[124]	Fair	RCT	240	Broad (13)	?	NR	NR	GI sx: ?
Bonelli, 2013 (NA)[95]	Fair	RCT	411	Antioxidant (4)	?	NR	?	NR
Chylack, 2002 (REACT)[85]	Fair	RCT	297	Antioxidant (3)	?	↔	NR	Any, serious, non-serious: ?
CTNS Study Group, 2008 (CTNS)[133]	Good	RCT	1020	Broad (26)	↔	?	NR	Any, GI-related, urogenital hospitalization: ↔ Hospitalization: ↓? Skin rash: ?
Hercberg, 2004 (SUVIMAX)[71]	Good	RCT	13017	Antioxidant (5)	↓?	↔	↔	AE WD: ?
Pike, 1995[122]	Fair	RCT	47	Broad (16)	?	NR	?	GI, skin rash: ?
Rucklidge, 2014[100]	Fair	RCT	80	Broad (36)	NR	NR	NR	GI, AE WD, sarcoidosis, other non-serious: ?
Sesso, 2008 (PHS-II)[80]	Good	RCT	14641	Broad (36)	↓?	↔	Any: ↓? Prostate: ↔ Lung, CRC: ↔?	Skin rash, nose bleed: ↑ Easy bruising, hematuria: ↔
Feskanich, 2002 (NHS-I)[140]	Good	Cohort	121700	Unknown/Variable	NA	NA	NA	Cataract: ↔ Hip fracture: ↑
Rautiainen, 2010 (SMC)[145]	Fair	Cohort	38984	Unknown/Variable	NA	NA	NA	Cataract: ↔?
Zheng Selin, 2013 (COSM)[142]	Fair	Cohort	27343	Unknown/Variable	NA	NA	NA	Cataract: ↔

*Includes only participants randomized to an intervention group assigned to take a multivitamin

Abbreviations: ACM = All-cause mortality; AE = Adverse event; CI = Confidence interval; COSM = Cohort of Swedish Men; CRC = Colorectal cancer; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; CVD = Cardiovascular disease; GI = Gastrointestinal; MAVIS = Mineral and Vitamin Intervention Trial; NA = Not applicable; NHS-I = Nurse' Health Study; NR = Not reported; PHS-II = Physicians' Health Study; RCT = Randomized controlled trial; REACT = Roche European American Cataract Trial; SMC = Swedish Mammography Cohort; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants; WD = Withdrawal
↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)

Appendix F Table 1. Summary of Results for Studies of Multivitamin Use

↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 2. Multivitamin Meta-Analysis Results: Results of Meta-Analyses by Outcome, Primary Analysis Listed First for Each Outcome, Followed by Sensitivity Analyses

Outcome	Model	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	REML-KH	0.94 (0.85 to 1.03)	8	30,108	0.0	0.00
	MH	0.94 (0.87 to 1.01)	8	30,108	NA	NA
	Full ascert. (REML-KH)	0.93 (0.84 to 1.04)	4	28,437	0	0
CVD mortality	MH	0.95 (0.83 to 1.09)	3	15,958	NA	NA
	REML-KH	0.95 (0.75 to 1.21)	3	15,958	0	0
Cancer mortality	REML-KH	0.96 (0.60 to 1.54)	3	15,958	28.0	0.02
	MH	0.90 (0.79 to 1.03)	3	15,958	NA	NA
Cancer incidence	REML-KH	0.92 (0.84 to 1.01)	3	27,417	0	0
	MH	0.92 (0.85 to 0.99)	3	27,417	NA	NA

Abbreviations: CI = Confidence interval; CVD = Cardiovascular disease; MH = Mantel-Haenszel common (fixed) effects model; NA = Not applicable because fixed effects model assumes $Tau^2=0$; OR = Odds ratio; Peto = Peto odds ratio; random effects REML model; REML-KH = random effects restricted maximum likelihood model with the Knapp-Hartung adjustment

Appendix F Table 3. Multivitamin Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Avenell, 2005 (MAVIS)[106]	Multivitamin vs. placebo		All-cause mortality	1	All	2.01 (0.60 to 6.72)	8/456 (1.8)	4/454 (0.9)	0.25
Baeksgaard, 1998[124]	Vitamin D + calcium + multivitamin vs. placebo	+ 1000 mg Calcium	All-cause mortality	2	All	0.91 (0.06 to 14.91)	1/70 (1.4)	1/64 (1.6)	NR
Bonelli, 2013 (NA)[95]	Multivitamin vs. placebo		All-cause mortality	5	All	0.66 (0.23 to 1.91)	6/164 (3.7)	9/166 (5.4)	NR
Chylack, 2002 (REACT)[85]	Multivitamin vs. placebo		All-cause mortality	2.8	All	3.11 (0.82 to 11.71)	9/149 (6.0)	3/148 (2.0)	0.07
CTNS Study Group, 2008 (CTNS)[133]	Multivitamin vs. placebo		All-cause mortality	13	All	0.94 (0.67 to 1.32)	77/510 (15.1)	81/510 (15.9)	NSD
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	7.5	All	RR=0.77 (0.57 to 1.00)	76/6364 (1.2)	98/6377 (1.5)	0.09
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	12.5	All	RR=0.87 (0.70 to 1.04)	156/6364 (2.5)	178/6377 (2.8)	0.19
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	7.5	Females	RR=1.03 (0.64 to 1.63)	36/3844 (0.9)	35/3869 (0.9)	0.92
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	12.5	Females	RR=0.99 (0.71 to 1.38)	70/3844 (1.8)	70/3869 (1.8)	0.95
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	7.5	Males	RR=0.63 (0.42 to 0.93)	40/2520 (1.6)	63/2508 (2.5)	0.02
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		All-cause mortality	12.5	Males	RR=0.78 (0.59 to 1.04)	86/2520 (3.4)	108/2508 (4.3)	0.09
Pike, 1995[122]	Multivitamin vs. placebo	1 tablet	All-cause mortality	1	All	3.36 (0.13 to 88.39)	1/17 (5.9)	0/18 (0.0)	NR
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	All-cause mortality	11.2	All	HR=0.94 (0.88 to 1.02)	1345/7317 (18.4)	1412/7324 (19.3)	0.13
Chylack, 2002 (REACT)[85]	Multivitamin vs. placebo		Any cancer deaths	2.8	All	1.50 (0.25 to 9.11)	3/149 (2.0)	2/148 (1.4)	NR

Appendix F Table 3. Multivitamin Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
CTNS Study Group, 2008 (CTNS)[133]	Multivitamin vs. placebo		Any cancer deaths	13	All	1.21 (0.77 to 1.90)	44/510 (8.6)	37/510 (7.3)	NSD
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Any cancer deaths	11.2	All	HR=0.88 (0.77 to 1.01)	403/7317 (5.5)	456/7324 (6.2)	0.07
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Colorectal cancer deaths	11.2	All	HR=0.95 (0.60 to 1.48)	37/7317 (0.5)	39/7324 (0.5)	0.81
Chylack, 2002 (REACT)[85]	Multivitamin vs. placebo		CVD deaths	2.8	All	2.00 (0.18 to 22.30)	2/149 (1.3)	1/148 (0.7)	NR
CTNS Study Group, 2008 (CTNS)[133]	Multivitamin vs. placebo		CVD deaths	13	All	0.73 (0.42 to 1.27)	23/510 (4.5)	31/510 (6.1)	NSD
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	CVD deaths	11.2	All	HR=0.95 (0.83 to 1.09)	408/7317 (5.6)	421/7324 (5.7)	0.47
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Lung cancer deaths	11.2	All	HR=0.89 (0.64 to 1.25)	65/7317 (0.9)	73/7324 (1.0)	0.50
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Prostate cancer deaths	11.2	All	HR=0.91 (0.66 to 1.26)	70/7317 (1.0)	78/7324 (1.1)	0.58

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; MAVIS = Mineral and Vitamin Intervention Trial; mg = Milligram; NR = Not reported; NSD = No significant difference; OR = Odds ratio; PHS-II = Physicians' Health Study; REACT = Roche European American Cataract Trial; RR = Risk ratio; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants

Appendix F Table 4. Multivitamin Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	7.5	All	RR=0.97 (0.77 to 1.20)	134/6481 (2.1)	137/6356 (2.1)	0.80
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	12.5	All	RR=0.97 (0.80 to 1.17)	222/5501 (4.0)	224/5553 (4.0)	0.73
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	7.5	Females	RR=1.17 (0.67 to 2.05)	27/3844 (0.7)	23/3869 (0.6)	0.57
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	12.5	Females	RR=1.33 (0.87 to 2.04)	50/3323 (1.5)	37/3321 (1.1)	0.19
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	7.5	Males	RR=0.82 (0.71 to 1.20)	107/2520 (4.2)	114/2508 (4.6)	0.54
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		CHD events	12.5	Males	RR=0.89 (0.72 to 1.09)	172/2178 (7.9)	187/2232 (8.4)	0.25
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	CVD events	11.2	All	HR=1.01 (0.91 to 1.10)	876 events/7317	856 events/7324	0.91
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	MI	11.2	All	HR=0.93 (0.80 to 1.09)	317/7317 (4.3)	335/7324 (4.6)	0.39
CTNS Study Group, 2008 (CTNS)[133]	Multivitamin vs. placebo		Other CVD	13	All	0.89 (0.69 to 1.15)	196/510 (38.4)	210/510 (41.2)	NSD
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Stroke	11.2	All	HR=1.06 (0.91 to 1.23)	332/7317 (4.5)	311/7324 (4.2)	0.48

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CHD =Coronary heart disease; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; MI = Myocardial infarction; NR = Not reported; NSD = No significant difference; OR = Odds ratio; PHS-II = Physicians' Health Study; RR = Risk ratio; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants

Appendix F Table 5. Multivitamin Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	7.5	All	RR=0.90 (0.76 to 1.06)	267/6364 (4.2)	295/6377 (4.6)	0.19
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	12.5	All	RR=0.93 (0.82 to 1.05)	490/5501 (8.9)	511/5553 (9.2)	0.27
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	7.5	Females	RR=1.04 (0.85 to 1.29)	179/3844 (4.7)	171/3869 (4.4)	0.53
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	12.5	Females	RR=1.01 (0.86 to 1.19)	283/3323 (8.5)	276/3321 (8.3)	0.91
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	7.5	Males	RR=0.69 (0.53 to 0.91)	88/2520 (3.5)	124/2508 (4.9)	0.008
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Any cancer incidence	12.5	Males	RR=0.84 (0.69 to 1.01)	207/2178 (9.5)	235/2232 (10.5)	0.06
Pike, 1995[122]	Multivitamin vs. placebo	1 tablet	Any cancer incidence	1	All	3.36 (0.13 to 88.39)	1/17 (5.9)	0/18 (0.0)	NR
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Any cancer incidence	11.2	All	HR=0.92 (0.86 to 1.00)	1290/7317 (17.6)	1379/7324 (18.8)	0.04
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Breast cancer	7.5	Females	0.96 (0.72 to 1.27)	95/3844 (2.5)	100/3869 (2.6)	
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Breast cancer	11.3	Females	0.88 (0.66 to 1.17)	88/2317 (3.8)	102/2367 (4.3)	NR
CTNS Study Group, 2008 (CTNS)[133]	Multivitamin vs. placebo		Cancer-related hospitalization	13	All	0.74 (0.46 to 1.17)	34/510 (6.7)	45/510 (8.8)	NSD
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Colorectal cancer	11.2	All	HR=0.89 (0.68 to 1.17)	99/7255 (1.4)	111/7264 (1.5)	0.39
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Digestive tract cancer	7.5	All	0.83 (0.52 to 1.31)	33/6364 (0.5)	40/6377 (0.6)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Digestive tract cancer	7.5	Females	1.01 (0.49 to 2.06)	15/3844 (0.4)	15/3869 (0.4)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Digestive tract cancer	7.5	Males	0.71 (0.39 to 1.31)	18/2520 (0.7)	25/2508 (1.0)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Genital cancer	7.5	All	0.89 (0.61 to 1.31)	49/6364 (0.8)	55/6377 (0.9)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Genital cancer	7.5	Females	0.83 (0.45 to 1.53)	19/3844 (0.5)	23/3869 (0.6)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Genital cancer	7.5	Males	0.93 (0.56 to 1.54)	30/2520 (1.2)	32/2508 (1.3)	NR

Appendix F Table 5. Multivitamin Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Hematological cancer	7.5	All	0.91 (0.49 to 1.69)	19/6364 (0.3)	21/6377 (0.3)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Hematological cancer	7.5	Females	0.78 (0.29 to 2.10)	7/3844 (0.2)	9/3869 (0.2)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Hematological cancer	7.5	Males	1.00 (0.45 to 2.22)	12/2520 (0.5)	12/2508 (0.5)	NR
Bonelli, 2013 (NA)[95]	Multivitamin vs. placebo		Laryngeal cancer	5	All	3.06 (0.12 to 75.54)	1/164 (0.6)	0/166 (0.0)	NR
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Lung cancer	11.2	All	HR=0.84 (0.61 to 1.14)	74/7300 (1.0)	88/7310 (1.2)	0.26
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	7.5	All	1.79 (0.79 to 4.06)	16/6481 (0.2)	9/6536 (0.1)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	12.5	All	1.33 (0.73 to 2.41)	25/6481 (0.4)	19/6536 (0.3)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	7.5	Females	HR=4.31 (1.23 to 15.13)	13/3912 (0.3)	3/3964 (0.1)	0.02
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	12.5	Females	1.92 (0.85 to 4.31)	17/3912 (0.4)	9/3964 (0.2)	0.11
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	7.5	Males	HR=0.49 (0.12 to 1.97)	3/2569 (0.1)	6/2572 (0.2)	0.32
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Melanoma skin cancer	12.5	Males	0.80 (0.32 to 2.03)	8/2569 (0.3)	10/2572 (0.4)	0.64
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Oral cavity cancer	7.5	All	0.50 (0.13 to 2.00)	3/6364 (0.0)	6/6377 (0.1)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Oral cavity cancer	7.5	Females	5.04 (0.24 to 104.91)	2/3844 (0.1)	0/3869 (0.0)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Oral cavity cancer	7.5	Males	0.17 (0.02 to 1.38)	1/2520 (0.0)	6/2508 (0.2)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Prostate cancer	8.9	Males	HR=0.88 (0.60 to 1.29)	49/2522 (1.9)	54/2512 (2.1)	0.73
Sesso, 2008 (PHS-II)[80]	Multivitamin vs. no multivitamin	NR	Prostate cancer	11.2	All	HR=0.98 (0.88 to 1.09)	683/6988 (9.8)	690/6992 (9.9)	0.76
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Respiratory tract cancer	7.5	All	0.47 (0.21 to 1.05)	9/6364 (0.1)	19/6377 (0.3)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Respiratory tract cancer	7.5	Females	0.60 (0.14 to 2.53)	3/3844 (0.1)	5/3869 (0.1)	NR

Appendix F Table 5. Multivitamin Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Respiratory tract cancer	7.5	Males	0.43 (0.16 to 1.11)	6/2520 (0.2)	14/2508 (0.6)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Thyroid cancer	7.5	All	1.37 (0.63 to 2.98)	15/6364 (0.2)	11/6377 (0.2)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Thyroid cancer	7.5	Females	2.42 (0.85 to 6.88)	12/3844 (0.3)	5/3869 (0.1)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Thyroid cancer	7.5	Males	0.50 (0.12 to 1.99)	3/2520 (0.1)	6/2508 (0.2)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Urinary tract cancer	7.5	All	1.13 (0.43 to 2.92)	9/6364 (0.1)	8/6377 (0.1)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Urinary tract cancer	7.5	Females	3.02 (0.31 to 29.06)	3/3844 (0.1)	1/3869 (0.0)	NR
Hercberg, 2004 (SUVIMAX)[71]	Multivitamin vs. placebo		Urinary tract cancer	7.5	Males	0.85 (0.29 to 2.54)	6/2520 (0.2)	7/2508 (0.3)	NR
Bonelli, 2013 (NA)[95]	Multivitamin vs. placebo		Uterine cancer	5	All	0.34 (0.01 to 8.29)	0/164 (0.0)	1/166 (0.6)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; HR = Hazard ratio; IG = Intervention group; NR = Not reported; OR = Odds ratio; PHS-II = Physicians' Health Study; RR = Risk ratio; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants

Appendix F Table 6. Multivitamin Adverse Events Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Abdominal pain	0.15	All	0.51 (0.11 to 2.29)	3/42 (7.1)	5/38 (13.2)
Avenell, 2005 (MAVIS)[106]		Multivitamin vs. placebo	Any AE	1	All	IRR=0.64 (0.22 to 1.93)	28/456 (6.1)	37/454 (8.1)
Chylack, 2002 (REACT)[85]		Multivitamin vs. placebo	Any AE	2.8	All	. (. to .)	./149 (.)	./148 (.)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	Any AE	13	All	0.80 (0.49 to 1.31)	30/510 (5.9)	37/510 (7.3)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin 5-9 yrs use vs. no multivitamin	Cataract	12	All	RR=1.11 (0.92 to 1.35)	206/100000 p-y	181/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin <2 yrs use vs. no multivitamin	Cataract	12	All	RR=1.16 (0.94 to 1.43)	214/100000 p-y	181/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin 2-4 yrs use vs. no multivitamin	Cataract	12	All	RR=1.16 (0.92 to 1.46)	218/100000 p-y	181/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin ≥10 yrs use vs. no multivitamin	Cataract	12	All	RR=1.04 (0.86 to 1.25)	197/100000 p-y	181/100000 p-y
Rautiainen, 2010 (SMC)[145]	NR	Multivitamin vs. no supplement use	Cataract	8.2	All	HR=1.09 (0.94 to 1.25)	252 events/2259	3/75524 p-y
Zheng Selin, 2013 (COSM)[142]		Multivitamin vs. no multivitamin	Cataract	8.4	All	HR=0.96 (0.85 to 1.07)	345/3532 (9.8)	1937/22015 (8.8)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Constipation	0.15	All	0.51 (0.15 to 1.71)	5/42 (11.9)	8/38 (21.1)
Sesso, 2008 (PHS-II)[80]	NR	Multivitamin vs. no multivitamin	Epistaxis	11.2	All	HR=1.10 (1.02 to 1.18)	1579/7317 (21.6)	1451/7324 (19.8)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	Gastrointestinal symptoms	13	All	0.89 (0.46 to 1.73)	17/510 (3.3)	19/510 (3.7)
Pike, 1995[122]	1 tablet	Multivitamin vs. placebo	Gastrointestinal symptoms	1	All	3.36 (0.13 to 88.39)	1/17 (5.9)	0/18 (0.0)

Appendix F Table 6. Multivitamin Adverse Events Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Gastrointestinal symptoms	0.15	All	1.44 (0.53 to 3.90)	13/42 (31.0)	9/38 (23.7)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	GI disease-related hospitalization	13	All	0.97 (0.68 to 1.38)	68/510 (13.3)	70/510 (13.7)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin current use vs. no multivitamin	Hip fracture	18	All	RR=1.32 (1.04 to 1.67)	262/. (.)	176/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin <5 yrs use vs. no multivitamin	Hip fracture	18	All	RR=1.05 (0.74 to 1.49)	39/. (.)	176/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin 5-9 yrs use vs. no multivitamin	Hip fracture	18	All	RR=1.25 (0.83 to 1.85)	33/. (.)	176/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin 10-14 yrs use vs. no multivitamin	Hip fracture	18	All	RR=1.29 (0.81 to 2.05)	24/. (.)	176/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Multivitamin >=15 yrs use vs. no multivitamin	Hip fracture	18	All	RR=1.28 (0.86 to 1.91)	42/. (.)	176/. (.)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	Hospitalization (all-cause)	13	All	0.78 (0.61 to 1.01)	286/510 (56.1)	316/510 (62.0)
Chylack, 2002 (REACT)[85]		Multivitamin vs. placebo	Hypercarotenodermia	2.8	All	13.45 (0.75 to 240.99)	6/149 (4.0)	0/148 (0.0)
Zheng Selin, 2013 (COSM)[142]		Multivitamin vs. no multivitamin	Kidney stones	11	All	RR=0.86 (0.62 to 1.19)	./. (.)	./. (.)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Nausea	0.15	All	1.50 (0.54 to 4.19)	12/42 (28.6)	8/38 (21.1)
Chylack, 2002 (REACT)[85]		Multivitamin vs. placebo	Non-serious: Intercurrent illness (NS)	2.8	All	1.94 (1.20 to 3.15)	107/149 (71.8)	84/148 (56.8)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Non-serious: Agitation (NS); anxiety (NS); dry mouth (NS); headache (NS); sedation (NS); sleep disruptions (NS)	0.15	All	. (. to .)	./42 (.)	./38 (.)
Sesso, 2008 (PHS-II)[80]	NR	Multivitamin vs. no multivitamin	Non-serious: Easy bruising (NS); hematuria (NS)	11.2	All	. (. to .)	./7317 (.)	./7324 (.)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Sarcoidosis	0.15	All	2.78 (0.11 to 70.39)	1/42 (2.4)	0/38 (0.0)

Appendix F Table 6. Multivitamin Adverse Events Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)
Chylack, 2002 (REACT)[85]		Multivitamin vs. placebo	Serious AEs	2.8	All	0.99 (0.02 to 50.39)	0/149 (0.0)	0/148 (0.0)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	Skin rash	13	All	1.25 (0.33 to 4.69)	5/510 (1.0)	4/510 (0.8)
Pike, 1995[122]	1 tablet	Multivitamin vs. placebo	Skin rash	1	All	3.36 (0.13 to 88.39)	1/17 (5.9)	0/18 (0.0)
Sesso, 2008 (PHS-II)[80]	NR	Multivitamin vs. no multivitamin	Skin rash	11.2	All	HR=1.07 (1.01 to 1.14)	2125/7317 (29.0)	2002/7324 (27.3)
CTNS Study Group, 2008 (CTNS)[133]		Multivitamin vs. placebo	Urogenital hospitalizations	13	All	1.07 (0.74 to 1.56)	66/510 (12.9)	62/510 (12.2)
Hercberg, 2004 (SUVIMAX)[71]		Multivitamin vs. placebo	Withdrawals due to AEs	8.9	Males	1.00 (0.02 to 50.22)	0/2522 (0.0)	0/2512 (0.0)
Rucklidge, 2014[100]		Multivitamin vs. placebo	Withdrawals due to AEs	0.15	All	2.78 (0.11 to 70.39)	1/42 (2.4)	0/38 (0.0)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; COSM = Cohort of Swedish Men; CTNS = Clinical Trial of Nutritional Supplements and Age-Related Cataract; GI = Gastrointestinal; HR = Hazard ratio; IG = Intervention group; MAVIS = Mineral and Vitamin Intervention Trial; NHS-I = Nurse' Health Study; NR = Not reported; NS = Not significant; OR = Odds ratio; PHS-II = Physicians' Health Study; REACT = Roche European American Cataract Trial; RR = Risk ratio; SMC = Swedish Mammography Cohort; SUVIMAX = The Supplémentation en Vitamines et Minéraux Antioxydants; yrs = Years

Appendix F Table 7. Beta Carotene and Vitamin A Meta-Analysis Results: Results of Meta-Analyses by Outcome, Primary Analysis Listed First for Each Outcome, Followed by Sensitivity Analyses

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality (beta carotene with or without vitamin A)	MH	1.06 (1.00 to 1.12)	6	112,820	NA	NA
	Peto	1.06 (1.00 to 1.12)	6	112,820	6.4	0.00
	Full ascert.(MH)	1.06 (1.01 to 1.12)	5	111,199	NA	NA
	Beta-carotene without vitamin A (MH)	1.06 (1.00 to 1.12)	5	94,506	NA	NA
All-cause mortality (beta carotene, vitamin A, or the combination)	MH	1.06 (1.01 to 1.12)	7	115,117	NA	NA
CVD mortality	Peto	1.10 (1.02 to 1.19)	5	94,506	0.0	0.0
	MH	1.10 (1.02 to 1.19)	5	94,506	NA	NA
	Full ascert. (Peto)	1.11 (1.02 to 1.20)	4	92,885	NA	NA
Cancer mortality	Peto	1.00 (0.87 to 1.14)	4	65,373	0.0	0.0
	MH	1.00 (0.87 to 1.14)	4	65,373	NA	NA
	Full ascert. (Peto)	1.00 (0.87 to 1.14)	4	65,373	0.0	0.0
Any cancer incidence	MH	0.99 (0.92 to 1.07)	2	61,947	NA	NA
	Peto	0.99 (0.92 to 1.07)	2	61,947	0.02	0.0
	Full ascert. (MH)	0.99 (0.92 to 1.07)	2	61,947	NA	NA
Colorectal cancer	Peto	1.00 (0.85 to 1.16)	4	109,394	0.0	0.0
	MH	1.00 (0.85 to 1.16)	4	109,394	NA	NA
	Full ascert. (Peto)	1.00 (0.85 to 1.16)	4	109,394	0.0	0.0
Lung cancer	Peto	1.20 (1.01 to 1.42)	4	94,830	38.85	0.01
	MH	1.21 (1.07 to 1.36)	4	94,830	NA	NA
	Full ascert. (Peto)	1.20 (1.01 to 1.42)	4	94,830	38.85	0.01
	Beta-carotene without vitamin A (MH)	1.12 (0.96 to 1.31)	3	76,516	NA	NA
Breast cancer	Peto	0.97 (0.80 to 1.16)	2	46,165	0.0	0.0
	MH	0.97 (0.81 to 1.16)	2	46,165	NA	NA
	Full ascert. (Peto)	0.97 (0.80 to 1.16)	2	46,165	0.0	0.0
Prostate cancer	Peto	1.03 (0.92 to 1.14)	3	48,665	0.0	0.0
	MH	1.03 (0.92 to 1.14)	3	48,665	NA	NA
	Full ascert. (Peto)	1.03 (0.92 to 1.14)	3	48,665	0.0	0.0

Abbreviations: ascert. = ascertainment; CI = Confidence interval; CVD = Cardiovascular disease; NA = Not applicable; No. = Number; MH = Mantel-Haenszel common effects model; OR = Odds ratio; Peto = Peto odds ratio random effects REML model

Appendix F Table 8. Summary of Results for Studies of Beta-Carotene Use

Author, Year (Study)	Quality Rating	Study Design	Study N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
ATBC Study Group, 1994 (ATBC)[75]	Good	RCT	29133	Beta-carotene (20 mg)	?		↑ Lung ↑? Prostate ↔? Others	
				Beta-carotene (20 mg) + Vitamin E (50 mg)	↑	↑	↑ Lung ↔ CRC ↑? Prostate	↑ Hypercarotenodermia ↔ Hospitalizations for pneumonia
Feskanich, 2002 (NHS-I)[140]	Fair	Cohort	121700	Beta-carotene (NR)				↔ Hip fracture
Green, 1999 (NSCPS)[72]	Good	RCT	1621	Beta-carotene (30 mg)	↓?	↓?	? Mortality ↔ Skin	↔ WD due to AE
Greenberg, 1990 (SCPS)[86]	Good	RCT	1805	Beta-carotene (50 mg)	↔	↑?	↔ Lung ↔ Mortality	↑ WD due to AE ↑ Hypercarotenodermia
Hennekens, 1996 (PHS-I)[74]	Good	RCT	22071	Beta-carotene (25 mg)	↔	↔	↔ Lung ↔ Mortality ↔ Any incident ↔CRC ↔Prostate	↑Hypercarotenodermia ↑GI symptoms ↔Serious AE
Lee, 2005 (WHS)[73]	Good	RCT	39876	Beta-carotene (25 mg)	↔	↔	↑? Lung ↔ Mortality ↔ Any incident ↔CRC ↔Breast	↑Hypercarotenodermia
Omenn, 1996 (CARET)[62]	Good	RCT	18314	Beta-carotene (30 mg) + Vitamin A (7500 RAE)	↑?	↑	↑ Lung ↔CRC ↔Breast ↔Prostate	↔ Any AE

*Primarily from hypercarotenodermia

Abbreviations: ACM = All-cause mortality; AE = Adverse event; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CRC = Colorectal cancer; CVD = Cardiovascular disease; GI = Gastrointestinal; NHS-I = Nurses' Health Study I; NR = Not reported; NSCPS = Nambour Skin Cancer Prevention Study; PHS-I = Physicians' Health Study-I; RCT = Randomized controlled trial; RAE = Retinol activity equivalents, SCPS = Skin Cancer Prevention Study; SKICAP = SKIn CAncer Prevention; WD = Withdrawal; WHS = Women's Health Study

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)
↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

Appendix F Table 8. Summary of Results for Studies of Beta-Carotene Use

↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 9. Summary of Results for Studies of Vitamin A Use

Study	Quality Rating	Study Design	Study N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Moon, 1997 (SKICAP)[63]	Fair	RCT	2297	Vitamin A (7500 RAE)	↔		↓SCC ↔BCC	↑? Any AE
Omenn, 1996 (CARET)[62]	Good	RCT	18314	Beta-carotene (30 mg) + Vitamin A (7500 RAE)	↑?	↑	↑ Lung ↔CRC ↔Breast ↔Prostate	↔ Any AE
Feskanich, 2002 (NHS-I)[140]	Fair	Cohort	121700	Vitamin A (NR)				↔? Cataract ↑? Hip fracture
Lim, 2004 (IWHS)[141]	Fair	Cohort	34703	Vitamin A (NR)				↔ Fractures ↑? Hip fracture

Abbreviations: ACM = All-cause mortality; AE = Adverse event; BCC = Basal cell carcinoma; CARET = The Beta-Carotene and Retinol Efficacy Trial; CVD = Cardiovascular disease; CRC = Colorectal cancer; IWHS = Iowa Women's Health Study; NR = Not reported; NHS-I = Nurses' Health Study I; RAE = retinol activity equivalents; SCC = squamous cell carcinoma; SKICAP = SKIn CAncer Prevention

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)
↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	All-cause mortality	24.1	All	1.02 (0.95 to 1.10)	5052/7282 (69.4)	5022/7287 (68.9)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	All-cause mortality	6.1	All	1.09 (1.02 to 1.17)	1851/14560 (12.7)	1719/14573 (11.8)	0.02
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	All-cause mortality	11	All	1.11 (1.05 to 1.17)	3129/14560 (21.5)	2883/14573 (19.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	All-cause mortality	14	All	1.10 (1.05 to 1.16)	4584/14560 (31.5)	4284/14573 (29.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	All-cause mortality	16	All	1.09 (1.04 to 1.14)	5555/14560 (38.2)	5276/14573 (36.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	All-cause mortality	24.1	All	1.07 (1.00 to 1.15)	5117/7278 (70.3)	5022/7287 (68.9)	NR
Green, 1999 (NSCPS)[72]	Beta-carotene vs. placebo	30 mg	All-cause mortality	4.5	All	RR=0.50 (0.24 to 1.03)	11/820 (1.3)	21/801 (2.6)	NR, NS
Greenberg, 1990 (SCPS)[86]	Beta-carotene vs. placebo	50 mg	All-cause mortality	5	All	IRR=1.08 (0.98 to 1.19)	79/913 (8.7)	72/892 (8.1)	NR, NS
Greenberg, 1990 (SCPS)[86]	Beta-carotene vs. placebo	50 mg	All-cause mortality	8.2	All	RR=1.03 (0.82 to 1.30)	146/913 (16.0)	139/892 (15.6)	0.80
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	All-cause mortality	12	All	RR=1.02 (0.93 to 1.11)	979/11036 (8.9)	968/11035 (8.8)	0.68
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	All-cause mortality	4.1	All	RR=1.07 (0.74 to 1.56)	59/19937 (0.3)	55/19939 (0.3)	0.70
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	3.7	All	IRR=1.17 (1.03 to 1.33)	56/9420 (0.6)	41/8894 (0.5)	0.02
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	10	All	1.13 (1.04 to 1.23)	1281/9420 (13.6)	1088/8894 (12.2)	

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	3.7	Asbestos-exposed (all male)	IRR=1.25 (1.01 to 1.56)	17.76/1000 p-y	14.3/1000 p-y	0.04
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	10	Asbestos-exposed (all male)	RR=0.96 (0.81 to 1.13)	283/1842 (15.4)	293/1851 (15.8)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	3.7	Female heavy smokers	RR=1.16 (0.88 to 1.52)	./3201 (.)	./3081 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	10	Female heavy smokers	RR=1.37 (1.16 to 1.62)	352/3044 (11.6)	239/2965 (8.1)	<0.05
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	3.7	Heavy smokers	IRR=1.13 (0.96 to 1.32)	13.26/1000 p-y	10.91/1000 p-y	0.14
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	10	Heavy smokers	RR=1.13 (1.02 to 1.24)	942/6902 (13.6)	754/6545 (11.5)	<0.05
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	3.7	Male heavy smokers	RR=1.10 (0.90 to 1.34)	./4175 (.)	./3797 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	All-cause mortality	10	Male heavy smokers	RR=1.00 (0.89 to 1.13)	590/3858 (15.3)	515/3580 (14.4)	NR, NS
Green, 1999 (NSCPS)[72]	Beta-carotene vs. placebo	30 mg	Any cancer deaths	4.5	All	0.42 (0.11 to 1.62)	3/820 (0.4)	7/801 (0.9)	NR
Greenberg, 1990 (SCPS)[86]	Beta-carotene vs. placebo	50 mg	Any cancer deaths	8.2	All	RR=0.83 (0.54 to 1.29)	38/913 (4.2)	44/892 (4.9)	0.41
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer deaths	12	All	RR=1.02 (0.89 to 1.18)	386/11036 (3.5)	380/11035 (3.4)	0.76
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer deaths	12.9	All	RR=1.00 (0.90 to 1.20)	414/11036 (3.8)	406/11035 (3.7)	0.71
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer deaths	4.1	All	RR=1.11 (0.67 to 1.85)	31/19937 (0.2)	28/19939 (0.1)	0.69

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Chronic liver disease deaths	22.1	All	HR=1.06 (0.74 to 1.51)	62/7274 (0.9)	59/7282 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Chronic liver disease deaths	22.1	All	HR=1.05 (0.82 to 1.36)	121/14543 (0.8)	116/14562 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Chronic liver disease deaths	22.1	All	HR=1.01 (0.70 to 1.45)	59/7269 (0.8)	59/7282 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Colorectal cancer deaths	6.1	All	RR=1.01 (0.56 to 1.79)	23/14564 (0.2)	24/14569 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	CVD deaths	6.1	All	1.11 (1.01 to 1.23)	905/14560 (6.2)	818/14573 (5.6)	NR
Green, 1999 (NSCPS)[72]	Beta-carotene vs. placebo	30 mg	CVD deaths	4.5	All	0.48 (0.18 to 1.30)	6/820 (0.7)	12/801 (1.5)	NR
Greenberg, 1990 (SCPS)[86]	Beta-carotene vs. placebo	50 mg	CVD deaths	8.2	All	RR=1.16 (0.82 to 1.64)	68/913 (7.4)	59/892 (6.6)	0.41
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	CVD deaths	12	All	RR=1.09 (0.93 to 1.27)	338/11036 (3.1)	313/11035 (2.8)	0.28
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	CVD deaths	4.1	All	RR=1.17 (0.54 to 2.53)	14/19937 (0.1)	12/19939 (0.1)	0.69
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	3.7	All	RR=1.26 (0.99 to 1.61)	./9420 (.)	./8894 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	10	All	RR=1.02 (0.88 to 1.19)	354/8744 (4.0)	319/8396 (3.8)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	3.7	Asbestos-exposed (all male)	RR=1.43 (0.97 to 2.12)	./2044 (.)	./2016 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	10	Asbestos-exposed (all male)	RR=0.91 (0.69 to 1.21)	95/1842 (5.2)	103/1851 (5.6)	NR, NS

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	3.7	Female heavy smokers	RR=1.42 (0.80 to 2.54)	./3201 (.)	./3081 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	10	Female heavy smokers	RR=1.44 (1.02 to 2.04)	83/3044 (2.7)	54/2965 (1.8)	<0.05
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	3.7	Heavy smokers	RR=1.16 (0.85 to 1.58)	./7376 (.)	./6878 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	10	Heavy smokers	RR=1.07 (0.89 to 1.29)	259/6902 (3.8)	216/6545 (3.3)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	3.7	Male heavy smokers	RR=1.05 (0.73 to 1.52)	./4175 (.)	./3797 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	CVD deaths	10	Male heavy smokers	RR=0.93 (0.75 to 1.16)	176/3858 (4.6)	162/3580 (4.5)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Esophageal cancer deaths	6.1	All	RR=0.67 (0.19 to 2.37)	4/7282 (0.1)	6/7287 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Esophageal cancer deaths	6.1	All	RR=0.67 (0.24 to 1.88)	6/14560 (0.0)	9/14573 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Esophageal cancer deaths	6.1	All	RR=0.34 (0.07 to 1.66)	2/7278 (0.0)	6/7287 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Hemorrhagic stroke deaths	6.1	All	1.16 (0.80 to 1.69)	59/14560 (0.4)	51/14573 (0.3)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Ischemic heart disease deaths	6.1	All	1.12 (1.00 to 1.26)	653/14560 (4.5)	586/14573 (4.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Ischemic stroke deaths	6.1	All	1.24 (0.87 to 1.77)	68/14560 (8.0)	55/14573 (6.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Laryngeal cancer deaths	6.1	All	RR=1.00 (0.20 to 4.96)	3/7282 (0.0)	3/7287 (0.0)	NR, NS

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Laryngeal cancer deaths	6.1	All	RR=1.01 (0.29 to 3.46)	5/14560 (0.0)	5/14573 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Laryngeal cancer deaths	6.1	All	RR=0.67 (0.11 to 4.00)	2/7278 (0.0)	3/7287 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Lung cancer deaths	6.1	All	1.16 (0.98 to 1.37)	302/14560 (2.1)	262/14573 (1.8)	NR
Greenberg, 1990 (SCPS)[86]	Beta-carotene vs. placebo	50 mg	Lung cancer deaths	8.2	All	0.74 (0.36 to 1.54)	13/913 (1.4)	17/892 (1.9)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Lung cancer deaths	12	All	1.02 (0.71 to 1.44)	63/11036 (0.6)	62/11035 (0.6)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	3.7	All	RR=1.46 (1.07 to 2.00)	./9420 (.)	./8894 (.)	0.02
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	10	All	RR=1.20 (1.01 to 1.43)	294/8744 (3.4)	227/8396 (2.7)	<0.05
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	3.7	Asbestos-exposed (all male)	RR=1.29 (0.75 to 2.22)	./2044 (.)	./2016 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	10	Asbestos-exposed (all male)	RR=1.16 (0.77 to 1.75)	50/1842 (2.7)	43/1851 (2.3)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	3.7	Female heavy smokers	RR=1.46 (0.81 to 2.62)	./3201 (.)	./3081 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	10	Female heavy smokers	RR=1.33 (0.96 to 1.84)	91/3044 (3.0)	63/2965 (2.1)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	3.7	Heavy smokers	RR=1.55 (1.06 to 2.28)	./7376 (.)	./6878 (.)	<0.05
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	10	Heavy smokers	RR=1.21 (1.00 to 1.47)	244/6902 (3.5)	184/6545 (2.8)	<0.05

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	3.7	Male heavy smokers	RR=1.62 (0.98 to 2.68)	./4175 (.)	./3797 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer deaths	10	Male heavy smokers	RR=1.14 (0.89 to 1.45)	153/3858 (4.0)	121/3580 (3.4)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Oral cavity/pharynx cancer deaths	6.1	All	RR=2.01 (0.37 to 10.95)	4/7282 (0.1)	2/7287 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Oral cavity/pharynx cancer deaths	6.1	All	RR=1.43 (0.55 to 3.76)	10/14560 (0.1)	7/14573 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Oral cavity/pharynx cancer deaths	6.1	All	RR=3.01 (0.61 to 14.93)	6/7278 (0.1)	2/7287 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Other CVD deaths	6.1	All	0.99 (0.77 to 1.27)	125/14560 (0.9)	126/14573 (0.9)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Pancreatic cancer deaths	6.1	All	RR=0.81 (0.53 to 1.26)	35/14560 (0.2)	48/14573 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Prostate cancer deaths	6.1	All	1.17 (0.62 to 2.19)	21/7282 (0.3)	18/7287 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Prostate cancer deaths	6.1	All	1.14 (0.69 to 1.88)	33/14560 (0.2)	29/14573 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Prostate cancer deaths	6.1	All	0.67 (0.32 to 1.39)	12/7278 (0.2)	18/7287 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Renal cell carcinoma deaths	6.1	All	0.43 (0.16 to 1.12)	6/7282 (0.1)	14/7287 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Renal cell carcinoma deaths	6.1	All	0.64 (0.34 to 1.20)	16/14560 (0.1)	25/14573 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Renal cell carcinoma deaths	6.1	All	0.71 (0.32 to 1.61)	10/7278 (0.1)	14/7287 (0.2)	NR

Appendix F Table 10. Beta-Carotene Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Urothelial cancer deaths	6.1	All	1.00 (0.29 to 3.46)	5/7282 (0.1)	5/7287 (0.1)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Urothelial cancer deaths	6.1	All	1.18 (0.53 to 2.64)	13/14560 (0.1)	11/14573 (0.1)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Urothelial cancer deaths	6.1	All	1.60 (0.52 to 4.90)	8/7278 (0.1)	5/7287 (0.1)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CG = Control group; CVD = Cardiovascular disease; IG = Intervention group; NR = Not reported; NS = Not significant; NSCPS = Nambour Skin Cancer Prevention Study; mg = Milligrams; IRR = Incident rate ratio; IU = International units; OR = Odds ratio; PHS-I = Physicians' Health Study-I; RR = Risk ratio; SCPS = Skin Cancer Prevention Study; WHS = Women's Health Study

Appendix F Table 11. Beta-Carotene Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	CVD events	12	All	RR=1.00 (0.91 to 1.09)	967/11036 (8.8)	972/11035 (8.8)	0.90
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	CVD events	4.1	All	RR=1.14 (0.87 to 1.49)	116/19937 (0.6)	102/19939 (0.5)	0.34
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	MI	12	All	RR=0.96 (0.84 to 1.09)	468/11036 (4.2)	489/11035 (4.4)	0.50
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	MI	4.1	All	RR=0.84 (0.56 to 1.27)	42/19937 (0.2)	50/19939 (0.3)	0.41
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Stroke	12	All	RR=0.96 (0.83 to 1.11)	367/11036 (3.3)	382/11035 (3.5)	0.60
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Stroke	4.1	All	RR=1.42 (0.96 to 2.10)	61/19937 (0.3)	43/19939 (0.2)	0.08

Abbreviations: CG = Control group; CVD = Cardiovascular disease; IG = Intervention group; MI = Myocardial infarction; PHS-I = Physicians' Health Study-I; RR = Risk ratio; mg = Milligrams; WHS = Women's Health Study

Appendix F Table 12. Beta-Carotene Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer incidence	12	All	RR=0.98 (0.91 to 1.06)	1273/11036 (11.5)	1293/11035 (11.7)	0.65
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer incidence	12.9	All	RR=1.00 (0.90 to 1.00)	1314/11036 (11.9)	1353/11035 (12.3)	0.41
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Any cancer incidence	4.1	All	RR=1.03 (0.89 to 1.18)	378/19937 (1.9)	369/19939 (1.9)	0.73
Green, 1999 (NSCPS)[72]	Beta-carotene vs. placebo	30 mg	Basal cell carcinoma	4.5	All	IRR=1.04 (0.73 to 1.27)	102/820 (12.4)	93/801 (11.6)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Brain cancer	12	All	0.81 (0.48 to 1.37)	25/11036 (0.2)	31/11035 (0.3)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Brain cancer	12.9	All	RR=0.80 (0.50 to 1.30)	25/11036 (0.2)	33/11035 (0.3)	0.29
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Brain cancer	4.1	All	0.67 (0.19 to 2.36)	4/19937 (0.0)	6/19939 (0.0)	NR, NS
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Breast cancer	4.1	All	1.01 (0.81 to 1.25)	169/19937 (0.8)	168/19939 (0.8)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Breast cancer	3.7	Female heavy smokers	RR=0.78 (0.55 to 1.12)	59/3208 (1.8)	65/3081 (2.1)	0.18
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Cervical cancer	4.1	All	0.67 (0.11 to 3.99)	2/19937 (0.0)	3/19939 (0.0)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Colon cancer	12.9	All	RR=0.90 (0.70 to 1.20)	128/11036 (1.2)	139/11035 (1.3)	0.48
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Colorectal cancer	24.1	All	0.97 (0.80 to 1.18)	203/7282 (2.8)	209/7287 (2.9)	NR

Appendix F Table 12. Beta-Carotene Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Colorectal cancer	8	All	RR=1.05 (0.75 to 1.47)	69/14560 (0.5)	66/14573 (0.5)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Colorectal cancer	11	All	1.05 (0.81 to 1.36)	116/14560 (0.8)	111/14573 (0.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Colorectal cancer	14	All	1.26 (1.01 to 1.56)	189/14560 (1.3)	151/14573 (1.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Colorectal cancer	24.1	All	0.93 (0.76 to 1.14)	195/7278 (2.7)	209/7287 (2.9)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Colorectal cancer	12	All	0.96 (0.77 to 1.19)	167/11036 (1.5)	174/11035 (1.6)	NR, NS
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Colorectal cancer	4.1	All	1.00 (0.62 to 1.61)	34/19937 (0.2)	34/19939 (0.2)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Colorectal cancer	3.7	All	RR=1.02 (0.70 to 1.50)	56/9420 (0.6)	50/8894 (0.6)	0.91
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Esophageal cancer	6.1	All	RR=0.86 (0.29 to 2.56)	6/7282 (0.1)	7/7287 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Esophageal cancer	6.1	All	RR=0.85 (0.38 to 1.90)	11/14560 (0.1)	13/14573 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Esophageal cancer	6.1	All	RR=0.72 (0.23 to 2.27)	5/7278 (0.1)	7/7287 (0.1)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Head and neck cancer	3.7	All	RR=1.26 (0.73 to 2.19)	32/9420 (0.3)	22/8894 (0.2)	0.41
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Laryngeal cancer	6.1	All	RR=0.71 (0.34 to 1.48)	12/7282 (0.2)	17/7287 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Laryngeal cancer	6.1	All	RR=0.65 (0.38 to 1.11)	22/14560 (0.2)	34/14573 (0.2)	NR, NS

Appendix F Table 12. Beta-Carotene Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Laryngeal cancer	6.1	All	RR=0.59 (0.27 to 1.29)	10/7278 (0.1)	17/7287 (0.2)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Leukemia	12	All	0.83 (0.53 to 1.31)	35/11036 (0.3)	42/11035 (0.4)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Leukemia	12.9	All	RR=0.80 (0.50 to 1.20)	36/11036 (0.3)	45/11035 (0.4)	0.31
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Leukemia	3.7	All	RR=2.18 (0.95 to 5.03)	18/9420 (0.2)	8/8894 (0.1)	0.06
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Leukemia/lymphoma	4.1	All	0.77 (0.41 to 1.46)	17/19937 (0.1)	22/19939 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Liver cancer	22.1	All	HR=1.26 (0.85 to 1.87)	56/7274 (0.8)	45/7282 (0.6)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Liver cancer	22.1	All	HR=1.13 (0.86 to 1.49)	110/14543 (0.8)	98/14562 (0.7)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Liver cancer	22.1	All	HR=1.21 (0.81 to 1.80)	54/7269 (0.7)	45/7282 (0.6)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Lung cancer	6.1	All	1.17 (0.97 to 1.41)	242/7282 (3.3)	208/7287 (2.9)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Lung cancer	24.1	All	1.02 (0.93 to 1.13)	951/7282 (13.1)	933/7287 (12.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Lung cancer	6.1	All	RR=1.18 (1.03 to 1.36)	474/14560 (3.3)	402/14573 (2.8)	0.01
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Lung cancer	8	All	RR=1.16 (1.02 to 1.33)	482/14560 (3.3)	412/14573 (2.8)	<0.05
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Lung cancer	11	All	1.17 (1.05 to 1.30)	748/14560 (5.1)	645/14573 (4.4)	NR

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Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Lung cancer	14	All	1.10 (1.00 to 1.21)	1009/14560 (6.9)	923/14573 (6.3)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Lung cancer	6.1	All	1.16 (0.96 to 1.40)	240/7278 (3.3)	208/7287 (2.9)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Lung cancer	24.1	All	1.05 (0.96 to 1.16)	976/7278 (13.4)	933/7287 (12.8)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Lung cancer	12	All	0.93 (0.69 to 1.26)	82/11036 (0.7)	88/11035 (0.8)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Lung cancer	12.9	All	RR=0.90 (0.70 to 1.20)	85/11036 (0.8)	93/11035 (0.8)	0.54
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Lung cancer	4.1	All	1.48 (0.85 to 2.57)	31/19937 (0.2)	21/19939 (0.1)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	3.7	All	IRR=1.28 (1.04 to 1.57)	229/9420 (2.4)	159/8894 (1.8)	0.02
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	6-yr post intervention period only	All	RR=1.12 (0.97 to 1.31)	376/8744 (4.3)	311/8396 (3.7)	NR
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	10	All	1.23 (1.09 to 1.39)	605/9420 (6.4)	470/8894 (5.3)	NR
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	3.7	Asbestos-exposed (all male)	IRR=1.40 (0.95 to 2.07)	62/2044 (3.0)	44/2016 (2.2)	0.08
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	10	Asbestos-exposed (all male)	RR=0.92 (0.65 to 1.30)	61/1842 (3.3)	66/1851 (3.6)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	3.7	Female heavy smokers	RR=1.19 (0.82 to 1.72)	./3201 (.)	./3081 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	10	Female heavy smokers	RR=1.33 (1.01 to 1.75)	127/3044 (4.2)	88/2965 (3.0)	<0.05

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Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	3.7	Heavy smokers	IRR=1.23 (0.96 to 1.56)	167/7376 (2.3)	115/6878 (1.7)	0.09
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	10	Heavy smokers	RR=1.18 (0.99 to 1.39)	315/6902 (4.6)	245/6545 (3.7)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	3.7	Male heavy smokers	RR=1.25 (0.91 to 1.73)	./4175 (.)	./3797 (.)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lung cancer	10	Male heavy smokers	RR=1.08 (0.87 to 1.34)	188/3858 (4.9)	157/3580 (4.4)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Lymphoma	12	All	1.08 (0.79 to 1.46)	86/11036 (0.8)	80/11035 (0.7)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Lymphoma	12.9	All	RR=1.00 (0.80 to 1.40)	89/11036 (0.8)	85/11035 (0.8)	0.77
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Lymphoma	3.7	All	RR=0.91 (0.42 to 1.98)	13/9420 (0.1)	13/8894 (0.1)	0.81
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Melanoma skin cancer	12	All	0.88 (0.63 to 1.23)	64/11036 (0.6)	73/11035 (0.7)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Melanoma skin cancer	12.9	All	RR=0.90 (0.60 to 1.20)	68/11036 (0.6)	77/11035 (0.7)	0.45
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Melanoma skin cancer	4.1	All	0.90 (0.49 to 1.68)	19/19937 (0.1)	21/19939 (0.1)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Mesothelioma	3.7	All	RR=1.52 (0.66 to 3.52)	14/9420 (0.1)	9/8894 (0.1)	0.32
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Oral cavity/pharyngeal cancer	6.1	All	RR=0.84 (0.42 to 1.66)	15/7282 (0.2)	18/7287 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Oral cavity/pharyngeal cancer	6.1	All	RR=0.97 (0.60 to 1.58)	32/14560 (0.2)	33/14573 (0.2)	NR, NS

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Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Oral cavity/pharyngeal cancer	6.1	All	RR=0.95 (0.49 to 1.84)	17/7278 (0.2)	18/7287 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Other cancer	6.1	All	0.94 (0.81 to 1.09)	356/14560 (2.4)	379/14573 (2.6)	NR, NS
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Ovarian cancer	4.1	All	1.33 (0.72 to 2.46)	24/19937 (0.1)	18/19939 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Pancreatic cancer	6.1	All	RR=0.46 (0.23 to 0.92)	12/7282 (0.2)	26/7287 (0.4)	<0.05
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Pancreatic cancer	24.1	All	0.92 (0.70 to 1.20)	101/7282 (1.4)	110/7287 (1.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Pancreatic cancer	6.1	All	RR=0.75 (0.49 to 1.14)	38/14560 (0.3)	51/14573 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Pancreatic cancer	6.1	All	RR=1.00 (0.52 to 1.73)	26/7278 (0.4)	26/7287 (0.4)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Pancreatic cancer	24.1	All	1.00 (0.77 to 1.31)	110/7278 (1.5)	110/7287 (1.5)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Pancreatic cancer	12	All	1.38 (0.79 to 2.42)	29/11036 (0.3)	21/11035 (0.2)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Pancreatic cancer	12.9	All	RR=1.40 (0.80 to 2.60)	29/11036 (0.3)	20/11035 (0.2)	0.20
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Pancreatic cancer	4.1	All	1.50 (0.42 to 5.32)	6/19937 (0.0)	4/19939 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Prostate cancer	6.1	All	1.20 (0.86 to 1.66)	80/7282 (1.1)	67/7287 (0.9)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Prostate cancer	24.1	All	0.97 (0.87 to 1.09)	656/7282 (9.0)	672/7287 (9.2)	NR

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Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Prostate cancer	6.1	All	1.24 (0.96 to 1.59)	138/14560 (0.9)	112/14573 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Prostate cancer	8	All	RR=1.26 (0.98 to 1.62)	138/14560 (0.9)	110/14573 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Prostate cancer	11	All	1.21 (1.02 to 1.44)	287/14560 (2.0)	238/14573 (1.6)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Prostate cancer	14	All	1.10 (0.96 to 1.25)	480/14560 (3.3)	440/14573 (3.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Prostate cancer	24.1	All	0.95 (0.85 to 1.07)	643/7278 (8.8)	672/7287 (9.2)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Prostate cancer	12	All	0.99 (0.87 to 1.12)	520/11036 (4.7)	527/11035 (4.8)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Prostate cancer	12.9	All	RR=1.00 (0.90 to 1.00)	551/11036 (5.0)	566/11035 (5.1)	0.41
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Prostate cancer	3.7	Males	RR=1.01 (0.80 to 1.27)	161/6212 (2.6)	139/5813 (2.4)	0.95
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Prostate cancer	11	Males	1.01 (0.88 to 1.16)	462/6197 (7.5)	428/5803 (7.4)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Rectal cancer	12.9	All	RR=1.10 (0.70 to 1.80)	42/11036 (0.4)	37/11035 (0.3)	0.58
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Renal cell carcinoma	6.1	All	0.78 (0.44 to 1.38)	21/7282 (0.3)	27/7287 (0.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Renal cell carcinoma	24.1	All	0.98 (0.73 to 1.31)	88/7282 (1.2)	90/7287 (1.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Renal cell carcinoma	6.1	All	RR=0.80 (0.60 to 1.30)	48/14560 (0.3)	54/14573 (0.4)	NR, NS

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Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Renal cell carcinoma	6.1	All	1.00 (0.59 to 1.71)	27/7278 (0.4)	27/7287 (0.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene and vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Renal cell carcinoma	24.1	All	0.97 (0.72 to 1.30)	87/7278 (1.2)	90/7287 (1.2)	NR
Green, 1999 (NSCPS)[72]	Beta-carotene vs. placebo	30 mg	Squamous cell carcinoma	4.5	All	IRR=1.35 (0.84 to 2.19)	40/820 (4.9)	28/801 (3.5)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Stomach cancer	6.1	All	RR=1.38 (0.81 to 2.36)	33/7282 (0.5)	24/7287 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Stomach cancer	24.1	All	1.04 (0.79 to 1.36)	108/7282 (1.5)	104/7287 (1.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Stomach cancer	6.1	All	RR=1.26 (0.88 to 1.80)	70/14560 (0.5)	56/14573 (0.4)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Stomach cancer	6.1	All	RR=1.55 (0.92 to 2.62)	37/7278 (0.5)	24/7287 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Stomach cancer	24.1	All	1.09 (0.83 to 1.42)	113/7278 (1.6)	104/7287 (1.4)	NR
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Stomach cancer	12	All	0.90 (0.49 to 1.68)	19/11036 (0.2)	21/11035 (0.2)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Stomach cancer	12.9	All	RR=0.90 (0.50 to 1.80)	20/11036 (0.2)	21/11035 (0.2)	0.87
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Stomach cancer	4.1	All	1.00 (0.06 to 15.99)	1/19937 (0.0)	1/19939 (0.0)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Thyroid cancer	12	All	8.01 (1.84 to 34.84)	16/11036 (0.1)	2/11035 (0.0)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Thyroid cancer	12.9	All	RR=9.50 (2.20 to 40.70)	19/11036 (0.2)	2/11035 (0.0)	0.003

Appendix F Table 12. Beta-Carotene Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Thyroid cancer	4.1	All	0.75 (0.32 to 1.78)	9/19937 (0.0)	12/19939 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Urinary bladder cancer	6.1	All	1.04 (0.76 to 1.43)	79/14560 (0.5)	76/14573 (0.5)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Urinary bladder cancer	12	All	1.51 (1.02 to 2.25)	62/11036 (0.6)	41/11035 (0.4)	NR, NS
Hennekens, 1996 (PHS-I)[74]	Beta-carotene vs. no beta-carotene	25 mg	Urinary bladder cancer	12.9	All	RR=1.50 (1.00 to 2.20)	62/11036 (0.6)	41/11035 (0.4)	0.4
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Urinary bladder cancer	4.1	All	0.83 (0.25 to 2.73)	5/19937 (0.0)	6/19939 (0.0)	NR, NS
Omenn, 1996 (CARET)[62]	Beta-carotene + vitamin A vs. placebo	30 mg + 25000 IU Vitamin A	Urinary bladder cancer	3.7	All	RR=1.08 (0.69 to 1.70)	42/9420 (0.4)	36/8894 (0.4)	0.73
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Urothelial cancer	6.1	All	1.16 (0.75 to 1.81)	43/7282 (0.6)	37/7287 (0.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. placebo	20 mg	Urothelial cancer	24.1	All	0.92 (0.75 to 1.12)	190/7282 (2.6)	206/7287 (2.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene vs. no beta-carotene	20 mg + 50 mg Vitamin E	Urothelial cancer	6.1	All	RR=1.00 (0.70 to 1.30)	85/14560 (0.6)	84/14573 (0.6)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Urothelial cancer	6.1	All	1.14 (0.73 to 1.77)	42/7278 (0.6)	37/7287 (0.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Beta-carotene + vitamin E vs. placebo	20 mg + 50 mg Vitamin E	Urothelial cancer	24.1	All	1.02 (0.84 to 1.24)	209/7278 (2.9)	206/7287 (2.8)	NR
Lee, 2005 (WHS)[73]	Beta-carotene vs. no beta-carotene	25 mg	Uterine cancer	4.1	All	1.15 (0.69 to 1.92)	31/19937 (0.2)	27/19939 (0.1)	NR, NS

*Studies providing estimates other than ORs display effect type

Appendix F Table 12. Beta-Carotene Cancer Results

Abbreviations: . = not reported; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CG = Control group; IG = Intervention group; IRR = Incident rate ratio; IU = International units; mg = Milligram; NR = Not reported; NS = Not significant; NSCPS = Nambour Skin Cancer Prevention Study; OR = Odds ratio; RR = Risk ratio; PHS-I = Physicians' Health Study-I; WHS = Women's Health Study

Appendix F Table 13. Beta-Carotene Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Omenn, 1996 (CARET)[62]	30 mg + 25000 IU Vitamin A	Beta-carotene + vitamin A vs. placebo	Any AE	3.7	All	. (. to .)	./9420 (.)	./8894 (.)
Hennekens, 1996 (PHS-I)[74]	25 mg	Beta-carotene vs. no beta-carotene	Gastrointestinal symptoms	12	All	2.25 (1.82 to 2.78)	275/11036 (2.5)	124/11035 (1.1)
Feskanich, 2002 (NHS-I)[140]	NR	Beta-carotene vs. no beta-carotene	Hip fracture	14	All	RR=0.91 (0.57 to 1.44)	21/. (.)	419/. (.)
ATBC Study Group, 1994 (ATBC)[75]	20 mg + 50 mg Vitamin E	Beta-carotene vs. no beta-carotene	Hypercarotenodermia	6.1	All	6.84 (6.37 to 7.36)	4950/14560 (34.0)	1020/14573 (7.0)
Greenberg, 1990 (SCPS)[86]	50 mg	Beta-carotene vs. placebo	Withdrawal due to Hypercarotenodermia	2	All	24.75 (1.46 to 418.66)	12/913 (1.3)	0/892 (0.0)
Hennekens, 1996 (PHS-I)[74]	25 mg	Beta-carotene vs. no beta-carotene	Hypercarotenodermia	12	All	1.16 (1.08 to 1.25)	1745/11036 (15.8)	1535/11035 (13.9)
Lee, 2005 (WHS)[73]	25 mg	Beta-carotene vs. no beta-carotene	Hypercarotenodermia	4.1	All	1.11 (1.04 to 1.18)	2131/19937 (10.7)	1944/19939 (9.7)
ATBC Study Group, 1994 (ATBC)[75]	20 mg	Beta-carotene vs. placebo	Non-serious: Hospitalized for pneumonia (NS)	6.1	All	. (. to .)	./7280 (.)	./7284 (.)
ATBC Study Group, 1994 (ATBC)[75]	20 mg + 50 mg Vitamin E	Beta-carotene vs. no beta-carotene	Non-serious: Hospitalized for pneumonia (NS)	6.1	All	RR=0.98 (0.85 to 1.11)	442/14560 (3.0)	456/14573 (3.1)
Hennekens, 1996 (PHS-I)[74]	25 mg	Beta-carotene vs. no beta-carotene	Serious AEs	12	All	. (. to .)	./11036 (.)	./11035 (.)
Green, 1999 (NSCPS)[72]	30 mg	Beta-carotene vs. placebo	Withdrawals due to AEs	4.5	All	0.99 (0.69 to 1.42)	65/820 (7.9)	64/801 (8.0)
Greenberg, 1990 (SCPS)[86]	50 mg	Beta-carotene vs. placebo	Withdrawals due to AEs	2	All	1.58 (0.99 to 2.49)	49/913 (5.4)	31/892 (3.5)

*Studies providing estimates other than ORs display effect type

Appendix F Table 13. Beta-Carotene Adverse Event Results

Abbreviations: . = not reported; AE = Adverse event; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CARET = The Beta-Carotene and Retinol Efficacy Trial; CG = Control group; IG = Intervention group; IU = International units; mg = Milligram; NHS-I = Nurses' Health Study I; NS = Not significant; OR = Odds ratio; PHS-I = Physicians' Health Study-I; RR = Risk ratio; SCPS = Skin Cancer Prevention Study; WHS = Women's Health Study

Appendix F Table 14. Vitamin A Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Moon, 1997 (SKICAP)[63]	Vitamin A vs. placebo	25000 IU	All-cause mortality	5	All	1.16 (0.80 to 1.69)	62/1157 (5.4)	53/1140 (4.6)	NR

Abbreviations: CG = Control group; IG = Intervention group; IU = International units; NR = Not reported; SKICAP = SKIn CAncer Prevention

Appendix F Table 15. Vitamin A Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Moon, 1997 (SKICAP)[63]	25000 IU	Vitamin A vs. placebo	Any AE	5.1	All	1.77 (1.49 to 2.09)	703/1124 (62.5)	554/1140 (48.6)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A <2 yrs use vs. no vitamin A	Cataract	12	All	RR=1.39 (0.97 to 1.98)	280/100000 p-y	193/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A 2-4 yrs use vs. no vitamin A	Cataract	12	All	RR=0.99 (0.51 to 1.92)	201/100000 p-y	193/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A 5-9 yrs use vs. no vitamin A	Cataract	12	All	RR=0.70 (0.35 to 1.41)	142/100000 p-y	193/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A ≥10 yrs use vs. no vitamin A	Cataract	12	All	RR=0.60 (0.27 to 1.34)	133/100000 p-y	193/100000 p-y
Lim, 2004 (IWHS)[141]	NR	Vitamin A vs. Placebo	Fractures	9.5	All	RR=1.00 (0.95 to 1.05)	2343/. (.)	4159/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A current use vs. no vitamin A	Hip fracture	18	All	RR=1.40 (0.99 to 1.99)	36/. (.)	462/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A <3 yrs use vs. no vitamin A	Hip fracture	18	All	RR=1.23 (0.65 to 2.30)	10/. (.)	462/. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin A >=3 yrs use vs. no vitamin A	Hip fracture	18	All	RR=1.31 (0.72 to 2.39)	12/. (.)	462/. (.)
Lim, 2004 (IWHS)[141]	NR	Vitamin A vs. Placebo	Hip fracture	9.5	All	RR=1.18 (0.99 to 1.41)	211/. (.)	324/. (.)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; IG = Intervention group; IU = International units; IWHS = Iowa Women's Health Study; NHS-I = Nurses' Health Study I; NR = Not reported; OR = Odds ratio; p-y = Person-years; RR = Risk ratio; SKICAP = SKIn CAncer Prevention

Appendix F Table 16. Summary of Results for Studies of Vitamin D Use

Author, Year (Study)	Final Quality Rating	Study Design	N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Aloia, 2005[130]	Fair	RCT	208	Vitamin D (30 mcg) + Calcium (NR NR)	?	NR	NR	NR
Aloia, 2018 (PODA)[102]	Fair	RCT	260	Vitamin D (3490 IU)	?	?	?	↔/? Extensive list of non-serious
Avenell, 2012 (RECORD)[88]	Fair	RCT	5292	Vitamin D (800 IU)	↔	↔	↔	↔ Fractures, GI sx
				Vitamin D (800 IU) + Calcium (1000 mg)	↔	↔	↔	↔ Fractures
Baeksgaard, 1998[124]	Fair	RCT	240	Vitamin D (560 IU) + Calcium (1000 mg)	?	NR	NR	? Constipation, nausea
Baron, 2015 (VCPPS)[90]	Good	RCT	2259	Vitamin D (1000 IU) +/- Calcium (1200 mg)	↔?	?	↔?	↔ Hypercalcemia, hypercreatininemia, kidney stone, fracture
Bischoff-Ferrari, 2020 (DO-HEALTH)[139]	Good	RCT	2157	Vitamin D (2000IU)	?	NR	NR	↓ Any AE ? Kidney stones
Brisson, 2017[94]	Good	RCT	405	Vitamin D (1000 IU)	NR	NR	NR	↔? Nausea, vomiting, other non-serious ? AE WD
				Vitamin D (2000 IU)				
				Vitamin D (3000 IU)				
Cooper, 2003[127]	Fair	RCT	187	Vitamin D (1428.6 IU) + Calcium (1000 mg)	?	NR	NR	↑? AE WD
Dawson-Hughes, 1991[110]	Fair	RCT	276	Vitamin D (400 IU) + Calcium (377 mg)	?	NR	NR	? Kidney stones, kidney failure/dialysis
Dawson-Hughes, 1997[123]	Fair	RCT	445	Vitamin D (700 IU) + Calcium (500 mg)	NR	NR	NR	? AE WD, GI sx
Dean, 2011[64]	Good	RCT	128	Vitamin D (5000 IU)	NR	NR	NR	? Any AE
Dukas, 2004[128]	Fair	RCT	380	Vitamin D (1 microgram)	?	?	?	↔ Any AE, skin sx
Fedirko, 2009[113]	Fair	RCT	92	Vitamin D (800 IU)	NR	NR	NR	? Any AE
				Vitamin D (800 IU) + Calcium (2.0 g)				
Gallagher, 2001 (STOP IT) [125]	Fair	RCT	246	Vitamin D (0.5 mcg)	?	?	?	↔? Major GI sx ? Deep vein thrombosis, gallstones or cholecystitis, stroke, psychiatric sx
Glendenning, 2012[116]	Fair	RCT	686	Vitamin D (1666.67 IU)*	?	?	↔?	↔? Fractures
Grady, 1991[121]	Fair	RCT	98	Vitamin D (0.5 mcg)	?	?	?	NR

Appendix F Table 16. Summary of Results for Studies of Vitamin D Use

Author, Year (Study)	Final Quality Rating	Study Design	N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Kenny, 2003[117]	Fair	RCT	65	Vitamin D (1000 IU) + Calcium (500 mg)	NR	NR	NR	? Any AE
Komulainen, 1999 (KOS)[112]	Fair	RCT	464	Vitamin D (300 IU) + Calcium (93 mg)	?	?	?	NR
Lappe, 2007[82]	Fair	RCT	1180	Calcium (1500 mg) + Vitamin D (1000 IU)	NR	NR	↓?	? Serious AE, kidney stones
Lappe, 2017[92]	Good	RCT	2303	Calcium (1500 mg) + Vitamin D (2000 IU)	?	NR	?	↔ AE WD, hypercalcemia ↔? Kidney stones ? Serious AEs
Lips, 1996[111]	Fair	RCT	2578	Vitamin D (400 IU)	↔	NR	NR	NR
Manson, 2018 (VITAL)[93]	Good	RCT	25871	Vitamin D (2000 IU)	↔	↔	↔	↔ Kidney stones, kidney failure, GI bleed, extensive non-serious
Murdoch, 2012[118]	Good	RCT	322	Vitamin D (3333.33 IU)*	NR	NR	?	↔ Serious AE, AE WD
Pittas, 2019[135]	Good	RCT	2423	Vitamin D (4000 IU)	↔?	NR	NR	↔ Serious AE
Rake, 2020[138]	Good	RCT	1615	Vitamin D (3333.33 IU)*	↔	↔?	Any incidence: ↔ Morality:?	↔ Any serious, AE WD
Salovaara, 2010 (OSTPRE-FPS)[134]	Fair	RCT	3432	Vitamin D (800 IU) + Calcium (1000 mg)	↔?	NR	NR	NR
Sanders, 2010 (Vital D)[115]	Fair	RCT	2258	Vitamin D (1370 IU)*	↔?	?	?	↔ Any AE ↔? Serious AE
Scragg, 2017 (ViDA)[91]	Good	RCT	5110	Vitamin D (3333 IU)*	↔	↔	↔	↔ Any AE, kidney stones, hypercalcemia, fractures
Toss, 2012[107]	Fair	RCT	56	Vitamin D (1600 IU) + Calcium (1000 mg)	NR	NR	NR	? Any AE, constipation
Trivedi, 2003[87]	Fair	RCT	2686	Vitamin D (1095.9 IU)*	↔	↔	↔	NR
Uusi-Rasi, 2015[120]	Fair	RCT	409	Vitamin D (800 IU)	?	NR	NR	NR
Wactawski-Wende, 2006 (WHI)[78]	Good	RCT	36282	Calcium (1000 mg) + Vitamin D (400 IU)	↓?	↔	↔	↔ Kidney stone, fractures
Witham, 2014[99]	Fair	RCT	68	Vitamin D (1667 IU)*	NR	?	NR	↔ Any AE, GI dx, dizziness, infection, musculoskeletal
Wood, 2012[119]	Fair	RCT	305	Vitamin D (1000 IU) Vitamin D (400 IU)	NR	?	NR	↔ Any AE ↔? Serious AE, AE WD, deep vein thrombosis, cellulitis, pneumonia, severe headache, GI sx

Appendix F Table 16. Summary of Results for Studies of Vitamin D Use

Author, Year (Study)	Final Quality Rating	Study Design	N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Zitterman, 2009[114]	Fair	RCT	200	Vitamin D (3332 IU)	NR	?	NR	NR
Ferraro, 2017 (NHS-II)[143]	Fair	Cohort	116430	Vitamin D (4 dose levels)	NA	NA	NA	↔ Kidney stones (<1000 IU) ↑ Kidney stones (>=1000 IU)
Feskanich, 2002 (NHS-I)[140]	Good	Cohort	121700	Vitamin D (4 dose levels)	NA	NA	NA	↔ Kidney stones
Taylor, 2004 (HPFS)[144]	Fair	Cohort	51529	Vitamin D 4 dose levels)	NA	NA	NA	↔ Kidney stones

*Bolus

Abbreviations: ACM = All-cause mortality; AE = Adverse event; CVD = Cardiovascular disease; GI = Gastrointestinal; HPFS = Health Professionals Follow-up Study; IU = International units; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; mg = Milligram; NA = Not applicable; NHS = Nurses' Health Study; NR = Not reported; OSTPRE-FPS = Osteoporosis Risk Factor and Prevention Fracture Prevention Study; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; RCT = Randomized controlled trial; RECORD = Randomised evaluation of calcium or vitamin D; sx = Symptoms; VCPPS = Vitamin D/Calcium Polyp Prevention Study; VITAL = VITamin D and OmegA-3 TriaL; ViDa = Vitamin D Assessment Study; WHI = Women's Health Initiative; WD = Withdrawal

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])

↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)

↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)

Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 17. Vitamin D Meta-Analysis Results, Showing Primary Analysis of Vitamin D With or Without Adjunctive Calcium First

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	MH	0.94 (0.89 to 1.00)	24	93,003	NA	NA
	Peto	0.94 (0.89 to 1.00)	24	93,003	0	0.0
	REML-KH	**0.94 (0.90 to 0.98)***	24	93,003	0	0.0
	MH, RR rather than OR	RR=0.95 (0.90 to 1.00)	24	93,003	NA	NA
	REML-KH, RR rather than OR	**RR=0.95 (0.91 to 0.98)***	24	93,003	0	0.0
	Full ascert. (MH)	0.94 (0.89 to 1.00)	10	79,652	NA	NA
	Full ascert. (REML-KH)	0.94 (0.8**9** to 1.00)	10	79,652	0	0.0
	Vit. D alone (MH)	0.96 (0.89 to 1.04)	17	50,319	NA	NA
	Vit. D + Ca (MH)	0.93 (0.85 to 1.01)	8	45,322	NA	NA
	Large bolus dosing (MH)	0.97 (0.83 to 1.13)	5	12,351	NA	NA
CVD mortality	MH	0.96 (0.86 to 1.07)	7	74,617	NA	NA
	Peto	0.96 (0.86 to 1.07)	7	74,617	0	0.0
	Full ascert. (MH)	0.99 (0.88 to 1.11)	5	71,551	NA	NA
	Vit. D alone (MH)	0.99 (0.86 to 1.13)	6	38,335	NA	NA
Composite CVD event	MH	1.00 (0.95 to 1.05)	6	72,430	NA	NA
	Peto	1.00 (0.95 to 1.05)	6	72,430	.01	0.0
	Full ascert. (MH)	1.01 (0.95 to 1.07)	3	67,261	NA	NA
	Vit. D alone (MH)	0.98 (0.90 to 1.07)	5	36,148	NA	NA
MI	MH	1.02 (0.91 to 1.14)	5	69,766	NA	NA
	Peto	1.02 (0.91 to 1.14)	5	69,766	0	0.0
	Full ascert. (MH)	1.02 (0.91 to 1.14)	4	69,520	NA	NA
	Vit. D alone (MH)	0.96 (0.80 to 1.17)	4	33,484	NA	NA
Stroke	MH	0.97 (0.87 to 1.09)	8	73,236	NA	NA
	Peto	0.97 (0.87 to 1.09)	8	73,236	0	0.0
	Full ascert. (MH)	0.96 (0.85 to 1.08)	4	69,520	NA	NA
	Vit. D alone (MH)	0.98 (0.92 to 1.04)	7	36,954	NA	NA
Cancer mortality	MH	**0.89 (0.80 to 0.99)***	6	74,237	NA	NA
	REML-KH	0.89 (0.76 to 1.03)	6	74,237	0	0.0
	Full ascert. (MH)	**0.89 (0.80 to 0.99)***	5	71,551	NA	NA
	Stated cancer aim (MH)	**0.87 (0.78 to 0.98)***	3	64,828	NA	NA
	Vit. D alone (MH)	0.88 (0.76 to 1.02)	5	37,955	NA	NA
	Vit. D + Calcium (MH)	0.90 (0.79 to 1.04)	2	38,920	NA	NA
Any cancer incidence	MH	0.97 (0.92 to 1.03)	17	82,019	NA	NA
	REML-KH	0.97 (0.92 to 1.03)	17	82,019	0	0.0
	Full ascert. (MH)	0.96 (0.91 to 1.02)	8	75,129	NA	NA
	Stated cancer aim (MH)	0.97 (0.91 to 1.03)	5	66,147	NA	NA

Appendix F Table 17. Vitamin D Meta-Analysis Results, Showing Primary Analysis of Vitamin D With or Without Adjunctive Calcium First

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
	Vit. D alone (MH)	0.99 (0.92 to 1.07)	14	44,418	NA	NA
	Vit. D + Calcium (MH)	0.97 (0.90 to 1.04)	4	40,239	NA	NA
	Large bolus dosing (MH)	1.04 (0.90 to 1.21)	6	12,673	NA	NA
Colorectal cancer	Peto	1.07 (0.89 to 1.27)	6	70,029	0	0.0
	MH	1.07 (0.89 to 1.27)	6	70,029	NA	NA
	Full ascert. (MH)	1.07 (0.89 to 1.29)	5	67,343	NA	NA
	Vit. D + Calcium (Peto)	1.06 (0.86 to 1.31)	3	39,213	NA	NA
Lung cancer	MH	0.90 (0.71 to 1.14)	4	40,287	NA	NA
	Peto	0.90 (0.71 to 1.14)	4	40,287	0	0.0
	Full ascert. (MH)	0.87 (0.68 to 1.12)	3	37,601	NA	NA
	Vit. D + Calcium (Peto)	0.87 (0.68 to 1.12)	3	37,601	NA	NA
Breast cancer	MH	0.96 (0.87 to 1.06)	5	65,406	NA	NA
	Peto	0.96 (0.87 to 1.06)	5	65,406	0	0.0
	Full ascert. (MH)	0.96 (0.87 to 1.05)	4	65,084	NA	NA
	Vit. D + Calcium (Peto)	0.89 (0.69 to 1.15)	3	39,213	NA	NA
Prostate cancer	NA (1 study, full ascertainment)	0.88 (0.72 to 1.06)	1	25,871	NA	NA

*Statistically significant at $p<0.05$

Abbreviations: CI = Confidence interval; CVD = Cardiovascular disease; MH = Mantel-Haenszel common effects model; MI = Myocardial infarction; NA = Not applicable; No. = Number; OR = Odds ratio; Peto = Peto odds ratio random effects REML model; REML-KH = random effects restricted maximum likelihood model with the Knapp-Hartung adjustment; Vit D = Vitamin D

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Aloia, 2005[130]	Vitamin D + calcium vs. calcium alone	30 mcg + NR Calcium	All-cause mortality	3	All	0.50 (0.04 to 5.55)	1/104 (1.0)	2/104 (1.9)	
Aloia, 2018 (PODA)[102]	Vitamin D vs. placebo	3490 IU	All-cause mortality	3	All	0.33 (0.01 to 8.19)	0/130 (0.0)	1/130 (0.8)	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	All-cause mortality	6.2	All	0.96 (0.82 to 1.13)	415/1306 (31.8)	434/1332 (32.6)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	All-cause mortality	6.2	All	HR=0.93 (0.85 to 1.02)	836/2649 (31.6)	881/2643 (33.3)	0.132
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	All-cause mortality	6.2	All	0.94 (0.80 to 1.11)	421/1343 (31.3)	434/1332 (32.6)	NR
Baeksgaard, 1998[124]	Vitamin D + calcium vs. placebo	560 IU + 1000 mg Calcium	All-cause mortality	2	All	0.32 (0.01 to 8.08)	0/65 (0.0)	1/64 (1.6)	NR
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	All-cause mortality	3.8	All	1.25 (0.58 to 2.69)	15/1130 (1.3)	12/1129 (1.1)	0.56
Bischoff-Ferrari, 2020[139]	Vitamin D alone vs. placebo	2000 IU	All-cause mortality	3	All	1.76 (0.51 to 6.07	7/272 (2.6)	4/270 (1.5)	
Cooper, 2003[127]	Vitamin D + calcium vs. Placebo + calcium	1428.6 IU + 1000 mg Calcium	All-cause mortality	2	All	1.01 (0.02 to 51.47)	0/93 (0.0)	0/94 (0.0)	NR
Dawson-Hughes, 1991[110]	Vitamin D + calcium vs. calcium alone	400 IU + 377 mg Calcium	All-cause mortality	1	All	1.01 (0.02 to 51.20)	0/124 (0.0)	0/125 (0.0)	
Dukas, 2004[128]	Vitamin D vs. placebo	1 microgram	All-cause mortality	0.7	All	0.97 (0.06 to 15.60)	1/193 (0.5)	1/187 (0.5)	0.982
Gallagher, 2001 (STOP IT)[125]	Vitamin D vs placebo	0.5 mcg	All-cause mortality	3	All	1.00 (0.06 to 16.17)	1/123 (0.8)	1/123 (0.8)	NR
Grady, 1991[121]	Vitamin D vs. placebo	0.5 mcg	All-cause mortality	0.5	All	2.94 (0.12 to 73.94)	1/50 (2.0)	0/48 (0.0)	
Komulainen, 1999 (KOS)[112]	Vitamin D + calcium vs calcium alone	300 IU + 93 mg Calcium	All-cause mortality	5	All	0.34 (0.01 to 8.42)	0/112 (0.0)	1/115 (0.9)	

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	All-cause mortality	4	All	0.77 (0.29 to 2.08)	7/1102 (0.6)	9/1095 (0.8)	NR, NS
Lips, 1996[111]	Vitamin D vs. placebo	400 IU	All-cause mortality	3.5	All	0.90 (0.75 to 1.08)	282/1291 (21.8)	306/1287 (23.8)	0.20
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	All-cause mortality	5.3	All	HR=0.99 (0.87 to 1.12)	485/12927 (3.8)	493/12944 (3.8)	NR, NS
Pittas, 2019 (D2d)[135]	Vitamin D vs. placebo	4000 IU	All-cause mortality	3.5	All	IRR=0.97 (0.28 to 3.35)	5/1211 (0.4)	5/1212 (0.4)	NR, NSD
Rake, 2020 (VIDAL)[138]	Vitamin D vs. no vitamin D	3333 IU	All-cause mortality	4	All	1.52 (0.89 to 2.61)	34/802 (4.2)	23/813 (2.8)	0.12
Salovaara, 2010 (OSTPRE-FPS)[134]	Vitamin D + Calcium vs. no intervention	800 IU + 1000 mg Calcium	All-cause mortality	3	All	1.15 (0.55 to 2.43)	15/1718 (0.9)	13/1714 (0.8)	
Sanders, 2010 (Vital D)[115]	Vitamin D vs. placebo	1370 IU	All-cause mortality	4	All	0.84 (0.55 to 1.29)	40/1131 (3.5)	47/1125 (4.2)	
Scragg, 2017 (ViDA)[115]	Vitamin D vs. placebo	3333 IU	All-cause mortality	3.3	All	1.12 (0.78 to 1.60)	65/2558 (2.5)	58/2550 (2.3)	0.53
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	All-cause mortality	5	All	RR=0.88 (0.74 to 1.06)	224/1345 (16.7)	247/1341 (18.4)	0.18
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	All-cause mortality	5	Females	RR=0.91 (0.53 to 1.56)	25/326 (7.7)	27/323 (8.4)	0.73
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	All-cause mortality	5	Males	RR=0.88 (0.73 to 1.07)	199/1019 (19.5)	220/1018 (21.2)	0.19
Uusi-Rasi, 2015[120]	Vitamin D vs. placebo	800 IU	All-cause mortality	2	All	1.00 (0.14 to 7.20)	2/204 (1.0)	2/205 (1.0)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	All-cause mortality	7	All	HR=0.91 (0.83 to 1.01)	744/18176 (4.1)	807/18106 (4.5)	0.07
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	All-cause mortality	11.9	All	HR=0.96 (0.90 to 1.03)	1775/18176 (9.8)	1823/18106 (10.1)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Any cancer deaths	6.2	All	0.96 (0.69 to 1.31)	78/1306 (6.0)	83/1332 (6.2)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Any cancer deaths	6.2	All	HR=0.85 (0.68 to 1.06)	151/2649 (5.7)	178/2643 (6.7)	0.157

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Any cancer deaths	6.2	All	0.86 (0.63 to 1.20)	73/1343 (5.4)	83/1332 (6.2)	NR
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Any cancer deaths	5.3	All	HR=0.83 (0.67 to 1.02)	154/12927 (1.2)	187/12944 (1.4)	NR, NS
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer deaths	3.3	All	HR=0.99 (0.60 to 1.64)	30/2558 (1.2)	30/2550 (1.2)	0.97
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer deaths	5	All	RR=0.86 (0.61 to 1.20)	63/1345 (4.7)	72/1341 (5.4)	0.37
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer deaths	5	Females	RR=0.53 (0.21 to 1.33)	7/326 (2.1)	13/323 (4.0)	0.18
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer deaths	5	Males	RR=0.93 (0.64 to 1.34)	56/1019 (5.5)	59/1018 (5.8)	0.69
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Any cancer deaths	7	All	HR=0.89 (0.77 to 1.03)	344/18176 (1.9)	382/18106 (2.1)	0.12
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Breast cancer deaths	6.2	All	1.79 (0.52 to 6.13)	7/1306 (0.5)	4/1332 (0.3)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Breast cancer deaths	6.2	All	1.07 (0.50 to 2.29)	14/2649 (0.5)	13/2643 (0.5)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Breast cancer deaths	6.2	All	1.74 (0.51 to 5.96)	7/1343 (0.5)	4/1332 (0.3)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Breast cancer deaths	7	All	HR=0.99 (0.55 to 1.76)	23/18176 (0.0)	23/18106 (0.0)	NS, NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Cerebrovascular death	7	All	HR=0.89 (0.62 to 1.29)	54 events/18176	60 events/18106	NS, NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CHD death	7	All	HR=1.01 (0.79 to 1.29)	130/18176 (0.7)	128/18106 (0.7)	NS, NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CHD death	11.9	All	HR=0.99 (0.84 to 1.18)	268/18176 (1.5)	265/18106 (1.5)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Colorectal cancer deaths	6.2	All	2.22 (0.84 to 5.86)	13/1306 (1.0)	6/1332 (0.5)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Colorectal cancer deaths	6.2	All	1.54 (0.76 to 3.10)	20/2649 (0.8)	13/2643 (0.5)	NR

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Colorectal cancer deaths	6.2	All	1.16 (0.39 to 3.45)	7/1343 (0.5)	6/1332 (0.5)	NR
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer deaths	5	All	RR=0.62 (0.24 to 1.60)	7/1345 (0.5)	11/1341 (0.8)	0.33
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer deaths	5	Females	0.11 (0.01 to 2.03)	0/326 (0.0)	4/323 (1.2)	0.04
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer deaths	5	Males	RR=0.97 (0.34 to 2.78)	7/1019 (0.7)	7/1018 (0.7)	0.96
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Colorectal cancer deaths	7	All	HR=0.82 (0.52 to 1.29)	34/18176 (0.2)	41/18106 (0.2)	0.39
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Congestive heart failure deaths	6.2	All	HR=0.70 (0.53 to 0.91)	89/2649 (3.4)	127/2643 (4.8)	0.009
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	CVD deaths	6.2	All	0.99 (0.79 to 1.24)	177/1306 (13.6)	182/1332 (13.7)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	CVD deaths (Fatal cardiac failure, MI, or stroke only)	6.2	All	HR=0.87 (0.73 to 1.03)	256/2649 (9.7)	291/2643 (11.0)	0.11
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	CVD deaths (Any CVD-related)	6.2	All	HR=0.91 (0.79 to 1.05)	350/2649 (13.2)	376/2643 (14.2)	0.175
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	CVD deaths	6.2	All	0.93 (0.75 to 1.17)	173/1343 (12.9)	182/1332 (13.7)	NR
Dukas, 2004[128]	Vitamin D vs. placebo	1 microgram	CVD deaths	0.7	All	0.32 (0.01 to 7.94)	0/193 (0.0)	1/187 (0.5)	NR
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	CVD deaths	5.3	All	HR=1.11 (0.88 to 1.40)	152/12927 (1.2)	138/12944 (1.1)	NR, NS
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	CVD deaths	3.3	All	1.20 (0.60 to 2.38)	18/2558 (0.7)	15/2550 (0.6)	NR
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD deaths	5	All	RR=0.84 (0.65 to 1.10)	101/1345 (7.5)	117/1341 (8.7)	0.20
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD deaths	5	Females	RR=0.99 (0.43 to 2.30)	11/326 (3.4)	11/323 (3.4)	0.99
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD deaths	5	Males	RR=0.83 (0.62 to 1.10)	90/1019 (8.8)	106/1018 (10.4)	0.19
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CVD deaths	7	All	HR=0.92 (0.77 to 1.10)	226/18176 (1.2)	244/18106 (1.3)	NR, NS

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CVD deaths	11.9	All	HR=1.03 (0.92 to 1.17)	549/18176 (3.0)	525/18106 (2.9)	NR, NS
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease deaths	5	All	RR=0.84 (0.56 to 1.27)	42/1345 (3.1)	49/1341 (3.7)	0.41
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease deaths	5	Females	RR=0.99 (0.25 to 3.96)	4/326 (1.2)	4/323 (1.2)	0.99
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease deaths	5	Males	RR=0.83 (0.54 to 1.28)	38/1019 (3.7)	45/1018 (4.4)	0.40
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Lung cancer deaths	6.2	All	0.68 (0.34 to 1.34)	14/1306 (1.1)	21/1332 (1.6)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Lung cancer deaths	6.2	All	0.70 (0.41 to 1.19)	24/2649 (0.9)	34/2643 (1.3)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Lung cancer deaths	6.2	All	0.47 (0.22 to 1.00)	10/1343 (0.7)	21/1332 (1.6)	NR
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer deaths	5	All	RR=0.89 (0.38 to 2.09)	10/1345 (0.7)	11/1341 (0.8)	0.78
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer deaths	5	Females	0.20 (0.01 to 4.12)	0/326 (0.0)	2/323 (0.6)	0.16
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer deaths	5	Males	RR=1.08 (0.44 to 2.65)	10/1019 (1.0)	9/1018 (0.9)	0.87
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	MI, fatal	6.2	All	HR=0.99 (0.73 to 1.33)	87/2649 (3.3)	88/2643 (3.3)	0.92
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	MI, fatal	5.3	All	HR=1.60 (0.84 to 3.06)	24/12927 (0.2)	15/12944 (0.1)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Other/unknown death	7	All	HR=0.95 (0.77 to 1.17)	174/18176 (1.0)	181/18106 (1.0)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Prostate cancer deaths	6.2	All	0.68 (0.11 to 4.07)	2/1306 (0.2)	3/1332 (0.2)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Prostate cancer deaths	6.2	All	1.00 (0.32 to 3.10)	6/2649 (0.2)	6/2643 (0.2)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Prostate cancer deaths	6.2	All	1.32 (0.30 to 5.92)	4/1343 (0.3)	3/1332 (0.2)	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Stroke deaths	6.2	All	HR=0.99 (0.75 to 1.30)	102/2649 (3.9)	101/2643 (3.8)	0.94

Appendix F Table 18. Vitamin D Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Stroke deaths	5.3	All	HR=0.84 (0.46 to 1.54)	19/12927 (0.1)	23/12944 (0.2)	NR, NS
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke deaths	5	All	RR=1.04 (0.61 to 1.77)	28/1345 (2.1)	26/1341 (1.9)	0.89
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke deaths	5	Females	RR=3.98 (0.44 to 35.64)	4/326 (1.2)	1/323 (0.3)	0.22
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke deaths	5	Males	RR=0.92 (0.52 to 1.61)	24/1019 (2.4)	25/1018 (2.5)	0.77

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; mg = Milligrams; MI = Myocardial infarction; NR = Not reported; NS = Not significant; OSTPRE-FPS = Osteoporosis Risk Factor and Prevention Fracture Prevention Study; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; RECORD = Randomised evaluation of calcium or vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study; ViDa = Vitamin D Assessment Study; VITAL = VITamin D and OmegA-3 TriaL; WHI = Women's Health Initiative

Appendix F Table 19. Vitamin D Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Angina	3.3	All	HR=1.43 (0.90 to 2.26)	45/2558 (1.8)	31/2550 (1.2)	0.13
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Angina	7	All	HR=1.08 (0.94 to 1.24)	404/18176 (2.2)	377/18106 (2.1)	0.30
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CHD events	11.9	All	HR=1.03 (0.94 to 1.13)	877/18176 (4.8)	845/18106 (4.7)	NR, NS
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Congestive heart failure	6.2	All	HR=0.75 (0.58 to 0.97)	102 events/2649	136 events/2643	0.027
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Coronary artery bypass graft	5.3	All	HR=0.75 (0.55 to 1.01)	73/12927 (0.6)	98/12944 (0.8)	NR, NS
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	CVD events	6.2	All	HR=0.92 (0.80 to 1.08)	339 events/2649	363 events/2643	0.32
Komulainen, 1999 (KOS)[112]	Vitamin D + calcium vs calcium alone	300 IU + 93 mg Calcium	CVD events	5	All	5.23 (0.25 to 110.08)	2/112 (1.8)	0/115 (0.0)	
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	CVD events	5.3	All	HR=0.97 (0.85 to 1.12)	396/12927 (3.1)	409/12944 (3.2)	0.69
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	CVD events	5.3	Females	HR=0.93 (0.76 to 1.14)	173/6547 (2.6)	186/6538 (2.8)	NR, NS
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	CVD events	5.3	Males	HR=1.01 (0.84 to 1.21)	223/6380 (3.5)	223/6406 (3.5)	NR, NS
Sanders, 2010 (Vital D)[115]	Vitamin D vs. placebo	1370 IU	CVD events	4	All	1.31 (0.63 to 2.70)	17/1131 (1.5)	13/1125 (1.2)	
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	CVD events	3.3	All	1.07 (0.89 to 1.28)	269/2558 (10.5)	253/2550 (9.9)	NR
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD events	5	All	RR=0.90 (0.77 to 1.06)	477/1345 (35.5)	503/1341 (37.5)	0.22

Appendix F Table 19. Vitamin D Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD events	5	Females	RR=0.89 (0.63 to 1.27)	85/326 (26.1)	91/323 (28.2)	0.52
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	CVD events	5	Males	RR=0.91 (0.76 to 1.09)	392/1019 (38.5)	412/1018 (40.5)	0.30
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	CVD events	7	All	HR=1.00 (0.94 to 1.07)	1832/18176 (10.1)	1810/18106 (10.0)	NR
Gallagher, 2001 (STOP IT)[125]	Vitamin D vs placebo	0.5 mcg	Deep venous thrombosis	3	All	0.33 (0.01 to 8.20)	0/123 (0.0)	1/123 (0.8)	NR
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Heart failure	3.3	All	HR=1.19 (0.84 to 1.68)	69/2558 (2.7)	57/2550 (2.2)	0.34
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Heart failure	7	All	HR=0.95 (0.82 to 1.09)	363/18023 (2.0)	381/17960 (2.1)	0.46
Glendenning, 2012[116]	Vitamin D vs placebo	1666.67 IU	Ischemic heart disease	0.75	All	0.47 (0.09 to 2.58)	2/353 (0.6)	4/333 (1.2)	0.44
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Ischemic heart disease	3.3	All	HR=1.22 (0.64 to 2.33)	21/2558 (0.8)	17/2550 (0.7)	0.54
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease	5	All	RR=0.94 (0.77 to 1.15)	224/1345 (16.7)	233/1341 (17.4)	0.57
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease	5	Females	RR=0.79 (0.48 to 1.29)	33/326 (10.1)	40/323 (12.4)	0.35
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Ischemic heart disease	5	Males	RR=0.98 (0.78 to 1.22)	191/1019 (18.7)	193/1018 (19.0)	0.86
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	MI	6.2	All	HR=0.97 (0.75 to 1.26)	114 events/2649	117 events/2643	0.84
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	MI	3.8	All	1.14 (0.41 to 3.16)	8/1130 (0.7)	7/1129 (0.6)	0.80
Gallagher, 2001 (STOP IT)[125]	Vitamin D vs placebo	0.5 mcg	MI	3	All	1.34 (0.29 to 6.14)	4/123 (3.3)	3/123 (2.4)	NR

Appendix F Table 19. Vitamin D Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	MI	5.3	All	HR=0.96 (0.78 to 1.19)	169/12927 (1.3)	176/12944 (1.4)	NR, NS
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	MI	3.3	All	HR=0.90 (0.54 to 1.50)	28/2558 (1.1)	31/2550 (1.2)	0.68
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	MI	7	All	HR=1.05 (0.91 to 1.20)	411/18176 (2.3)	390/18106 (2.2)	0.52
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	MI	11.9	All	HR=1.03 (0.92 to 1.15)	659/18176 (3.6)	637/18106 (3.5)	NR, NS
Witham, 2014[99]	Vitamin D vs. placebo	1667 IU	MI	0.5	All	. (. to .)	0 events/34	1 events/34	NR, NS
Aloia, 2018 (PODA)[102]	Vitamin D vs. placebo	3490 IU	Other CVD	3	All	1.52 (0.42 to 5.53)	6/130 (4.6)	4/130 (3.1)	NR, NS
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Other CVD	5.3	All	HR=0.96 (0.86 to 1.08)	536/12927 (4.1)	558/12944 (4.3)	NR, NS
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Other CVD	3.3	All	HR=0.74 (0.34 to 1.61)	11/2558 (0.4)	15/2550 (0.6)	0.45
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Other CVD	3.3	All	HR=0.93 (0.62 to 1.39)	45/2558 (1.8)	48/2550 (1.9)	0.71
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Other CVD	3.3	All	HR=0.88 (0.51 to 1.52)	24/2558 (0.9)	27/2550 (1.1)	0.65
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Percutaneous transluminal coronary angioplasty	5.3	All	HR=0.97 (0.79 to 1.19)	182/12927 (1.4)	188/12944 (1.5)	NR, NS
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Stroke	6.2	All	HR=1.06 (0.85 to 1.32)	160 events/2649	149 events/2643	0.61
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	Stroke	3.8	All	1.80 (0.60 to 5.40)	9/1130 (0.8)	5/1129 (0.4)	0.28
Gallagher, 2001 (STOP IT)[125]	Vitamin D vs placebo	0.5 mcg	Stroke	3	All	1.34 (0.29 to 6.14)	4/123 (3.3)	3/123 (2.4)	NR

Appendix F Table 19. Vitamin D Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Glendenning, 2012[116]	Vitamin D vs placebo	1666.67 IU	Stroke	0.75	All	1.42 (0.24 to 8.54)	3/353 (0.8)	2/333 (0.6)	1.00
Grady, 1991[121]	Vitamin D vs. placebo	0.5 mcg	Stroke	0.5	All	0.31 (0.01 to 7.89)	0/50 (0.0)	1/48 (2.1)	
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Stroke	5.3	All	HR=0.95 (0.76 to 1.20)	141/12927 (1.1)	149/12944 (1.2)	NR, NS
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Stroke	3.3	All	HR=0.95 (0.55 to 1.62)	26/2558 (1.0)	27/2550 (1.1)	0.84
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke	5	All	RR=1.02 (0.77 to 1.36)	105/1345 (7.8)	101/1341 (7.5)	0.87
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke	5	Females	RR=1.19 (0.60 to 2.37)	19/326 (5.8)	16/323 (5.0)	0.62
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Stroke	5	Males	RR=0.99 (0.72 to 1.36)	86/1019 (8.4)	85/1018 (8.3)	0.96
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Stroke	7	All	HR=0.95 (0.82 to 1.10)	362/18176 (2.0)	377/18106 (2.1)	0.51
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Stroke	11.9	All	HR=1.04 (0.93 to 1.16)	690/18176 (3.8)	659/18106 (3.6)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Stroke, Hemorrhagic	7	All	HR=0.84 (0.59 to 1.19)	58/18176 (0.3)	68/18106 (0.4)	0.33
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Stroke, Ischemic	7	All	HR=0.98 (0.82 to 1.18)	225/18176 (1.2)	228/18106 (1.3)	0.84
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	Transient ischemic attack	3.8	All	3.00 (0.31 to 28.91)	3/1130 (0.3)	1/1129 (0.1)	0.62
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Transient ischemic attack	7	All	HR=1.16 (0.95 to 1.42)	213/18176 (1.2)	182/18106 (1.0)	0.13
Aloia, 2018 (PODA)[102]	Vitamin D vs. placebo	3490 IU	Vascular disorders (unspecified)	3	All	2.30 (0.84 to 6.24)	13/130 (10.0)	6/130 (4.6)	NR, NS

*Studies providing estimates other than ORs display effect type

Appendix F Table 19. Vitamin D Cardiovascular Disease Results

Abbreviations: CG = Control group; CHD = Coronary heart disease; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; mcg = Microgram; mg = Milligram; MI = Myocardial infarction; NR = Not reported; NS = Not significant; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; VCPPS = Vitamin D/Calcium Polyp Prevention Study; ViDa = Vitamin D Assessment Study; VITAL = VITamin D and OmegA-3 TriaL; WHI = Women's Health Initiative

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Anal cancer	7	All	HR=0.20 (0.02 to 1.71)	1/17343 (0.0)	5/17327 (0.0)	0.29
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer (excluding skin)	3.3	All	HR=0.99 (0.76 to 1.29)	111/2558 (4.3)	111/2550 (4.4)	0.96
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer (excluding skin)	5	All	RR=1.11 (0.86 to 1.42)	144/1345 (10.8)	130/1341 (9.6)	0.43
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer (excluding skin)	5	Females	RR=0.77 (0.39 to 1.55)	15/326 (4.6)	19/323 (5.9)	0.47
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer (excluding skin)	5	Males	RR=1.17 (0.89 to 1.54)	129/1019 (12.7)	111/1018 (10.9)	0.26
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer (invasive only)	3.3	All	HR=0.97 (0.76 to 1.24)	128/2558 (5.0)	131/2550 (5.1)	0.80
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Any cancer incidence	6.2	All	HR=1.07 (0.92 to 1.25)	338/2649 (12.8)	315/2643 (11.9)	0.376
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Any cancer incidence	6.2	All	. (. to .)	369 events/2649	354 events/2643	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Any cancer incidence	6.2	All	1.14 (0.90 to 1.44)	172/1343 (12.8)	152/1332 (11.4)	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Any cancer incidence	6.2	All	1.13 (0.89 to 1.43)	166/1306 (12.7)	152/1332 (11.4)	NR
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	Any cancer incidence	3.8	All	0.76 (0.51 to 1.12)	47/1130 (4.2)	61/1129 (5.4)	0.17
Gallagher, 2001 (STOP IT)[125]	Vitamin D vs placebo	0.5 mcg	Any cancer incidence	3	All	1.21 (0.36 to 4.08)	6/123 (4.9)	5/123 (4.1)	NR
Glendenning, 2012[116]	Vitamin D vs placebo	1666.67 IU	Any cancer incidence	0.75	All	1.21 (0.60 to 2.41)	19/353 (5.4)	15/333 (4.5)	0.73

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Grady, 1991[121]	Vitamin D vs. placebo	0.5 mcg	Any cancer incidence	0.5	All	2.94 (0.12 to 73.94)	1/50 (2.0)	0/48 (0.0)	
Komulainen, 1999 (KOS)[112]	Vitamin D + calcium vs calcium alone	300 IU + 93 mg Calcium	Any cancer incidence	5	All	0.68 (0.11 to 4.14)	2/112 (1.8)	3/115 (2.6)	
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Any cancer incidence	4	All	RR=0.40 (0.20 to 0.82)	13/446 (2.9)	20/288 (6.9)	0.013
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Any cancer incidence	4	All	HR=0.70 (0.47 to 1.02)	45/1102 (4.1)	64/1095 (5.8)	0.06
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Any cancer incidence	5.3	All	HR=0.96 (0.88 to 1.06)	793/12927 (6.1)	824/12944 (6.4)	0.47
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Any cancer incidence	5.3	Females	HR=1.02 (0.87 to 1.18)	341/6547 (5.2)	336/6538 (5.1)	NR, NS
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Any cancer incidence	5.3	Males	HR=0.93 (0.82 to 1.06)	452/6380 (7.1)	488/6406 (7.6)	NR, NS
Murdoch, 2012[118]	Vitamin D vs. placebo	3333.33 IU	Any cancer incidence	1.5	All	4.08 (0.45 to 36.88)	4/161 (2.5)	1/161 (0.6)	
Rake, 2020 (VIDAL)[138]	Vitamin D vs. no vitamin D	3333 IU	Any cancer incidence	2	All	0.85 (0.47 to 1.53)	21/802 (2.6)	25/813 (3.1)	0.6
Sanders, 2010 (Vital D)[115]	Vitamin D vs. placebo	1370 IU	Any cancer incidence	4	All	0.69 (0.26 to 1.83)	7/1131 (0.6)	10/1125 (0.9)	
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer incidence	3.3	All	HR=1.01 (0.81 to 1.25)	165/2558 (6.5)	163/2550 (6.4)	0.95
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer incidence	3.3	Females	HR=1.09 (0.75 to 1.59)	57/1046 (5.4)	53/1093 (4.8)	0.66
Scragg, 2017 (ViDA)[91]	Vitamin D vs. placebo	3333 IU	Any cancer incidence	3.3	Males	HR=0.96 (0.74 to 1.25)	108/1512 (7.1)	110/1457 (7.5)	0.76
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer incidence	5	All	RR=1.09 (0.86 to 1.36)	188/1345 (14.0)	173/1341 (12.9)	0.47

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer incidence	5	Females	RR=0.95 (0.54 to 1.68)	25/326 (7.2)	26/323 (8.0)	0.85
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Any cancer incidence	5	Males	RR=1.11 (0.87 to 1.42)	163/1019 (16.0)	147/1018 (14.4)	0.39
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Any cancer incidence	7	All	HR=0.98 (0.90 to 1.05)	1306/17343 (7.5)	1333/17327 (7.7)	0.78
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Any cancer incidence	11.9	All	HR=0.97 (0.92 to 1.02)	2554/18176 (14.1)	2617/18106 (14.5)	NR, NS
Wood, 2012[119]	Vitamin D vs placebo	400 IU	Any cancer incidence	1	All	1.00 (0.02 to 50.88)	0/102 (0.0)	0/102 (0.0)	
Wood, 2012[119]	Vitamin D vs placebo	1000 IU	Any cancer incidence	1	All	3.06 (0.12 to 76.00)	1/101 (1.0)	0/102 (0.0)	
Zitterman, 2009[114]	Vitamin D vs. placebo	3332 IU	Any cancer incidence	1	All	0.33 (0.01 to 8.30)	0/82 (0.0)	1/83 (1.2)	
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Biliary tract cancer	7	All	HR=1.43 (0.61 to 3.35)	13/17343 (0.1)	9/17327 (0.1)	0.88
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Bone, connective tissue, and skin cancer incidence (overall)	7	All	HR=0.96 (0.85 to 1.07)	563/17343 (3.2)	589/17327 (3.4)	0.12
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Brain cancer	7	All	HR=1.58 (0.72 to 3.49)	16/17343 (0.1)	10/17327 (0.1)	0.13
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Breast cancer	6.2	All	. (. to .)	43 events/2649	37 events/2643	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Breast cancer	6.2	All	. (. to .)	23 events/1343	16 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Breast cancer	6.2	All	. (. to .)	20 events/1306	16 events/1332	NR
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Breast cancer	4	All	0.40 (0.13 to 1.23)	5/446 (1.1)	8/288 (2.8)	NR

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Breast cancer	4	All	HR=0.79 (0.43 to 1.43)	19/1102 (1.7)	24/1095 (2.2)	NR, NS
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Breast cancer	5.3	All	HR=1.02 (0.79 to 1.31)	124/12927 (1.0)	122/12944 (0.9)	NR, NS
Murdoch, 2012[118]	Vitamin D vs. placebo	3333.33 IU	Breast cancer	1.5	All	3.04 (0.31 to 29.52)	3/161 (1.9)	1/161 (0.6)	
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Breast cancer	7	All	HR=0.96 (0.86 to 1.07)	668/18176 (0.5)	693/18106 (0.5)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Breast cancer-in situ	11.9	All	HR=0.82 (0.68 to 0.99)	198/18176 (1.1)	238/18106 (1.3)	<0.05
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Breast cancer-invasive	11.9	All	HR=1.04 (0.94 to 1.14)	851/18176 (4.7)	816/18106 (4.5)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Cervical cancer	7	All	12.99 (0.73 to 230.65)	6/17343 (0.0)	0/17327 (0.0)	
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Colon cancer	7	All	HR=0.98 (0.76 to 1.27)	117/17343 (0.7)	118/17327 (0.7)	0.72
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Colorectal cancer	6.2	All	. (. to .)	41 events/2649	30 events/2643	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Colorectal cancer	6.2	All	. (. to .)	17 events/1343	8 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Colorectal cancer	6.2	All	. (. to .)	24 events/1306	8 events/1332	NR
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	Colorectal cancer	3.8	All	1.50 (0.25 to 8.99)	3/1130 (0.3)	2/1129 (0.2)	1.00
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Colorectal cancer	4	All	0.32 (0.03 to 3.56)	1/446 (0.2)	2/288 (0.7)	NR
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Colorectal cancer	4	All	0.66 (0.19 to 2.35)	4/1102 (0.4)	6/1095 (0.5)	NR

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Colorectal cancer	5.3	All	HR=1.09 (0.73 to 1.62)	51/12927 (0.4)	47/12944 (0.4)	NR, NS
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer	5	All	RR=1.02 (0.60 to 1.74)	28/1345 (2.1)	27/1341 (2.0)	0.94
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer	5	Females	RR=0.49 (0.12 to 1.98)	3/326 (0.9)	6/323 (1.9)	0.32
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Colorectal cancer	5	Males	RR=1.18 (0.65 to 2.12)	25/1019 (2.5)	21/1018 (2.1)	0.59
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Colorectal cancer	7	All	HR=1.08 (0.86 to 1.34)	168/18176 (0.9)	154/18106 (0.9)	0.51
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Colorectal cancer	11.9	All	HR=0.95 (0.80 to 1.13)	256/18176 (1.4)	267/18106 (1.5)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Digestive organs and peritoneum (overall), cancer	7	All	HR=0.94 (0.78 to 1.13)	227/17343 (1.3)	240/17327 (1.4)	0.69
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Endometrium	4	All	0.66 (0.11 to 3.97)	2/1102 (0.2)	3/1095 (0.3)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Endometrium	7	All	HR=0.95 (0.71 to 1.28)	85/17343 (0.5)	88/17327 (0.5)	0.56
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Esophageal cancer	7	All	HR=0.50 (0.19 to 1.32)	6/17343 (0.0)	12/17327 (0.1)	0.09
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Eye cancer	7	All	HR=0.99 (0.25 to 3.94)	4/17343 (0.0)	4/17327 (0.0)	0.93
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Gallbladder cancer	7	All	HR=1.04 (0.15 to 7.38)	2/17343 (0.0)	2/17327 (0.0)	0.95
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Genital cancer	7	All	HR=1.07 (0.85 to 1.35)	155/17343 (0.9)	144/17327 (0.8)	0.78

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Genital cancer	7	All	HR=2.56 (0.68 to 9.65)	8/17343 (0.0)	3/17327 (0.0)	0.50
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Laryngeal cancer	7	All	HR=1.45 (0.24 to 8.69)	3/17343 (0.0)	2/17327 (0.0)	0.77
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Leukemia	7	All	HR=0.97 (0.58 to 1.63)	28/17343 (0.2)	29/17327 (0.2)	0.92
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Liver cancer	7	All	HR=0.45 (0.14 to 1.47)	4/17343 (0.0)	9/17327 (0.1)	0.36
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Lung cancer	6.2	All	. (. to .)	24 events/2649	32 events/2643	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Lung cancer	6.2	All	. (. to .)	14 events/1343	18 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Lung cancer	6.2	All	. (. to .)	10 events/1306	18 events/1332	NR
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Lung cancer	4	All	0.21 (0.02 to 2.06)	1/446 (0.2)	3/288 (1.0)	NR
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Lung cancer	4	All	2.49 (0.48 to 12.87)	5/1102 (0.5)	2/1095 (0.2)	NR
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer	5	All	RR=1.12 (0.56 to 2.25)	17/1345 (1.3)	15/1341 (1.1)	0.75
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer	5	Females	0.20 (0.01 to 4.12)	0/326 (0.0)	2/323 (0.6)	0.16
Trivedi, 2003[87]	Vitamin D vs. placebo	1095.9 IU	Lung cancer	5	Males	RR=1.29 (0.62 to 2.68)	17/1019 (1.7)	13/1018 (1.3)	0.49
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Lung cancer	7	All	HR=0.86 (0.67 to 1.12)	109/17343 (0.6)	126/17327 (0.7)	0.28
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Lung cancer	11.1	All	HR=0.91 (0.71 to 1.17)	207/18176 (1.1)	241/18106 (1.3)	NR, NS

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Lymph, leukemia, myeloma	4	All	0.32 (0.06 to 1.76)	2/446 (0.4)	4/288 (1.4)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Lymphatic and hematopoietic tissue malignant cancer	7	All	HR=7.00 (0.61 to 1.04)	97/17343 (0.6)	122/17327 (0.7)	0.16
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Lymphoma, Hodgkin's	7	All	HR=0.26 (0.06 to 1.23)	2/17343 (0.0)	8/17327 (0.0)	0.14
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Lymphoma, non-Hodgkin's	7	All	HR=0.72 (0.49 to 1.05)	47/17343 (0.3)	65/17327 (0.4)	0.20
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Melanoma skin cancer	4	All	0.50 (0.09 to 2.71)	2/1102 (0.2)	4/1095 (0.4)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Melanoma skin cancer	7	All	HR=0.91 (0.63 to 1.32)	54/17343 (0.3)	60/17327 (0.3)	0.27
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Multiple myeloma	7	All	HR=1.09 (0.59 to 2.01)	21/17343 (0.1)	20/17327 (0.1)	0.59
Aloia, 2018 (PODA)[102]	Vitamin D vs. placebo	3490 IU	Neoplasms (benign, malignant, unknown)	3	All	1.00 (0.38 to 2.61)	9/130 (6.9)	9/130 (6.9)	NR, NS
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Neuroendocrine cancer	4	All	0.50 (0.09 to 2.71)	2/1102 (0.2)	4/1095 (0.4)	NR
Baron, 2015 (VCPPS)[90]	Vitamin D vs. no vitamin D	1000 IU + 1200 mg Calcium	Non-CRC cancer incidence	3.8	All	0.73 (0.49 to 1.10)	44/1130 (3.9)	59/1129 (5.2)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Oral cavity cancer	7	All	HR=1.43 (0.51 to 4.02)	9/17343 (0.1)	6/17327 (0.0)	0.64
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Oral cavity, lip, pharynx cancer	7	All	HR=1.33 (0.61 to 2.89)	15/17343 (0.1)	11/17327 (0.1)	0.34
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Other cancer	7	All	HR=1.86 (0.34 to 10.17)	4/17343 (0.0)	2/17327 (0.0)	0.48

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lappe, 2017[92]	Calcium + vitamin D vs. placebo	1500 mg + 2000 IU Vitamin D	Ovarian cancer	4	All	0.09 (0.00 to 1.63)	0/1102 (0.0)	5/1095 (0.5)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Ovarian cancer	7	All	HR=0.98 (0.66 to 1.44)	50/17343 (0.3)	51/17327 (0.3)	0.98
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Pancreatic cancer	7	All	HR=0.88 (0.55 to 1.41)	32/17343 (0.2)	36/17327 (0.2)	0.46
Avenell, 2012 (RECORD)[88]	Vitamin D vs. no vitamin D	800 IU + 1000 mg Calcium	Prostate cancer	6.2	All	. (. to .)	17 events/2649	12 events/2643	NR
Avenell, 2012 (RECORD)[88]	Vitamin D vs. placebo	800 IU	Prostate cancer	6.2	All	. (. to .)	9 events/1343	8 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium + vitamin D vs. placebo	1000 mg + 800 IU Vitamin D	Prostate cancer	6.2	All	. (. to .)	8 events/1306	8 events/1332	NR
Manson, 2018 (VITAL)[93]	Vitamin D vs. placebo	2000 IU	Prostate cancer	5.3	All	HR=0.88 (0.72 to 1.07)	192/12927 (1.5)	219/12944 (1.7)	NR, NS
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Rectal cancer	7	All	HR=1.42 (0.88 to 2.28)	41/17343 (0.2)	29/17327 (0.2)	0.16
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Renal cell carcinoma	7	All	HR=1.02 (0.60 to 1.74)	28/17343 (0.2)	27/17327 (0.2)	0.26
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Renal cell carcinoma	7	All	HR=1.17 (1.02 to 1.34)	449/18176 (2.5)	381/18106 (2.1)	0.02
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Respiratory tract cancer	7	All	HR=0.87 (0.68 to 1.12)	114/17343 (0.7)	130/17327 (0.8)	0.29
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Respiratory tract cancer	7	All	HR=1.92 (0.17 to 21.24)	2/17343 (0.0)	1/17327 (0.0)	0.71
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Retroperitoneum	7	All	HR=0.86 (0.26 to 2.77)	5/17343 (0.0)	6/17327 (0.0)	0.89

Appendix F Table 20. Vitamin D Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Small intestine	7	All	HR=1.88 (0.34 to 10.28)	4/17343 (0.0)	2/17327 (0.0)	0.51
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Thyroid cancer	7	All	HR=0.90 (0.49 to 1.65)	20/17343 (0.1)	22/17327 (0.1)	0.97
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Tongue cancer	7	All	HR=0.25 (0.03 to 2.20)	1/17343 (0.0)	4/17327 (0.0)	0.34
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Unknown primary site	7	All	HR=1.37 (0.71 to 2.66)	21/17343 (0.1)	15/17327 (0.1)	0.07
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Ureteral cancer	7	All	5.00 (0.24 to 104.07)	2/17343 (0.0)	0/17327 (0.0)	
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Urinary bladder cancer	7	All	HR=1.49 (0.88 to 2.53)	34/17343 (0.2)	23/17327 (0.1)	0.12
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Urinary organs, other	7	All	HR=0.48 (0.09 to 2.62)	2/17343 (0.0)	4/17327 (0.0)	0.72
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Urinary tract cancer	7	All	HR=1.24 (0.86 to 1.78)	66/17343 (0.4)	53/17327 (0.3)	0.04
Lappe, 2007[82]	Calcium + vitamin D vs. placebo	1500 mg + 1000 IU Vitamin D	Uterine cancer	4	All	1.94 (0.08 to 47.85)	1/446 (0.2)	0/288 (0.0)	NR
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Uterine cancer	7	All	HR=1.25 (0.49 to 3.17)	10/17343 (0.1)	8/17327 (0.0)	0.70
Wactawski-Wende, 2006 (WHI)[78]	Calcium + vitamin D vs. placebo	1000 mg + 400 IU Vitamin D	Vulvar cancer	7	All	HR=0.99 (0.20 to 4.91)	3 events/17343	3 events/17327	0.97

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; CG = Control group; HR = Hazard ratio; IG = Intervention group; IU = International units; KOS = Kuopio Osteoporosis Risk Factor and Prevention Study; mg = Milligram; NR = Not reported; Not significant; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; RECORD = Randomised evaluation of calcium or vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study; ViDa = Vitamin D Assessment Study; VITAL = VITamin D and OmegA-3 TriaL; WHI = Women's Health Initiative

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Bischoff-Ferrari, 2020 (DO-HEALTH)[139]	2000 IU	Vitamin D vs. No vitamin D	Any AE	3	All	0.71 (0.38 to 1.31)	17/1076 (1.6)	26/1081 (2.4)
Dean, 2011[64]	5000 IU	Vitamin D vs. placebo	Any AE	0.12	All	0.34 (0.01 to 8.47)	0/63 (0.0)	1/65 (1.5)
Dukas, 2004[128]	1 microgram	Vitamin D vs. placebo	Any AE	0.7	All	0.81 (0.54 to 1.23)	75/193 (38.9)	82/187 (43.9)
Fedirko, 2009[113]	800 IU + 2 g Calcium	Vitamin D + calcium vs. placebo	Any AE	0.5	All	1.00 (0.02 to 52.53)	0/23 (0.0)	0/23 (0.0)
Fedirko, 2009[113]	800 IU	Vitamin D vs. placebo	Any AE	0.5	All	1.00 (0.02 to 52.53)	0/23 (0.0)	0/23 (0.0)
Kenny, 2003[117]	1000 IU + 500 mg Calcium	Vitamin D + calcium vs. calcium alone	Any AE	0.5	All	1.07 (0.02 to 55.57)	0/29 (0.0)	0/31 (0.0)
Sanders, 2010 (Vital D)[115]	1370 IU	Vitamin D vs. placebo	Any AE	4	All	1.14 (0.92 to 1.40)	223/1131 (19.7)	200/1125 (17.8)
Scragg, 2017 (ViDA)[91]	3333 IU	Vitamin D vs. placebo	Any AE	3.3	All	HR=1.03 (0.90 to 1.18)	419/2539 (16.5)	399/2517 (15.8)
Toss, 2012[107]	1600 IU + 1000 mg Calcium	Vitamin D + Calcium vs. Calcium alone	Any AE: NSD between groups	1	All	. (. to .)	./22 (.)	./23 (.)
Witham, 2014[99]	1667 IU	Vitamin D vs. placebo	Any AE	0.5	All	. (. to .)	35 events/34	38 events/34
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Any AE	1	All	. (. to .)	17 events/102	20 events/102
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Any AE	1	All	. (. to .)	15 events/101	20 events/102
Baeksgaard, 1998[124]	560 IU + 1000 mg Calcium	Vitamin D + calcium vs. placebo	Constipation	2	All	5.08 (0.24 to 107.89)	2/65 (3.1)	0/64 (0.0)
Baeksgaard, 1998[124]	+ 1000 mg Calcium	Vitamin D + calcium + multivitamin vs. placebo	Constipation	2	All	4.71 (0.22 to 99.94)	2/70 (2.9)	0/64 (0.0)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Constipation	5.3	All	HR=0.99 (0.95 to 1.03)	5133/12927 (39.7)	5162/12944 (39.9)
Toss, 2012[107]	1600 IU + 1000 mg Calcium	Vitamin D + Calcium vs. Calcium alone	Constipation	1	All	1.06 (0.26 to 4.32)	5/22 (22.7)	5/23 (21.7)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Diarrhea	5.3	All	HR=0.97 (0.94 to 1.01)	5511/12927 (42.6)	5668/12944 (43.8)

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Bischoff-Ferrari, 2020 (DO-HEALTH)[139]	2000 IU	Vitamin D vs. No vitamin D	Disorders of mineral metabolism	3	All	. (. to .)	1.4/ p-y	1.2/ p-y
Gallagher, 2001 (STOP IT)[125]	0.5 mcg	Vitamin D vs placebo	Gallstones or cholecystitis	3	All	7.17 (0.37 to 140.37)	3/123 (2.4)	0/123 (0.0)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Gastrointestinal bleeding	5.3	All	HR=0.84 (0.73 to 0.98)	341/12927 (2.6)	403/12944 (3.1)
Avenell, 2012 (RECORD)[88]	800 IU + 1000 mg Calcium	Vitamin D vs. no vitamin D	Gastrointestinal symptoms	3.75	All	0.93 (0.80 to 1.08)	363/2649 (13.7)	386/2643 (14.5)
Dawson-Hughes, 1997[123]	700 IU + 500 mg Calcium	Vitamin D + calcium vs. placebo	Gastrointestinal symptoms	3	All	2.19 (0.40 to 12.08)	4/187 (2.1)	2/202 (1.0)
Witham, 2014[99]	1667 IU	Vitamin D vs. placebo	Gastrointestinal symptoms	0.5	All	. (. to .)	4 events/34	5 events/34
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Gastrointestinal symptoms	1	All	7.21 (0.37 to 141.40)	3/102 (2.9)	0/102 (0.0)
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Gastrointestinal symptoms	1	All	3.06 (0.12 to 76.00)	1/101 (1.0)	0/102 (0.0)
Aloia, 2018 (PODA)[102]	3490 IU	Vitamin D vs. placebo	GI disease	3	All	0.94 (0.48 to 1.84)	20/130 (15.4)	21/130 (16.2)
Brisson, 2017[94]	1000 IU	Vitamin D vs. placebo	Kidney disease	1	All	1.00 (0.02 to 50.91)	0/96 (0.0)	0/96 (0.0)
Brisson, 2017[94]	2000 IU	Vitamin D vs. placebo	Kidney disease	1	All	0.97 (0.02 to 49.37)	0/99 (0.0)	0/96 (0.0)
Brisson, 2017[94]	3000 IU	Vitamin D vs. placebo	Kidney disease	1	All	0.96 (0.02 to 48.87)	0/100 (0.0)	0/96 (0.0)
Dawson-Hughes, 1991[110]	400 IU + 377 mg Calcium	Vitamin D + calcium vs. calcium alone	Kidney failure or dialysis	1	All	0.33 (0.01 to 8.26)	0/124 (0.0)	1/125 (0.8)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Kidney failure or dialysis	5.3	All	HR=0.97 (0.72 to 1.30)	85/12927 (0.7)	88/12944 (0.7)
Baron, 2015 (VCPPS)[90]	1000 IU + 1200 mg Calcium	Vitamin D vs. no vitamin D	Kidney stones	3.8	All	0.67 (0.37 to 1.21)	19/1130 (1.7)	28/1129 (2.5)
Bischoff-Ferrari, 2020 (DO-HEALTH)[139]	2000 IU	Vitamin D vs. No vitamin D	Kidney stones	3	All	. (. to .)	.7/ p-y	.7/ p-y
Dawson-Hughes, 1991[110]	400 IU + 377 mg Calcium	Vitamin D + calcium vs. calcium alone	Kidney stones	1	All	1.01 (0.02 to 51.20)	0/124 (0.0)	0/125 (0.0)
Ferraro, 2017 (NHS-II)[143]	IU	Vitamin D 1-399 vs no vitamin D	Kidney stones	20	All	HR=0.94 (0.84 to 1.04)	770 events/.	1357 events/.

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Ferraro, 2017 (NHS-II)[143]	IU	Vitamin D 400-599 vs no vitamin D	Kidney stones	20	All	HR=1.00 (0.89 to 1.13)	635 events/.	1357 events/.
Ferraro, 2017 (NHS-II)[143]	IU	Vitamin D 600-999 vs no vitamin D	Kidney stones	20	All	HR=1.10 (0.92 to 1.32)	196 events/.	1357 events/.
Ferraro, 2017 (NHS-II)[143]	IU	Vitamin D >=1000 vs no vitamin D	Kidney stones	20	All	HR=1.38 (1.03 to 1.85)	56 events/.	1357 events/.
Feskanich, 2002 (NHS-I)[140]	IU	Vitamin D 1-399 IU/day vs. no vitamin D	Kidney stones	26	All	HR=0.89 (0.76 to 1.04)	250 events/.	671 events/.
Feskanich, 2002 (NHS-I)[140]	IU	Vitamin D 400-599 IU/day vs. no vitamin D	Kidney stones	26	All	HR=1.09 (0.94 to 1.27)	340 events/.	671 events/.
Feskanich, 2002 (NHS-I)[140]	IU	Vitamin D 600-999 IU/day vs. no vitamin D	Kidney stones	26	All	HR=1.05 (0.83 to 1.33)	62 events/.	671 events/.
Feskanich, 2002 (NHS-I)[140]	IU	Vitamin D >=1000 IU/day vs. no vitamin D	Kidney stones	26	All	HR=1.03 (0.71 to 1.51)	8 events/.	671 events/.
Gallagher, 2001 (STOP IT)[125]	0.5 mcg	Vitamin D vs placebo	Kidney stones	3	All	0.33 (0.01 to 8.20)	0/123 (0.0)	1/123 (0.8)
Lappe, 2007[82]	2000 IU + 1500 mg calcium	Vitamin D + calcium vs. placebo	Kidney stones	4	All	0.64 (0.04 to 10.35)	1/446 (0.2)	1/288 (0.3)
Lappe, 2017[92]	2000 IU + 1500 mg calcium	Vitamin D + calcium vs. placebo	Kidney stones	4	All	1.60 (0.72 to 3.54)	16/1102 (1.4)	10/1095 (0.9)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Kidney stones	5.3	All	HR=1.12 (0.99 to 1.28)	477/12927 (3.7)	426/12944 (3.3)
Scragg, 2017 (ViDA)[91]	3333 IU	Vitamin D vs. placebo	Kidney stones	3.3	All	HR=0.62 (0.24 to 1.26)	7/2558 (0.3)	11/2550 (0.4)
Scragg, 2017 (ViDA)[91]	3333 IU	Vitamin D vs. placebo	Kidney stones	3.3	All	HR=0.90 (0.66 to 1.23)	76/2539 (3.0)	82/2517 (3.3)
Taylor, 2004 (HPFS)[144]	IU	Vitamin D <400 IU/day vs no use	Kidney stones	26	All	HR=0.90 (0.78 to 1.04)	343 events/.	1068 events/.
Taylor, 2004 (HPFS)[144]	IU	Vitamin D 400-599 IU/day vs no use	Kidney stones	26	All	HR=1.00 (0.86 to 1.15)	426 events/.	1068 events/.
Taylor, 2004 (HPFS)[144]	IU	Vitamin D 600-999 IU/day vs no use	Kidney stones	26	All	HR=0.93 (0.74 to 1.18)	98 events/.	1068 events/.
Taylor, 2004 (HPFS)[144]	IU	Vitamin D >=1000 IU/day vs no use	Kidney stones	26	All	HR=1.23 (0.81 to 1.86)	28 events/.	1068 events/.

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Wactawski-Wende, 2006 (WHI)[78]	400 IU	Vitamin D + calcium vs. placebo	Kidney stones	7	All	HR=1.17 (1.02 to 1.34)	449/18176 (0.3)	381/18106 (0.3)
Gallagher, 2001 (STOP IT)[125]	0.5 mcg	Vitamin D vs placebo	Major GI AEs	3	All	0.89 (0.46 to 1.73)	20/123 (16.3)	22/123 (17.9)
Baeksgaard, 1998[124]	560 IU + 1000 mg Calcium	Vitamin D + calcium vs. placebo	Nausea	2	All	0.19 (0.01 to 4.05)	0/65 (0.0)	2/64 (3.1)
Baeksgaard, 1998[124]	+ 1000 mg Calcium	Vitamin D + calcium + multivitamin vs. placebo	Nausea	2	All	0.18 (0.01 to 3.76)	0/70 (0.0)	2/64 (3.1)
Brisson, 2017[94]	1000 IU	Vitamin D vs. placebo	Nausea	1	All	1.29 (0.73 to 2.30)	43/96 (44.8)	37/96 (38.5)
Brisson, 2017[94]	2000 IU	Vitamin D vs. placebo	Nausea	1	All	0.95 (0.53 to 1.70)	37/99 (37.4)	37/96 (38.5)
Brisson, 2017[94]	3000 IU	Vitamin D vs. placebo	Nausea	1	All	0.72 (0.40 to 1.29)	31/100 (31.0)	37/96 (38.5)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Nausea	5.3	All	HR=0.98 (0.94 to 1.03)	3519/12927 (27.2)	3589/12944 (27.7)
Aloia, 2018 (PODA)[102]	3490 IU	Vitamin D vs. placebo	Non-serious: General disorders and administration site conditions (NS); Hypercalcemia (NS); Hypercalciuria (NS); Infections (NS); Injury, poisoning, and procedural complications (NS); Metabolism and nutrition disorders (NS); Musculoskeletal and connective tissue disorders (NS); Nervous system disorders (NS); Responiratory, thoracic, and mediastinal disorders (NS); Surgical and medical procedures (NS)	3	All	. (. to .)	./130 (.)	9 events/130
Baron, 2015 (VCPPS)[90]	1000 IU + 1200 mg Calcium	Vitamin D vs. no vitamin D	Non-serious: Hypercalcemia (NS); Hypercreatininemia (NS)	3	All	. (. to .)	./1115 (.)	./1113 (.)

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Brisson, 2017[94]	1000 IU	Vitamin D vs. placebo	Fatigue (NS), headache (NS), weakness (NS), decreasing appetite (NS), arrhythmia (NS)	1	All	. (. to .)	./96 (.)	./96 (.)
Brisson, 2017[94]	2000 IU	Vitamin D vs. placebo	Non-serious: Fatigue (NS), headache (NS), weakness (NS), decreasing appetite (NS), arrhythmia (NS)	1	All	. (. to .)	./99 (.)	./96 (.)
Brisson, 2017[94]	3000 IU	Vitamin D vs. placebo	Non-serious: Fatigue (NS), headache (NS), weakness (NS), decreasing appetite (NS), confusion (NS), arrhythmia (NS)	1	All	. (. to .)	./100 (.)	./96 (.)
Dukas, 2004[128]	1 microgram	Vitamin D vs. placebo	Non-serious: Itching (NS), skin eruption (NS)	0.7	All	. (. to .)	./. (.)	./. (.)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Non-serious: Easy bruising (NS); hypercalcemia (NS); parathyroid condition (NS)	5.3	All	. (. to .)	./12927 (.)	./12944 (.)
Murdoch, 2012[118]	3333.33 IU	Vitamin D vs. placebo	Non-serious: NR	1.5	All	. (. to .)	700 events/161	792 events/161
Scragg, 2017 (ViDA)[91]	3333 IU	Vitamin D vs. placebo	Non-serious: Hypercalcemia (NS)	3.3	All	. (. to .)	./2558 (.)	./2550 (.)
Witham, 2014[99]	1667 IU	Vitamin D vs. placebo	Non-serious: Dizziness (NS); Infection (NS); Musculoskeletal AE (NS)	0.5	All	. (. to .)	./34 (.)	./34 (.)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Parathyroid condition	5.3	All	HR=0.81 (0.55 to 1.17)	50/12927 (0.4)	62/12944 (0.5)
Gallagher, 2001 (STOP IT)[125]	0.5 mcg	Vitamin D vs placebo	Psychiatric symptoms	3	All	1.80 (0.51 to 6.30)	7/123 (5.7)	4/123 (3.3)
Aloia, 2018 (PODA)[102]	3490 IU	Vitamin D vs. placebo	Serious AEs	3	All	1.00 (0.02 to 50.78)	0/130 (0.0)	0/130 (0.0)
Murdoch, 2012[118]	3333.33 IU	Vitamin D vs. placebo	Serious AEs	1.5	All	. (. to .)	21 events/161	19 events/161
Pittas, 2019 (D2d)[135]	4000 IU	Vitamin D vs. placebo	Serious AEs	3.5	All	IRR=1.00 (0.83 to 1.20)	7.53/100 p-y	7.52/100 p-y
Rake, 2020 (VIDAL)[138]	3333 IU	Vitamin D vs no vitamin D	Serious AEs	2	All	1.02 (0.66 to 1.57)	46/395 (11.6)	45/392 (11.5)
Sanders, 2010 (Vital D)[115]	1370 IU	Vitamin D vs. placebo	Serious AEs	4	All	1.22 (0.99 to 1.50)	244/1131 (21.6)	207/1125 (18.4)

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	7 events/102	4 events/102
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	1 events/102	0 events/102
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	1 events/102	1 events/102
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	0 events/102	1 events/102
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	8 events/101	4 events/102
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	0 events/102	1 events/102
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Serious AEs	1	All	. (. to .)	0 events/102	0 events/102
Rake, 2020 (VIDAL)[138]	3333 IU	Vitamin D vs no vitamin D	Serious AEs requiring hospitalization	2	All	1.00 (0.74 to 1.36)	95/802 (11.8)	96/813 (11.8)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Skin rash	5.3	All	HR=0.94 (0.90 to 0.99)	3268/12927 (25.3)	3430/12944 (26.5)
Manson, 2018 (VITAL)[93]	2000 IU	Vitamin D vs. placebo	Stomach upset or pain	5.3	All	HR=1.00 (0.96 to 1.04)	4860/12927 (37.6)	4870/12944 (37.6)
Brisson, 2017[94]	1000 IU	Vitamin D vs. placebo	Vomiting	1	All	0.74 (0.31 to 1.79)	10/96 (10.4)	13/96 (13.5)
Brisson, 2017[94]	2000 IU	Vitamin D vs. placebo	Vomiting	1	All	1.23 (0.56 to 2.72)	16/99 (16.2)	13/96 (13.5)
Brisson, 2017[94]	3000 IU	Vitamin D vs. placebo	Vomiting	1	All	0.95 (0.42 to 2.18)	13/100 (13.0)	13/96 (13.5)
Aloia, 2018 (PODA)[102]	3490 IU	Vitamin D vs. placebo	Withdrawals due to AEs	3	All	0.59 (0.14 to 2.52)	3/130 (2.3)	5/130 (3.8)
Brisson, 2017[94]	1000 IU	Vitamin D vs. placebo	Withdrawals due to AEs	1	All	1.00 (0.02 to 50.91)	0/96 (0.0)	0/96 (0.0)
Brisson, 2017[94]	2000 IU	Vitamin D vs. placebo	Withdrawals due to AEs	1	All	0.97 (0.02 to 49.37)	0/99 (0.0)	0/96 (0.0)
Brisson, 2017[94]	3000 IU	Vitamin D vs. placebo	Withdrawals due to AEs	1	All	0.96 (0.02 to 48.87)	0/100 (0.0)	0/96 (0.0)
Cooper, 2003[127]	1428.6 IU + 1000 mg Calcium	Vitamin D + calcium vs. Placebo + calcium	Withdrawals due to AEs	2	All	8.75 (1.07 to 71.45)	8/93 (8.6)	1/94 (1.1)
Dawson-Hughes, 1997[123]	700 IU + 500 mg Calcium	Vitamin D + calcium vs. placebo	Withdrawals due to AEs	3	All	2.20 (0.54 to 8.92)	6/187 (3.2)	3/202 (1.5)
Pittas, 2019 (D2d)[135]	4000 IU	Vitamin D vs. placebo	Withdrawals due to AEs	3.5	All	IRR=1.23 (0.80 to 1.90)	1.51/100 p-y	1.22/100 p-y
Rake, 2020 (VIDAL)[138]	3333 IU	Vitamin D vs no vitamin D	Withdrawals due to AEs	2	All	0.99 (0.34 to 2.86)	7/395 (1.8)	7/392 (1.8)
Wood, 2012[119]	400 IU	Vitamin D vs placebo	Withdrawals due to AEs	1	All	2.58 (0.49 to 13.60)	5/102 (4.9)	2/102 (2.0)

Appendix F Table 21. Vitamin D Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Wood, 2012[119]	1000 IU	Vitamin D vs placebo	Withdrawals due to AEs	1	All	2.06 (0.37 to 11.52)	4/101 (4.0)	2/102 (2.0)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; GI = Gastrointestinal; HPFS = Health Professionals Follow-up Study; HR = Hazard ratio; IG = Intervention group; IU = International units; NHS = Nurses' Health Study; NS = Not significant; NSD = No significant difference; PODA = The physical performance, osteoporosis prevention, and vitamin D in older African Americans; RECORD = Randomised evaluation of calcium or vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study; ViDa = Vitamin D Assessment Study; VITAL = VITamin D and OmegA-3 TriaL

Appendix F Table 22. Summary of Results for Studies of Vitamin E Use

Author, Year (Study)	Quality Rating	Study Design	Study N*	Supplement (daily dose)	ACM	CVD	Cancer	Harms
ATBC Study Group, 1994 (ATBC)[75]	Good	RCT	29133	Vitamin E (50 mg)	↔	↔?	↓? (prostate) ↔ (other)	↔? (hosp. for pneumonia)
de Gaetano, 2001 (PPP)[103]	Good	RCT	4495	Vitamin E (300 mg)	↔	↔	↔	↔ (any AE) ? (epistaxis, GI bleed, intracranial bleed, GI disease)
Hodis, 2002 (VEAPS)[126]	Fair	RCT	353	Vitamin E (400 IU)	?	?	?	NR
Lee, 2005 (WHS)[73]	Good	RCT	39876	Vitamin E (300 IU)	↔	↔	↔	↔ (epistaxis, trivial increase in risk)
Lippman, 2009 (SELECT)[79]	Good	RCT	34888	Vitamin E (400 IU)	↔	↔	↔	↔ (dermatitis, trivial increase in risk) ↔ (fatigue, halitosis, nail changes)
				Selenium (200 mcg) + Vitamin E (400 IU)	↔	↔	↔	↔ (dermatitis)
Magliano, 2006 (MAVET)[131]	Fair	RCT	409	Vitamin E (500 IU)	↔?	?	?	NR
McNeil, 2004 (VECAT)[129]	Good	RCT	1193	Vitamin E (500 IU)	↔?	NR	NR	↔ (serious AE, AE WD, any AE, non-cataract ophthalmic events)
Salonen, 2000 (ASAP)[76]	Fair	RCT	520	Vitamin E (182 mg)	?	?	NR	↔? (AE WD)
				Vitamin C (500 mg) + Vitamin E (182 mg)	?	?	NR	↔? (AE WD)
Sesso, 2008 (PHS-II)[80]	Good	RCT	14641	Vitamin E (200 IU)	↔	↔	↔	↔ (epistaxis, skin rash, trivial increase in risk ↔ (bruising, hematuria)
Feskanich, 2002 (NHS-I)[140]	Fair	Cohort	121700	Vitamin E (NR, reported by duration of use)	NR	NR	NR	↔ (cataract)
Zheng Selin, 2013 (COSM)[142]	Fair	Cohort	27343	Vitamin E (NR)	NR	NR	NR	↑ (cataract)

*Includes only participants randomized to an intervention group assigned to take vitamin E

Abbreviations: ACM = All-cause mortality; AE = Adverse event; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; COSM = Cohort of Swedish Men; CVD = Cardiovascular disease; GI = Gastrointestinal; hosp. = Hospitalization; IU = International unit; MAVET = Melbourne Atherosclerosis Vitamin E Trial; mcg = Microgram; mg = Milligram; NHS-I = Nurses' Health Study I; NR = Not reported; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; RCT = Randomized controlled trial; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; VECAT = Vitamin E, Cataract and Age-related Maculopathy Trial; WD = Withdrawal; WHS = Women's Health Study

Appendix F Table 22. Summary of Results for Studies of Vitamin E Use

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)
↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 23. Vitamin E Meta-Analysis Results:. Results of Meta-Analyses by Outcome, Primary Analysis Listed First for Each Outcome, Followed by Sensitivity Analyses

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	MH	1.02 (0.97 to 1.07)	9	107,772	NA	NA
	Peto	1.02 (0.97 to 1.07)	9	107,772	0	.00
	Full ascert. (MH)	1.02 (0.95 to 1.09)	5	77,638	NA	NA
CVD mortality	Peto	0.88 (0.74 to 1.04)	6	77,114	29.5	.01
	MH	0.90 (0.80 to 1.02)	6	77,114	NA	NA
	Full ascert. (Peto)	0.90 (0.80 to 1.02)	4	76,445	NA	NA
Composite CVD event	MH	0.96 (0.90 to 1.04)	4	62,136	NA	NA
	Peto	0.96 (0.90 to 1.04)	4	62,136	0	.00
	Full ascert. (MH)	0.96 (0.90 to 1.04)	3	61,804	NA	NA
MI	Peto	0.94 (0.82 to 1.06)	4	59,344	0	.00
	MH	0.94 (0.82 to 1.06)	4	59,344	NA	NA
	Full ascert. (Peto)	0.93 (0.82 to 1.06)	3	59,012	NA	NA
Stroke	Peto	0.97 (0.87 to 1.10)	5	76,777	0	.00
	MH	0.97 (0.87 to 1.10)	5	76,777	NA	NA
	Full ascert. (Peto)	0.98 (0.87 to 1.10)	4	76,445	NA	NA
Cancer mortality	MH	1.05 (0.94 to 1.16)	4	72,359	NA	NA
	Peto	1.01 (0.85 to 1.20)	4	72,359	47.9	.01
	Full ascert. (MH)	1.06 (0.95 to 1.18)	3	71,950	NA	NA
Any cancer incidence	MH	1.02 (0.98 to 1.08)	5	76,777	NA	NA
	Peto	1.02 (0.98 to 1.08)	5	76,777	0	.00
	Full ascert. (MH)	1.02 (0.97 to 1.08)	3	71,950	NA	NA
Colorectal cancer	Peto	0.98 (0.82 to 1.16)	3	71,950	0	.00
	MH	0.98 (0.82 to 1.16)	3	71,950	NA	NA
	Full ascert. (Peto)	0.98 (0.82 to 1.16)	3	71,950	NA	NA
Lung cancer	Peto	1.00 (0.87 to 1.14)	4	86,523	0	.00
	MH	1.00 (0.87 to 1.14)	4	86,523	NA	NA
	Full ascert. (Peto)*	1.00 (0.87 to 1.14)	4	86,523	NA	NA
Breast cancer	Peto	1.00 (0.90 to 1.13)	2	40,208	0	.00
	MH	1.00 (0.90 to 1.13)	2	40,208	NA	NA
	Full ascert. (Peto)	1.00 (0.90 to 1.12)	1	86,523	NA	NA
Prostate cancer	Peto	0.95 (0.72 to 1.25)	4	46979	80.1	.05
	MH	1.01 (0.92 to 1.11)	4	46979	NA	NA
	Full ascert. (Peto)	1.01 (0.92 to 1.11)	3	46,647	NA	NA

*Full-studies with full ascertainment of the outcome

Abbreviations: CI = Confidence interval; CVD = Cardiovascular disease; MH = Mantel-Haenszel common effects model; MI = Myocardial infarction; NA = Not applicable; OR = Odds ratio; Peto = Peto odds ratio random effects REML model; REML-KH = Random effects restricted maximum likelihood model with the Knapp-Hartung adjustment

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	All-cause mortality	24.1	All	1.03 (0.96 to 1.10)	5065/7286 (69.5)	5022/7287 (68.9)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	All-cause mortality	6.1	All	1.02 (0.95 to 1.09)	1800/14564 (12.4)	1770/14569 (12.1)	0.6
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	All-cause mortality	11	All	0.99 (0.93 to 1.05)	2993/14564 (20.6)	3019/14569 (20.7)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	All-cause mortality	14	All	1.01 (0.96 to 1.06)	4453/14564 (30.6)	4415/14569 (30.3)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	All-cause mortality	16	All	1.01 (0.96 to 1.06)	5433/14564 (37.3)	5398/14569 (37.1)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	All-cause mortality	4	All	RR=1.07 (0.77 to 1.49)	72/2231 (3.2)	68/2264 (3.0)	NS
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	All-cause mortality	3	All	2.11 (0.19 to 23.52)	2/162 (1.2)	1/170 (0.6)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	All-cause mortality	10	All	RR=1.04 (0.93 to 1.16)	636/19937 (3.2)	615/19939 (3.1)	.53
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	All-cause mortality	5.5	All	HR=0.94 (0.77 to 1.13)	359/8703 (4.1)	382/8696 (4.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	All-cause mortality	7.1	All	HR=0.96 (0.82 to 1.12)	542/8702 (6.2)	564/8696 (6.5)	0.47
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	All-cause mortality	5.5	All	HR=0.93 (0.77 to 1.13)	358/8737 (4.1)	382/8696 (4.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	All-cause mortality	7.1	All	HR=1.01 (0.86 to 1.17)	571/8737 (6.5)	564/8696 (6.5)	0.91
Magliano, 2006 (MAVET)[131]	Vitamin E vs. placebo	500 IU	All-cause mortality	4	All	0.51 (0.22 to 1.16)	9/205 (4.4)	17/204 (8.3)	0.10

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
McNeil, 2004 (VECAT)[129]	Vitamin E vs. placebo	500 IU	All-cause mortality	4	All	1.86 (0.88 to 3.91)	20/595 (3.4)	11/598 (1.8)	0.10
Salonen, 2000 (ASAP)[76]	Vitamin C + vitamin E vs. placebo	500 mg + 544 IU Vitamin E	All-cause mortality	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Salonen, 2000 (ASAP)[76]	Vitamin E vs. Placebo	182 mg	All-cause mortality	3	All	3.05 (0.31 to 29.68)	3/130 (2.3)	1/130 (0.8)	
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	All-cause mortality	8	All	HR=1.07 (0.97 to 1.18)	841/7315 (11.5)	820/7326 (11.2)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Any cancer deaths	10	All	RR=1.12 (0.95 to 1.32)	308/19937 (1.5)	275/19939 (1.4)	0.17
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer deaths	5.5	All	HR=0.93 (0.67 to 1.30)	117/8703 (1.3)	125/8696 (1.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Any cancer deaths	5.5	All	HR=0.84 (0.60 to 1.18)	106/8737 (1.2)	125/8696 (1.4)	NR, NS
Magliano, 2006 (MAVET)[131]	Vitamin E vs. placebo	500 IU	Any cancer deaths	4	All	0.35 (0.11 to 1.12)	4/205 (2.0)	11/204 (5.4)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Any cancer deaths	8	All	HR=1.13 (0.95 to 1.34)	273/7315 (3.7)	250/7326 (3.4)	NR
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Bladder cancer deaths	7.1	All	0.50 (0.12 to 2.00)	3/8703 (0.0)	6/8696 (0.1)	NR
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Bladder cancer deaths	7.1	All	1.00 (0.32 to 3.09)	6/8737 (0.1)	6/8696 (0.1)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Chronic liver disease deaths	22.1	All	HR=0.97 (0.68 to 1.40)	57/7280 (0.8)	59/7282 (0.8)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Chronic liver disease deaths	22.1	All	0.96 (0.74 to 1.24)	116/14549 (0.8)	121/14556 (0.8)	
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Colorectal cancer deaths	6.1	All	RR=0.92 (0.51 to 1.64)	22/14564 (0.2)	24/14569 (0.2)	NR, NS

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer deaths	5.5	All	HR=1.49 (0.52 to 4.28)	15/8703 (0.2)	10/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Colorectal cancer deaths	5.5	All	HR=1.30 (0.44 to 3.83)	13/8737 (0.1)	10/8696 (0.1)	NR, NS
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Colorectal cancer deaths	8	All	HR=0.68 (0.39 to 1.18)	21/7315 (0.3)	32/7326 (0.4)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	CVD deaths	4	All	RR=0.86 (0.49 to 1.52)	22/2231 (1.0)	26/2264 (1.1)	NS
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	CVD deaths	10	All	RR=0.76 (0.59 to 0.98)	106/19937 (0.5)	140/19939 (0.7)	0.03
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD deaths	5.5	All	HR=0.82 (0.60 to 1.13)	117/8703 (1.3)	142/8696 (1.6)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	CVD deaths	5.5	All	HR=0.84 (0.61 to 1.15)	119/8737 (1.4)	142/8696 (1.6)	NR, NS
Magliano, 2006 (MAVET)[131]	Vitamin E vs. placebo	500 IU	CVD deaths	4	All	0.49 (0.09 to 2.72)	2/205 (1.0)	4/204 (2.0)	NR
Salonen, 2000 (ASAP)[76]	Vitamin C + vitamin E vs. placebo	500 mg + 544 IU Vitamin E	CVD deaths	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Salonen, 2000 (ASAP)[76]	Vitamin E vs. Placebo	182 mg	CVD deaths	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	CVD deaths	8	All	HR=1.07 (0.90 to 1.28)	258/7315 (3.5)	251/7326 (3.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Esophageal cancer deaths	6.1	All	RR=0.50 (0.13 to 2.00)	3/7286 (0.0)	6/7287 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Esophageal cancer deaths	6.1	All	RR=0.50 (0.17 to 1.47)	5/14564 (0.0)	10/14569 (0.1)	NR, NS

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Hemorrhagic stroke deaths	6.1	All	1.50 (1.03 to 2.20)	66/14564 (0.5)	44/14569 (0.3)	NR
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Hemorrhagic stroke deaths	5.5	All	HR=1.49 (0.46 to 4.84)	12/8703 (0.1)	8/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Hemorrhagic stroke deaths	5.5	All	HR=1.12 (0.32 to 3.92)	9/8737 (0.1)	8/8696 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Ischemic heart disease deaths	6.1	All	0.94 (0.84 to 1.06)	602/14564 (4.1)	637/14569 (4.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Ischemic stroke deaths	6.1	All	0.84 (0.59 to 1.19)	56/14564 (0.4)	67/14569 (0.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Laryngeal cancer deaths	6.1	All	RR=0.67 (0.11 to 4.00)	2/7286 (0.0)	3/7287 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Lung cancer deaths	6.1	All	1.02 (0.87 to 1.21)	285/14564 (2.0)	279/14569 (1.9)	NR
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer deaths	5.5	All	HR=0.95 (0.53 to 1.69)	39/8703 (0.4)	41/8696 (0.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Lung cancer deaths	5.5	All	HR=0.92 (0.52 to 1.65)	38/8737 (0.4)	41/8696 (0.5)	NR, NS
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Lung cancer deaths	8	All	HR=1.05 (0.69 to 1.60)	44/7315 (0.6)	43/7326 (0.6)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	MI, fatal	3	All	1.05 (0.07 to 16.92)	1/162 (0.6)	1/170 (0.6)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	MI, fatal	10	All	RR=0.86 (0.40 to 1.85)	12/19937 (0.1)	14/19939 (0.1)	0.70
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	MI, fatal	8	All	HR=0.75 (0.43 to 1.31)	22/7315 (0.3)	30/7326 (0.4)	NR

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Non-CVD deaths	4	All	RR=1.21 (0.80 to 1.81)	50/2231 (2.2)	42/2264 (1.9)	NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Oral cavity/pharynx cancer deaths	6.1	All	RR=2.51 (0.49 to 12.92)	5/7286 (0.1)	2/7287 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Oral cavity/pharynx cancer deaths	6.1	All	RR=1.84 (0.68 to 4.97)	11/14564 (0.1)	6/14569 (0.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Other CVD deaths	6.1	All	1.06 (0.83 to 1.36)	129/14564 (0.9)	122/14569 (0.8)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Other CVD deaths	10	All	0.59 (0.34 to 1.02)	20/19937 (0.1)	34/19939 (0.2)	
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Pancreatic cancer deaths	6.1	All	RR=1.11 (0.72 to 1.72)	49/14564 (0.3)	34/14569 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Prostate cancer deaths	6.1	All	0.61 (0.29 to 1.29)	11/7286 (0.2)	18/7287 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Prostate cancer deaths	6.1	All	0.59 (0.35 to 0.99)	23/14564 (0.2)	39/14569 (0.3)	<0.05
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer deaths	5.5	All	1.00 (0.02 to 50.36)	0/8703 (0.0)	0/8696 (0.0)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Prostate cancer deaths	5.5	All	1.00 (0.02 to 50.17)	0/8737 (0.0)	0/8696 (0.0)	NR, NS
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Prostate cancer deaths	8	All	HR=1.01 (0.64 to 1.58)	37/7315 (0.5)	39/7326 (0.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Renal cell carcinoma deaths	6.1	All	0.79 (0.36 to 1.73)	11/7286 (0.2)	14/7287 (0.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Renal cell carcinoma deaths	6.1	All	1.05 (0.57 to 1.94)	21/14564 (0.1)	20/14569 (0.1)	NR

Appendix F Table 24. Vitamin E Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Stroke deaths	10	All	RR=0.88 (0.49 to 1.57)	21/19937 (0.1)	24/19939 (0.1)	0.66
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Stroke deaths	8	All	HR=0.86 (0.58 to 1.27)	45/7315 (0.6)	56/7326 (0.8)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Sudden death	10	All	0.74 (0.49 to 1.13)	38/19937 (0.2)	51/19939 (0.3)	
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Urothelial cancer deaths	6.1	All	1.20 (0.37 to 3.93)	6/7286 (0.1)	5/7287 (0.1)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Urothelial cancer deaths	6.1	All	1.40 (0.62 to 3.15)	14/14564 (0.1)	10/14569 (0.1)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; MAVET = Melbourne Atherosclerosis Vitamin E Trial; mcg = Micrograms; mg = Milligrams; MI = Myocardial infarction; NR = Not reported; NS = Not significant; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; RR = Risk ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; WHS = Women's Health Study

Appendix F Table 25. Vitamin E Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Congestive heart failure	10	All	HR=0.91 (0.70 to 1.19)	106/19913 (0.5)	114/19902 (0.6)	0.48
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Congestive heart failure	8	All	HR=1.02 (0.87 to 1.20)	289/7315 (4.0)	294/7326 (4.0)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	CVD events	4	All	RR=1.07 (0.74 to 1.56)	56/2231 (2.5)	53/2264 (2.3)	NS
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	CVD events	3	All	0.83 (0.32 to 2.16)	8/162 (4.9)	10/170 (5.9)	0.81
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	CVD events	10	All	RR=0.93 (0.82 to 1.05)	482/19937 (2.4)	517/19939 (2.6)	0.26
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD events	5.5	All	RR=0.99 (0.89 to 1.10)	1041/8703 (12.0)	1050/8696 (12.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD events	7.1	All	HR=0.97 (0.86 to 1.09)	943/8702 (10.8)	969/8696 (11.1)	0.51
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	CVD events	5.5	All	RR=0.98 (0.88 to 1.09)	1034/8737 (11.8)	1050/8696 (12.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	CVD events	7.1	All	HR=0.93 (0.83 to 1.05)	909/8737 (10.4)	969/8696 (11.1)	0.11
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	CVD events	8	All	HR=1.01 (0.90 to 1.13)	620 events/7315	625 events/7326	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Heart failure	10	All	HR=1.25 (0.83 to 1.89)	53/19913 (0.3)	42/19902 (0.2)	0.28
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Heart failure	10	All	HR=0.59 (0.37 to 0.92)	30/19913 (0.1)	51/19902 (0.3)	0.02
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	MI	4	All	RR=0.89 (0.52 to 1.58)	22/2231 (1.0)	25/2264 (1.1)	NS

Appendix F Table 25. Vitamin E Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	MI	3	All	1.32 (0.35 to 5.01)	5/162 (3.1)	4/170 (2.4)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	MI	10	All	RR=1.01 (0.82 to 1.23)	196/19937 (1.0)	195/19939 (1.0)	0.96
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	MI	8	All	HR=0.90 (0.75 to 1.07)	240/7315 (3.3)	271/7326 (3.7)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	MI, nonfatal	4	All	RR=1.01 (0.56 to 2.03)	19/2231 (0.8)	18/2264 (0.8)	NS
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	MI, nonfatal	3	All	1.41 (0.31 to 6.40)	4/162 (2.5)	3/170 (1.8)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	MI, nonfatal	10	All	RR=1.02 (0.83 to 1.25)	184/19937 (0.9)	181/19939 (0.9)	0.87
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Other CVD	4	All	RR=0.94 (0.77 to 1.16)	158/2231 (7.1)	170/2264 (7.5)	NS
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Peripheral artery disease	4	All	RR=0.54 (0.30 to 0.99)	16/2231 (0.7)	30/2264 (1.3)	0.043
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Stroke	4	All	RR=1.24 (0.66 to 2.31)	22/2231 (1.0)	18/2264 (0.8)	NS
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Stroke	3	All	0.21 (0.01 to 4.35)	0/162 (0.0)	2/170 (1.2)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Stroke	10	All	RR=0.98 (0.82 to 1.17)	241/19937 (1.2)	246/19939 (1.2)	0.82
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke	5.5	All	1.18 (0.85 to 1.64)	79/8703 (0.9)	67/8696 (0.8)	
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Stroke	8	All	HR=1.07 (0.89 to 1.29)	237/7315 (3.2)	227/7326 (3.1)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Stroke, Hemorrhagic	10	All	RR=0.92 (0.61 to 1.38)	44/19937 (0.2)	48/19939 (0.2)	0.68

Appendix F Table 25. Vitamin E Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, Hemorrhagic	5.5	All	RR=1.09 (0.37 to 3.19)	12/8703 (0.1)	11/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Stroke, Hemorrhagic	5.5	All	RR=0.63 (0.18 to 2.20)	7/8737 (0.1)	11/8696 (0.1)	NR, NS
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Stroke, Hemorrhagic	8	All	HR=1.74 (1.04 to 2.91)	39/7315 (0.5)	23/7326 (0.3)	<0.05
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Stroke, Ischemic	10	All	RR=0.99 (0.81 to 1.20)	194/19937 (1.0)	197/19939 (1.1)	0.88
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, Ischemic	5.5	All	RR=1.20 (0.75 to 1.90)	67/8703 (0.8)	56/8696 (0.6)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Stroke, Ischemic	5.5	All	RR=0.87 (0.53 to 1.44)	49/8737 (0.6)	56/8696 (0.6)	NR, NS
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Stroke, Ischemic	8	All	HR=1.00 (0.82 to 1.22)	191/7315 (2.6)	196/7326 (2.7)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Stroke, nonfatal	4	All	RR=1.56 (0.77 to 3.13)	20/2231 (0.9)	13/2264 (0.6)	NS
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Stroke, nonfatal	10	All	RR=0.99 (0.82 to 1.19)	220/19937 (1.1)	222/19939 (1.1)	0.93
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, nonfatal	5.5	All	1.08 (0.81 to 1.43)	99/8703 (1.1)	92/8696 (1.1)	NR
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Stroke, nonfatal	5.5	All	0.76 (0.55 to 1.03)	70/8737 (0.8)	92/8696 (1.1)	NR
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Transient ischemic attack	4	All	RR=0.96 (0.60 to 1.53)	33/2231 (1.5)	35/2264 (1.5)	NS

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; mcg = Microgram; mg = Milligram; MI = Myocardial infarction; NR = Not reported; NS = Not significant; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; RR = Risk ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; WHS = Women's Health Study

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
de Gaetano, 2001 (PPP)[103]	Vitamin E vs. no vitamin E	300 mg	Any cancer incidence	4	All	1.09 (0.80 to 1.49)	86/2231 (3.9)	80/2264 (3.5)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Any cancer incidence	3	All	1.94 (0.64 to 5.92)	9/162 (5.6)	5/170 (2.9)	0.17
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Any cancer incidence	10	All	RR=1.01 (0.94 to 1.08)	1437/19937 (7.2)	1428/19939 (7.2)	0.87
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Any cancer incidence	5.5	All	HR=1.03 (0.91 to 1.17)	856/8737 (9.8)	824/8696 (9.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Any cancer incidence	7.1	All	HR=1.07 (0.96 to 1.19)	1190/8737 (13.6)	1108/8696 (12.7)	0.13
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Any cancer incidence	8	All	HR=1.04 (0.95 to 1.13)	984/7315 (13.5)	959/7326 (13.1)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Bile duct cancer	3	All	3.17 (0.13 to 78.31)	1/162 (0.6)	0/170 (0.0)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Bladder cancer	3	All	0.35 (0.01 to 8.60)	0/162 (0.0)	1/170 (0.6)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Breast cancer	3	All	2.11 (0.19 to 23.52)	2/162 (1.2)	1/170 (0.6)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Breast cancer	10	All	RR=1.00 (0.90 to 1.12)	616/19937 (3.1)	614/19939 (3.1)	0.95
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Colorectal cancer	24.1	All	0.98 (0.80 to 1.19)	204/7286 (2.8)	209/7287 (2.9)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Colorectal cancer	8	All	RR=0.78 (0.55 to 1.09)	59/14564 (0.4)	76/14569 (0.5)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Colorectal cancer	11	All	0.92 (0.71 to 1.20)	109/14564 (0.7)	118/14569 (0.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Colorectal cancer	14	All	0.95 (0.77 to 1.18)	166/14564 (1.1)	174/14569 (1.2)	NR

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Colorectal cancer	10	All	RR=1.00 (0.77 to 1.31)	107/19937 (0.5)	107/19939 (0.5)	0.99
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Colorectal cancer	5.5	All	HR=1.09 (0.69 to 1.73)	66/8737 (0.8)	60/8696 (0.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Colorectal cancer	7.1	All	HR=1.09 (0.72 to 1.64)	85/8737 (1.0)	75/8696 (0.9)	0.60
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Colorectal cancer	8	All	HR=0.88 (0.64 to 1.19)	75/7315 (1.0)	87/7326 (1.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Esophageal cancer	6.1	All	RR=0.86 (0.29 to 2.56)	6/7286 (0.1)	7/7287 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Esophageal cancer	6.1	All	RR=0.85 (0.38 to 1.89)	11/14564 (0.1)	13/14569 (0.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Laryngeal cancer	6.1	All	RR=1.00 (0.51 to 1.97)	17/7286 (0.2)	17/7287 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Laryngeal cancer	6.1	All	RR=0.93 (0.55 to 1.58)	27/14564 (0.2)	29/14569 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Liver cancer	22.1	All	HR=1.18 (0.79 to 1.75)	53/7280 (0.7)	45/7282 (0.6)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Liver cancer	22.1	All	HR=1.06 (0.81 to 1.39)	107/14549 (0.7)	101/14556 (0.7)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Lung cancer	6.1	All	0.98 (0.81 to 1.19)	204/7286 (2.8)	208/7287 (2.9)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Lung cancer	24.1	All	0.98 (0.89 to 1.08)	915/7286 (12.6)	933/7287 (12.8)	
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Lung cancer	6.1	All	RR=1.00 (0.87 to 1.14)	433/14564 (3.0)	443/14569 (3.0)	0.8

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Lung cancer	8	All	RR=0.99 (0.87 to 1.13)	444/14564 (3.0)	450/14569 (3.1)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Lung cancer	11	All	0.96 (0.86 to 1.07)	682/14564 (4.7)	711/14569 (4.9)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Lung cancer	14	All	1.01 (0.92 to 1.10)	969/14564 (6.7)	963/14569 (6.6)	NR
Lee, 2005 (WHS)[73]	Vitamin E vs. no vitamin E	300 IU	Lung cancer	10	All	RR=1.09 (0.83 to 1.44)	107/19937 (0.5)	98/19939 (0.5)	0.52
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Lung cancer	5.5	All	HR=1.00 (0.64 to 1.55)	67/8737 (0.8)	67/8696 (0.8)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Lung cancer	7.1	All	HR=1.11 (0.76 to 1.61)	104/8737 (1.2)	92/8696 (1.1)	0.49
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Lung cancer	8	All	HR=0.89 (0.60 to 1.31)	48/7315 (0.7)	55/7326 (0.8)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Lymphoma, non-Hodgkin's	3	All	0.35 (0.01 to 8.60)	0/162 (0.0)	1/170 (0.6)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Melanoma skin cancer	3	All	0.35 (0.01 to 8.60)	0/162 (0.0)	1/170 (0.6)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Nasal cancer	3	All	3.17 (0.13 to 78.31)	1/162 (0.6)	0/170 (0.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Oral cavity/pharyngeal cancer	6.1	All	RR=0.84 (0.42 to 1.66)	15/7286 (0.2)	18/7287 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Oral cavity/pharyngeal cancer	6.1	All	RR=0.97 (0.60 to 1.58)	32/14564 (0.2)	33/14569 (0.2)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Other cancer	6.1	All	1.06 (0.92 to 1.23)	378/14564 (2.6)	357/14569 (2.5)	NR, NS
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Ovarian cancer	3	All	3.17 (0.13 to 78.31)	1/162 (0.6)	0/170 (0.0)	NR

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Pancreatic cancer	6.1	All	RR=0.96 (0.56 to 1.67)	25/7286 (0.3)	26/7287 (0.4)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Pancreatic cancer	24.1	All	1.04 (0.80 to 1.35)	114/7286 (1.6)	110/7287 (1.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Pancreatic cancer	6.1	All	RR=1.34 (0.88 to 2.05)	51/14564 (0.4)	38/14569 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Prostate cancer	6.1	All	0.64 (0.44 to 0.94)	43/7286 (0.6)	67/7287 (0.9)	<0.05
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Prostate cancer	24.1	All	0.88 (0.78 to 0.98)	596/7286 (8.2)	672/7287 (9.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Prostate cancer	6.1	All	0.65 (0.51 to 0.84)	99/14564 (0.7)	151/14569 (1.0)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Prostate cancer	8	All	RR=0.66 (0.52 to 0.86)	99/14564 (0.7)	149/14569 (1.0)	<0.05
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Prostate cancer	11	All	0.77 (0.65 to 0.92)	229/14564 (1.6)	296/14569 (2.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Prostate cancer	14	All	0.81 (0.71 to 0.93)	414/14564 (2.8)	506/14569 (3.5)	NR
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Prostate cancer	3	All	3.19 (0.33 to 30.97)	3/162 (1.9)	1/170 (0.6)	NR
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Prostate cancer	5.5	All	HR=1.13 (0.95 to 1.35)	473/8737 (5.4)	416/8696 (4.8)	0.06
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Prostate cancer	7.1	All	HR=1.17 (1.00 to 1.36)	620/8737 (7.1)	529/8696 (6.1)	0.008
Sesso, 2008 (PHS-II)[80]	Vitamin E vs. no vitamin E	200 IU	Prostate cancer	8	All	HR=0.97 (0.85 to 1.09)	493/7315 (6.7)	515/7326 (7.0)	NR

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Hodis, 2002 (VEAPS)[126]	Vitamin E vs. placebo	400 IU	Renal cancer	3	All	3.17 (0.13 to 78.31)	1/162 (0.6)	0/170 (0.0)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Renal cell carcinoma	6.1	All	1.00 (0.59 to 1.71)	27/7286 (0.4)	27/7287 (0.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Renal cell carcinoma	24.1	All	1.02 (0.76 to 1.37)	92/7286 (1.3)	90/7287 (1.2)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Renal cell carcinoma	6.1	All	RR=1.10 (0.70 to 1.60)	54/14564 (0.4)	48/14569 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Stomach cancer	6.1	All	RR=1.34 (0.78 to 2.29)	32/7286 (0.4)	24/7287 (0.3)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Stomach cancer	24.1	All	1.10 (0.84 to 1.43)	114/7286 (1.6)	104/7287 (1.4)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Stomach cancer	6.1	All	RR=1.21 (0.85 to 1.74)	69/14564 (0.5)	57/14569 (0.4)	NR, NS
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Urinary bladder cancer	6.1	All	1.10 (0.80 to 1.50)	81/14564 (0.6)	74/14569 (0.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Vitamin E vs. placebo	400 IU	Urinary bladder cancer	7.1	All	HR=1.06 (0.72 to 1.53)	56/8737 (0.6)	53/8696 (0.6)	0.79
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Urothelial cancer	6.1	All	1.27 (0.83 to 1.96)	47/7286 (0.6)	37/7287 (0.5)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. placebo	50 mg	Urothelial cancer	24.1	All	1.03 (0.84 to 1.25)	211/7286 (2.9)	206/7287 (2.8)	NR
ATBC Study Group, 1994 (ATBC)[75]	Vitamin E vs. no vitamin E	50 mg + 20 mg Beta-carotene	Urothelial cancer	6.1	All	RR=1.10 (0.80 to 1.50)	89/14564 (0.6)	80/14569 (0.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer incidence	5.5	All	HR=1.02 (0.90 to 1.16)	846/8703 (9.7)	824/8696 (9.5)	NR, NS

Appendix F Table 26. Vitamin E Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer incidence	7.1	All	HR=1.02 (0.92 to 1.14)	1149/8702 (13.2)	1108/8696 (12.7)	0.60
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer	5.5	All	HR=1.28 (0.82 to 2.00)	77/8703 (0.9)	60/8696 (0.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer	7.1	All	HR=1.21 (0.81 to 1.81)	93/8702 (1.1)	75/8696 (0.9)	0.22
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer	5.5	All	HR=1.16 (0.76 to 1.78)	78/8703 (0.9)	67/8696 (0.8)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer	7.1	All	HR=1.11 (0.76 to 1.62)	104/8702 (1.2)	92/8696 (1.1)	0.48
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer	5.5	All	HR=1.05 (0.88 to 1.25)	437/8702 (5.0)	416/8696 (4.8)	0.52
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer	7.1	All	HR=1.05 (0.89 to 1.22)	555/8702 (6.4)	529/8696 (6.1)	0.46
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Urinary bladder cancer	7.1	All	HR=1.05 (0.71 to 1.51)	55/8703 (0.6)	53/8696 (0.6)	0.86

*Studies providing estimates other than ORs display effect type

Abbreviations: ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; HR = Hazard ratio; IG = Intervention group; IU = International units; mcg = Microgram; mg = Milligram; NR = Not reported; NS = Not significant; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; RR = Risk ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VEAPS = Vitamin E Atherosclerosis Progression Study; WHS = Women's Health Study

Appendix F Table 27. Vitamin E Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Any AE	4	All	1.12 (0.87 to 1.43)	138/2231 (6.2)	126/2264 (5.6)
McNeil, 2004 (VECAT)[129]	500 IU	Vitamin E vs. placebo	Any AE	4	All	1.19 (0.95 to 1.50)	351/595 (59.0)	327/598 (55.0)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin E <2 yrs use vs. no vitamin E	Cataract	12	All	RR=1.26 (0.96 to 1.65)	224/100000 p-y	184/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin E 2-4 yrs use vs. no vitamin E	Cataract	12	All	RR=0.97 (0.68 to 1.39)	182/100000 p-y	184/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin E 5-9 yrs use vs. no vitamin E	Cataract	12	All	RR=1.13 (0.88 to 1.44)	223/100000 p-y	184/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin E ≥10 yrs use vs. no vitamin E	Cataract	12	All	RR=0.99 (0.74 to 1.32)	216/100000 p-y	184/100000 p-y
Sesso, 2008 (PHS-II)[80]	200 IU	Vitamin E vs. no vitamin E	Cataract	8	All	HR=0.99 (0.88 to 1.11)	579 events/5771	595 events/5774
Zheng Selin, 2013 (COSM)[142]	NR	Vitamin E vs. no vitamin E	Cataract	8.4	All	HR=1.57 (1.10 to 2.22)	32/144 (22.2)	1937/22015 (8.8)
Lippman, 2009 (SELECT)[79]	400 IU	Vitamin E vs. placebo	Dermatitis	5.5	All	RR=1.14 (0.98 to 1.32)	591/8737 (6.8)	516/8696 (5.9)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Epistaxis	4	All	1.01 (0.06 to 16.23)	1/2231 (0.0)	1/2264 (0.0)
Lee, 2005 (WHS)[73]	300 IU	Vitamin E vs. no vitamin E	Epistaxis	10	All	RR=1.06 (1.01 to 1.11)	./19937 (.)	./19939 (.)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Gastrointestinal bleeding	4	All	1.01 (0.44 to 2.35)	11/2231 (0.5)	11/2264 (0.5)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	GI disease	4	All	1.22 (0.37 to 4.00)	6/2231 (0.3)	5/2264 (0.2)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Intracranial bleeding	4	All	5.08 (0.24 to 105.84)	2/2231 (0.1)	0/2264 (0.0)

Appendix F Table 27. Vitamin E Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
ATBC Study Group, 1994 (ATBC)[75]	50 mg + 20 mg Beta-carotene	Vitamin E vs. no vitamin E	Non-serious: Hospitalized for pneumonia (NS)	6.1	All	. (. to .)	./14564 (.)	./14569 (.)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Non-serious: Bleeding (NS); Ocular bleeding (NS); Other bleeding (NS)	4	All	. (. to .)	./2231 (.)	./2264 (.)
Lippman, 2009 (SELECT)[79]	400 IU	Vitamin E vs. placebo	Non-serious: Fatigue (NS); Halitosis (NS); Nail changes (NS)	5.5	All	. (. to .)	./8737 (.)	./8696 (.)
McNeil, 2004 (VECAT)[129]	500 IU	Vitamin E vs. placebo	Non-serious: Noncataract-related opthalmic event (NS)	4	All	1.40 (1.00 to 1.98)	87/595 (15.0)	65/598 (12.0)
Sesso, 2008 (PHS-II)[80]	200 IU	Vitamin E vs. no vitamin E	Hematuria (NS), easy bruising (NS), epistaxis (NS), peptic ulcer (NS), constipation (NS), diarrhea (NS), gastritis (NS), nausea (NS), fatigue (NS), drowsiness (NS), skin discoloration or rashes (NS), and migraine (NS)	8	All	. (. to .)	./7329 (.)	./7312 (.)
McNeil, 2004 (VECAT)[129]	500 IU	Vitamin E vs. placebo	Serious AEs	4	All	1.00 (0.76 to 1.31)	127/595 (21.3)	128/598 (21.4)
de Gaetano, 2001 (PPP)[103]	300 mg	Vitamin E vs. no vitamin E	Withdrawals due to AEs	4	All	. (. to .)	25/2231 (1.1)	./2264 (.)
McNeil, 2004 (VECAT)[129]	500 IU	Vitamin E vs. placebo	Withdrawals due to AEs	4	All	0.94 (0.47 to 1.89)	16/595 (2.7)	17/598 (2.8)
Salonen, 2000 (ASAP)[76]	182 mg	Vitamin E vs. Placebo	Withdrawals due to AEs	3	All	0.87 (0.31 to 2.47)	7/130 (5.4)	8/130 (6.2)

*Studies providing estimates other than ORs display effect type

Abbreviations: = not reported; AE = Adverse event; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; ATBC = Alpha-Tocopherol Beta Carotene Cancer Prevention; CG = Control group; COSM = Cohort of Swedish Men; GI = Gastrointestinal; HR = Hazard ratio; IG = Intervention group; IU = International units; mg = Milligram; NHS-I = Nurses' Health Study I; NS = Not significant; NR = Not reported; PHS-II = Physicians' Health Study II; PPP = Primary Prevention Project; p-y = Person-year; RR = Risk ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial; VECAT = Vitamin E, Cataract and Age-related Maculopathy Trial; WHS = Women's Health Study

Appendix F Table 28. Summary of Results for Studies of Folic Acid, Either Alone or With Vitamin B12

Study	Quality Rating	Study Design	N Rand.	Supplement (daily dose)	ACM	CVD	Cancer	AE
Cole, 2007 (AFPPS)[83]	Fair	3x2 factorial RCT	1,021	Folic acid (1,000 mcg/day)	↔?	?	Any: ↑ Breast: NR CRC: ? Other: ↑ Prostate: ↑?	NR Paradoxical effect for prostate cancer (↑?) NSD between groups on CVD outcomes.
Durga, 2007 (FACIT)[132]	Fair	RCT	819	Folic acid (800 mcg/day)	?	NR	NR	Any, GI: ?
Logan, 2008 (ukCAP)[108]	Fair	RCT	939	Folic acid (500 mcg/day)	?	?	Breast: NR CRC: ? Non-CRC: ?	GI: ↔ GI bleeding, peptic ulcer: ? Withdrawals due to AEs: ↔
Wu, 2009[109]	Good	RCT	672	Folic acid (1,000 mcg/day)	?	?	Any: ↔ Breast: ? CRC: ? Lung: ? Prostate: ?	Withdrawals due to AEs: ?
van Wijngaarden, 2014 (B-PROOF)[96]	Fair	RCT	2,919	Folic acid (400 mcg/day) Vitamin B12 (500 mcg/day)	↔	↔?	Any: ↑? Any in women: ↑? CRC: ↑ Other: ? Breast: NR Lung: ?	Withdrawals due to AEs: ↔?

Abbreviations: ACM = All-cause mortality; AE = Adverse event; AFPPS = Aspirin/Folate Polyp Prevention Study; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; CRC = Colorectal cancer; CVD = Cardiovascular disease; FACIT = Folic Acid and Carotid Intima-media Thickness; GI = Gastrointestinal; mcg = Micrograms; NR = Not reported; NSD = No significant difference; RCT = Randomized controlled trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)
↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 29. Folic Acid Meta-Analysis Results: Results of Meta-Analyses by Outcome, Primary Analysis Listed First for Each Outcome, Followed by Sensitivity Analyses

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	Peto	0.71 (0.49, 1.03)	5	6,370	21.2	0.04
	MH	0.73 (0.53, 0.99)	5	6,370	NA	NA
MI	MH	1.26 (0.86, 1.85)	4	3,201	NA	NA
Stroke	Peto	0.95 (0.50, 1.81)	4	3,201		
Any cancer incidence	Peto	1.42 (1.10, 1.84)	3	4,612	0	0
	MH	1.43 (1.10, 1.86)	3	4,612	NA	NA
Colorectal cancer	Peto	1.16 (0.50, 2.66)	4	5,538	37.3	0.27
	MH	1.35 (0.72, 1.86)	4	5,538	NA	NA

Abbreviations: CI = Confidence interval; MH = Mantel-Haenszel common effects model; NA = Not applicable; No. = Number; OR = Odds ratio; Peto = Peto odds ratio random effects REML model

Appendix F Table 30. Folic Acid Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	All-cause mortality	6.2	All	0.51 (0.23 to 1.10)	10/516 (1.9)	19/505 (3.8)	0.09
Durga, 2007 (FACIT)[132]	Folic acid vs. placebo	800 mcg	All-cause mortality	3	All	2.06 (0.61 to 6.88)	8/406 (2.0)	4/413 (1.0)	NR
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	All-cause mortality	3	All	0.52 (0.22 to 1.25)	8/470 (1.7)	15/469 (3.2)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	All-cause mortality	2	All	0.88 (0.56 to 1.37)	37/1461 (2.5)	42/1458 (2.9)	0.571
Wu, 2009[109]	Folic acid vs placebo	1 mg	All-cause mortality	6.5	All	0.45 (0.18 to 1.12)	7/338 (2.0)	15/334 (4.0)	0.08
Wu, 2009[109]	Folic acid vs placebo	1 mg	CVD deaths	6.5	All	0.14 (0.01 to 2.72)	0/338 (0.0)	3/334 (0.9)	0.12

Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; CG = Control group; CVD = Cardiovascular disease; FACIT = Folic Acid and Carotid Intima-media Thickness; IG = Intervention group; NR = Not reported; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; Vit D = Vitamin D

Appendix F Table 31. Folic Acid Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Coronary revascularization	6.2	All	0.98 (0.48 to 1.98)	16/516 (3.1)	16/505 (3.2)	>0.99
Wu, 2009[109]	Folic acid vs placebo	1 mg	CVD events	6.5	All	1.42 (0.54 to 3.79)	10/338 (3.0)	7/334 (2.1)	
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	MI	6.2	All	1.73 (0.72 to 4.17)	14/516 (2.7)	8/505 (1.6)	0.28
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	MI	3	All	7.03 (0.36 to 136.47)	3/470 (0.6)	0/469 (0.0)	>0.05
Wu, 2009[109]	Folic acid vs placebo	1 mg	MI, nonfatal	6.5	All	6.02 (0.72 to 50.26)	6/338 (2.0)	1/334 (0.3)	0.12
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	Other CVD	3	All	1.29 (0.48 to 3.49)	9/470 (1.9)	7/469 (1.5)	>0.05
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Stroke	6.2	All	1.78 (0.59 to 5.33)	9/516 (1.7)	5/505 (1.0)	0.42
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	Stroke	3	All	1.00 (0.06 to 16.00)	1/470 (0.2)	1/469 (0.2)	>0.05
van Wijngaarden, 2014 (B-PROOF)	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Stroke	2	Vascular subgroup (randomly selected)	0.72 (0.45 to 1.15)	46/295 (15.6)	60/274 (21.9)	0.17
van Wijngaarden, 2014 (B-PROOF)	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	MI	2	Vascular subgroup (randomly selected)	1.19 (0.66 to 2.14)	45/295 (15.3)	43/274 (15.7)	0.56
van Wijngaarden, 2014 (B-PROOF)	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	CVD events	2	Vascular subgroup (randomly selected)	1.08 (0.86 to 1.36)	181/295 (61.4)	170/274 (62.0)	0.50
van Wijngaarden, 2014 (B-PROOF)	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Stroke	2	Vascular subgroup (randomly selected), females only	0.33 (0.15 to 0.71)	16/130 (12.3)	36/122 (29.5)	
Wu, 2009[109]	Folic acid vs placebo	1 mg	Stroke	6.5	All	1.32 (0.29 to 5.95)	4/338 (1.0)	3/334 (0.9)	1.00
Wu, 2009[109]	Folic acid vs placebo	1 mg	Stroke, nonfatal	6.5	All	1.32 (0.29 to 5.95)	4/338 (1.0)	3/334 (0.9)	1.00

*Studies providing estimates other than ORs display effect type

Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; CG = Control group; CVD = Cardiovascular disease; IG = Intervention group; mg = Milligram; MI = Myocardial infarction; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix F Table 32. Folic Acid Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Adenomas	6.2	All	RR=1.35 (0.98 to 1.86)	70/304 (23.1)	52/303 (17.1)	0.07
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Any cancer incidence	6.2	All	1.62 (1.05 to 2.50)	57/516 (11.0)	36/505 (7.1)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Any cancer incidence	2	All	HR=1.56 (1.04 to 2.31)	63/1461 (4.3)	42/1458 (2.9)	0.038
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Any cancer incidence	6.5	All	HR=1.25 (1.00 to 1.57)	171/1257 (13.6)	143/1267 (11.3)	0.05
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Any cancer incidence	2	Females	HR=2.35 (1.23 to 4.50)	31/736 (4.2)	13/725 (1.8)	0.010
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Any cancer incidence	2	Males	HR=1.16 (0.69 to 1.94)	32/725 (4.4)	29/733 (4.0)	0.580
Wu, 2009[109]	Folic acid vs placebo	1 mg	Any cancer incidence	6.5	All	0.99 (0.55 to 1.78)	24/338 (7.0)	24/334 (7.0)	0.97
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Basal cell carcinoma	13.5	All	HR=0.85 (0.57 to 1.27)	45/443 (10.2)	50/431 (11.6)	0.42
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Breast cancer	2	All	2.34 (0.60 to 9.05)	7/1454 (0.5)	3/1452 (0.2)	NR
Wu, 2009[109]	Folic acid vs placebo	1 mg	Breast cancer	6.5	All	0.84 (0.25 to 2.79)	5/206 (2.4)	6/208 (2.9)	0.75
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Colorectal cancer	6.2	All	0.73 (0.16 to 3.29)	3/516 (0.6)	4/505 (0.8)	0.72
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	Colorectal cancer	3	All	1.00 (0.29 to 3.47)	5/470 (1.1)	5/469 (1.1)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Colorectal cancer	2	All	2.81 (1.01 to 7.83)	14/1454 (1.0)	5/1452 (0.3)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Colorectal cancer	6.5	All	HR=1.77 (1.08 to 2.90)	43/1257 (3.4)	25/1267 (2.0)	0.02
Wu, 2009[109]	Folic acid vs placebo	1 mg	Colorectal cancer	6.5	All	0.33 (0.03 to 3.16)	1/338 (0.3)	3/334 (0.9)	0.37

Appendix F Table 32. Folic Acid Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Ear/nose/throat cancer	2	All	3.00 (0.12 to 73.65)	1/1454 (0.1)	0/1452 (0.0)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Female reproductive system cancer	2	Females	2.96 (0.31 to 28.55)	3/736 (0.4)	1/725 (0.1)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Hematological cancer	2	All	0.83 (0.25 to 2.73)	5/1454 (0.3)	6/1452 (0.4)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Lung cancer	2	All	1.00 (0.32 to 3.10)	6/1454 (0.4)	6/1452 (0.4)	NR
Wu, 2009[109]	Folic acid vs placebo	1 mg	Lung cancer	6.5	All	1.32 (0.29 to 5.95)	4/338 (1.0)	3/334 (0.9)	1.00
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Male reproductive system cancer	2	Males	0.91 (0.37 to 2.25)	9/725 (1.2)	10/733 (1.4)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Melanoma skin cancer	2	All	2.00 (0.37 to 10.94)	4/1454 (0.3)	2/1452 (0.1)	NR
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Muskuloskeletal cancer	2	All	3.00 (0.12 to 73.65)	1/1454 (0.1)	0/1452 (0.0)	NR
Logan, 2008 (ukCAP)[108]	Folate vs. no folate	0.5 mg	Non-CRC cancer incidence	3	All	1.13 (0.43 to 2.94)	9/470 (1.9)	8/469 (1.7)	>0.05
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Other cancer	6.2	All	1.73 (1.10 to 2.72)	54/516 (10.5)	32/505 (6.3)	0.02
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Other GI cancer	2	All	7.02 (0.86 to 57.12)	7/1454 (0.5)	1/1452 (0.1)	NR
Cole, 2007 (AFPPS)[83]	Folic acid vs. placebo	1 mg	Prostate cancer	7	Males	HR=2.58 (1.14 to 5.86)	25/327 (7.6)	9/316 (2.8)	0.02
Wu, 2009[109]	Folic acid vs placebo	1 mg	Prostate cancer	6.5	All	0.79 (0.23 to 2.65)	5/132 (3.8)	6/126 (4.8)	0.75
van Wijngaarden, 2014 (B-PROOF)[96]	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	500 mcg + 400 mcg Folic acid	Urinary tract cancer	2	All	0.86 (0.29 to 2.55)	6/1454 (0.4)	7/1452 (0.5)	NR

*Studies providing estimates other than ORs display effect type

Appendix F Table 32. Folic Acid Cancer Results

Abbreviations: AFPPS = Aspirin/Folate Polyp Prevention Study; B-PROOF = B-Vitamins for the PRevention Of Osteoporotic Fractures; CG = Control group; CRC = Colorectal cancer; GI = Gastrointestinal; HR = Hazard ratio; IG = Intervention group; NR = Not reported; RR = Risk ratio; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; Vit D = Vitamin D

Appendix F Table 33. Folic Acid Adverse Event Outcomes

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)
Durga, 2007 (FACIT)[132]	800 mcg	Folic acid vs. placebo	Any AE	3	All	0.72 (0.23 to 2.30)	5/406 (1.2)	7/413 (1.7)
Logan, 2008 (ukCAP)[108]	0.5 mg	Folate vs. no folate	Gastrointestinal bleeding	3	All	0.66 (0.19 to 2.36)	4/470 (0.8)	6/469 (1.3)
Durga, 2007 (FACIT)[132]	800 mcg	Folic acid vs. placebo	Gastrointestinal symptoms	3	All	0.34 (0.01 to 8.33)	0/406 (0.0)	1/413 (0.2)
Logan, 2008 (ukCAP)[108]	0.5 mg	Folate vs. no folate	Gastrointestinal symptoms	3	All	1.07 (0.79 to 1.44)	115/470 (24.3)	109/469 (23.2)
Logan, 2008 (ukCAP)[108]	0.5 mg	Folate vs. no folate	Peptic ulcer	3	All	0.33 (0.03 to 3.20)	1/470 (0.2)	3/469 (0.6)
van Wijngaarden, 2014 (B-PROOF)[96]	0.5 mg + 400 mcg Folic acid	Vitamin B12 + Folic Acid + Vit D vs. Vit D alone	Withdrawals due to AEs	2	All	1.08 (0.50 to 2.30)	14/1461 (1.0)	13/1458 (0.9)
Wu, 2009[109]	1 mg	Folic acid vs placebo	Withdrawals due to AEs	6.5	All	0.14 (0.02 to 1.13)	1/338 (0.3)	7/334 (2.1)
Logan, 2008 (ukCAP)[108]	0.5 mg	Folate vs. no folate	Withdrawals due to GI AE	3	All	1.15 (0.77 to 1.71)	59/470 (12.5)	52/469 (11.1)

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; FACIT = Folic Acid and Carotid Intima-media Thickness; IG = Intervention group; GI = Gastrointestinal; mcg = Microgram; mg = Milligram; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix F Table 34. Summary of Results for Studies of Vitamin B3 and B6 Use

Study	Quality Rating	Study Design	N Rand.	Supplement (daily dose)	ACM	CVD	Cancer	AE
Chen, 2015 (ONTRAC)[101]	Good	RCT	386	Vitamin B3, nicotinamide (1,000 mg)	?	?	?	? Serious AE, cardiac chest pain
Feskanich, 2002 (NHS-I)[140, 152]	Fair	Cohort	75,864 cohort from 121,700	Vitamin B6 (NR)	NR	NR	NR	↔? (hip fracture)

Abbreviations: ACM = All-cause mortality; AE = Adverse event; CVD = Cardiovascular disease; mg = Milligram; NHS-I = Nurses' Health Study; NR = Not reported; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer; RCT = Randomized controlled trial

Appendix F Table 35. Vitamin B3 Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	All-cause mortality	1	All	2.01 (0.18 to 22.36)	2/193 (1.0)	1/193 (0.5)	NR

Abbreviation: CG = Control group; IG = Intervention group; mg = Milligram; NR = Not reported; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer

Appendix F Table 36. Vitamin B3 Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Heart failure	1	All	1.51 (0.25 to 9.13)	3/193 (1.6)	2/193 (1.0)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	MI	1	All	7.11 (0.36 to 138.58)	3/193 (1.6)	0/193 (0.0)	NR
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Other CVD	1	All	2.02 (0.37 to 11.17)	4/193 (2.1)	2/193 (1.0)	NR
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Other CVD	1	All	0.12 (0.01 to 0.97)	1/193 (0.5)	8/193 (4.1)	NR
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Stroke	1	All	0.33 (0.01 to 8.19)	0/193 (0.0)	1/193 (0.5)	NR, NS

Abbreviation: CG = Control group; IG = Intervention group; mg = Milligram; NR = Not reported; NS = Not significant; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer

Appendix F Table 37. Vitamin B3 Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Any cancer incidence	1	All	2.54 (0.49 to 13.25)	5/193 (2.6)	2/193 (1.0)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Bladder cancer	1	All	3.02 (0.12 to 74.49)	1/193 (0.5)	0/193 (0.0)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Colorectal cancer	1	All	3.02 (0.12 to 74.49)	1/193 (0.5)	0/193 (0.0)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Duodenal cancer	1	All	0.33 (0.01 to 8.19)	0/193 (0.0)	1/193 (0.5)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Lung cancer	1	All	1.00 (0.06 to 16.10)	1/193 (0.5)	1/193 (0.5)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Lymphoma, non-Hodgkin's	1	All	3.02 (0.12 to 74.49)	1/193 (0.5)	0/193 (0.0)	NR, NS
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Neoplasms (benign, malignant, unknown)	1	All	2.04 (0.60 to 6.90)	8/193 (4.1)	4/193 (2.1)	NR
Chen, 2015 (ONTRAC)[101]	Vitamin B3 vs. placebo	1000 mg	Prostate cancer	1	All	3.02 (0.12 to 74.49)	1/193 (0.5)	0/193 (0.0)	NR, NS

Abbreviation: CG = Control group; IG = Intervention group; mg = Milligram; NR = Not reported; NS = Not significant; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer

Appendix F Table 38. Vitamin B3, Vitamin B6, and Vitamin B12 Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Chen, 2015 (ONTRAC)[101]	1000 mg	Vitamin B3 vs. placebo	Cardiac chest pain	1	All	. (. to .)	8/193 (4.1)	1/193 (0.5)
Chen, 2015 (ONTRAC)[101]	1000 mg	Vitamin B3 vs. placebo	Serious AEs	1	All	. (. to .)	./193 (.)	./193 (.)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin B12 vs. no vitamin B12	Hip fracture	20.9	All	. (. to .)	./. (.)	./. (.)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin B6 vs. no vitamin B6	Hip fracture	20.9	All	. (. to .)	./. (.)	./. (.)
Feskanich, 2002 (NHS-I)[140]	<2 mg/day	Vitamin B6 vs. no vitamin B6	Hip fracture	20.9	All	RR 1.37 (1.12 to 1.69)	./. (.)	./. (.)
Feskanich, 2002 (NHS-I)[140]	≥25 mg/day	Vitamin B6 vs. no vitamin B6	Hip fracture	20.9	All	RR 1.41 (1.10 to 1.80)	./. (.)	./. (.)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; IG = Intervention group; mg = Milligram; NHS-I = Nurses' Health Study; NR = Not reported; ONTRAC = Oral Nicotinamide to Reduce Actinic Cancer

Appendix F Table 39. Summary of Results for Studies of Vitamin C Use

Author, Year (Study)	Quality Rating	Study Design	Study N*	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Salonen, 2000 (ASAP)[76]	Fair	RCT	390	Vitamin C (500 mg)	?	?	NR	? WD AE
				Vitamin C (500 mg) + Vitamin E (182 mg)	?	?	NR	? WD AE
Sesso, 2008 (PHS-II)[80]	Good	RCT	14641	Vitamin C (500 mg)	↔	↔	↔	↔ Nonserious AE: (e.g., GI symptoms, hematuria, easy bruising, epistaxis, peptic ulcer, fatigue, drowsiness, skin symptoms, migraine ↔ Cataracts
Feskanich, 2002 (NHS-I)[140]	Fair	Cohort	121700	Vitamin C (NR)	NR	NR	NR	↔ Cataracts
Rautiainen, 2010 (SMC)[145]	Fair	Cohort	38984	Vitamin C (~1000 mg)	NR	NR	NR	↑ Cataracts
Taylor, 2004 (HPFS)[144]	Fair	Cohort	51529	Vitamin C (1 - ≥1000 mg)	NR	NR	NR	↑? Kidney stones
Zheng Selin, 2013 (COSM)[142, 245]	Fair	Cohort	27343	Vitamin C (~1000 mg)	NR	NR	NR	↑ Cataracts ↑ Kidney stones

* Includes only participants randomized to an intervention group assigned to take vitamin C

Abbreviations: ACM = All-cause mortality; AE = Adverse event; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; COSM = Cohort of Swedish Men; CVD = Cardiovascular disease; HPFS = Health Professionals Followup Study; mg = Milligram; NHS-I = Nurses' Health Study I; NR = Not reported; PHS-II = Physicians' Health Study II; RCT = Randomized controlled trial; SMC = Swedish Mammography Cohort; WD = Withdrawal

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)
↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])
↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)
? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)
Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 40. Vitamin C Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Salonen, 2000 (ASAP)[76]	Vitamin C vs. Placebo	500 mg	All-cause mortality	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Salonen, 2000 (ASAP)[76]	Vitamin C + vitamin E vs. placebo	500 mg + 544 IU Vitamin E	All-cause mortality	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	All-cause mortality	8	All	HR=1.07 (0.97 to 1.18)	857/7329 (11.7)	804/7312 (11.0)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Any cancer deaths	8	All	HR=1.06 (0.97 to 1.18)	268/7329 (3.7)	255/7312 (3.5)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Colorectal cancer deaths	8	All	HR=1.04 (0.61 to 1.78)	27/7329 (0.4)	26/7312 (0.4)	NR
Salonen, 2000 (ASAP)[76]	Vitamin C vs. Placebo	500 mg	CVD deaths	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Salonen, 2000 (ASAP)[76]	Vitamin C + vitamin E vs. placebo	500 mg + 544 IU Vitamin E	CVD deaths	3	All	1.00 (0.06 to 16.16)	1/130 (0.8)	1/130 (0.8)	
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	CVD deaths	8	All	HR=1.02 (0.85 to 1.21)	256/7329 (3.5)	253/7312 (3.5)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Lung cancer deaths	8	All	HR=0.82 (0.53 to 1.25)	39/7329 (0.5)	48/7312 (0.7)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	MI, fatal	8	All	HR=1.37 (0.79 to 2.38)	30/7329 (0.4)	22/7312 (0.3)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Prostate cancer deaths	8	All	HR=1.46 (0.92 to 2.31)	45/7329 (0.6)	31/7312 (0.4)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Stroke deaths	8	All	HR=0.77 (0.52 to 1.14)	44/7329 (0.6)	57/7312 (0.8)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; CG = Control group; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; mg = Milligram; MI = Myocardial infarction; NR = Not reported; PHS-II = Physicians' Health Study II

Appendix F Table 41. Vitamin C Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Congestive heart failure	8	All	HR=1.02 (0.87 to 1.20)	293/7329 (4.0)	290/7312 (4.0)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	CVD events	8	All	HR=0.99 (0.89 to 1.11)	619 events/7329	626 events/7312	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	MI	8	All	HR=1.04 (0.87 to 1.24)	260/7329 (3.5)	251/7312 (3.4)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Stroke	8	All	HR=0.89 (0.74 to 1.07)	218/7329 (3.0)	246/7312 (3.4)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Stroke, Hemorrhagic	8	All	HR=0.95 (0.57 to 1.56)	30/7329 (0.4)	32/7312 (0.4)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Stroke, Ischemic	8	All	HR=0.87 (0.71 to 1.07)	180/7329 (2.5)	207/7312 (2.8)	NR

Abbreviations: . = not reported; CG = Control group; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; mg = Milligram; MI = Myocardial infarction; NR = Not reported; PHS-II = Physicians' Health Study II

Appendix F Table 42. Vitamin C Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Any cancer incidence	8	All	HR=1.01 (0.92 to 1.10)	973/7329 (13.3)	970/7312 (13.3)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Colorectal cancer	8	All	HR=0.86 (0.63 to 1.17)	75/7329 (1.0)	87/7312 (1.2)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Lung cancer	8	All	HR=0.95 (0.64 to 1.39)	50/7329 (0.7)	53/7312 (0.7)	NR
Sesso, 2008 (PHS-II)[80]	Vitamin C vs. no vitamin C	500 mg	Prostate cancer	8	All	HR=1.02 (0.90 to 1.15)	508/7329 (6.9)	500/7312 (6.8)	NR

Abbreviations: . = not reported; CG = Control group; HR = Hazard ratio; IG = Intervention group; mg = Milligram; NR = Not reported; PHS-II = Physicians' Health Study II

Appendix F Table 43. Vitamin C Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin C <2 yrs use vs. no vitamin C	Cataract	12	All	RR=1.08 (0.88 to 1.32)	210/100000 p-y	188/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin C 2-4 yrs use vs. no vitamin C	Cataract	12	All	RR=1.01 (0.76 to 1.33)	201/100000 p-y	188/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin C 5-9 yrs use vs. no vitamin C	Cataract	12	All	RR=1.05 (0.84 to 1.31)	213/100000 p-y	188/100000 p-y
Feskanich, 2002 (NHS-I)[140]	NR	Vitamin C ≥10 yrs use vs. no vitamin C	Cataract	12	All	RR=0.95 (0.76 to 1.20)	200/100000 p-y	188/100000 p-y
Rautiainen, 2010 (SMC)[145]	1000 mg	Vitamin C vs. no supplement	Cataract	8.2	All	HR=1.25 (1.05 to 1.50)	143 events/1225	3/75524 p-y
Sesso, 2008 (PHS-II)[80]	500 mg	Vitamin C vs. no vitamin C	Cataract	8	All	HR=1.02 (0.91 to 1.14)	593 events/5799	581 events/5746
Zheng Selin, 2013 (COSM)[142]	Varies	Vitamin C vs. no vitamin C	Cataract	8.4	All	HR=1.21 (1.04 to 1.41)	188/1652 (11.4)	1937/22015 (8.8)
Taylor, 2004 (HPFS)[144]	1-99 mg	Vitamin C 1-99 mg/day vs. no use or other doses	Kidney stones	14	All	RR=0.95 (0.81 to 1.12)	298 events/.	618 events/.
Taylor, 2004 (HPFS)[144]	100-499 mg	Vitamin C 100-499 mg/day vs. no use or other doses	Kidney stones	14	All	RR=0.91 (0.78 to 1.07)	208 events/.	618 events/.
Taylor, 2004 (HPFS)[144]	500-999 mg	Vitamin C 500-999 mg/day vs. no use or other doses	Kidney stones	14	All	RR=1.11 (0.93 to 1.34)	161 events/.	618 events/.
Taylor, 2004 (HPFS)[144]	≥1000 mg	Vitamin C ≥1000 mg/day vs. no use or other doses	Kidney stones	14	All	RR=1.16 (0.97 to 1.39)	188 events/.	618 events/.

Appendix F Table 43. Vitamin C Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Zheng Selin, 2013 (COSM)[142]	Varied	Vitamin C vs. no vitamin C	Kidney stones	11	All	RR=1.92 (1.33 to 2.77)	31/907 (3.4)	405/22448 (1.8)
Sesso, 2008 (PHS-II)[80]	500 mg	Vitamin C vs. no vitamin C	Non-serious: Hematuria (NS), easy bruising (NS), epistaxis (NS), peptic ulcer (NS), constipation (NS), diarrhea (NS), gastritis (NS), nausea (NS), fatigue (NS), drowsiness (NS), skin discoloration or rashes (NS), and migraine (NS)	8	All	. (. to .)	./7329 (.)	./7312 (.)
Salonen, 2000 (ASAP)[76]	500 mg	Vitamin C vs. Placebo	Withdrawals due to AEs	3	All	0.74 (0.25 to 2.19)	6/130 (4.6)	8/130 (6.2)
Salonen, 2000 (ASAP)[76]	500 mg + 544 IU Vitamin E	Vitamin C + vitamin E vs. placebo	Withdrawals due to AEs	3	All	0.87 (0.31 to 2.47)	7/130 (5.4)	8/130 (6.2)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; CG = Control group; COSM = Cohort of Swedish Men; HPFS = Health Professionals Followup Study; HR = Hazard ratio; IG = Intervention group; IU = International units; mg = Milligram; NHS-I = Nurses' Health Study I; NR = Not reported; NS = Not significant; PHS-II = Physicians' Health Study II; p-y = Person-years; RR = Risk ratio; SMC = Swedish Mammography Cohort; yrs = Years

Appendix F Table 44. Calcium Meta-Analysis Results

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	MH	1.05 (0.92 to 1.21)	6	8,394	NA	NA
	Peto	1.05 (0.92 to 1.21)	6	8,394	0	0.0
	REML-KH	1.05 (0.94 to 1.19)	6	8,394	0	0.0
	Full ascert. (MH)	1.05 (0.90 to 1.21)	3	5,574	NA	NA
CVD mortality	MH	1.03 (0.84 to 1.27)	3	5,574	NA	NA
	Peto	0.95 (0.66 to 1.35)	3	5,574	28.3	0.04
	Full ascert. (MH)	1.03 (0.84 to 1.27)	3	5,574	NA	NA
Composite CVD event	MH	1.11 (0.90 to 1.36)	4	4,076	NA	NA
	Peto	1.11 (0.90 to 1.36)	4	4,076	0	0.0
MI	MH	1.18 (0.72 to 1.92)	3	3,361	NA	NA
	Peto	1.09 (0.23 to 5.27)	3	3,361	78.6	1.38
Stroke	MH	1.21 (0.87 to 1.69)	4	5,536	NA	NA
	Peto	1.21 (0.87 to 1.68)	4	5,536	0	0.0
	Full ascert. (MH)	1.23 (0.86 to 1.77)	3	4,606	NA	NA
Any cancer incidence	REML-KH	0.94 (0.41 to 2.11)	3	5,051	49.2	0.04
	Full ascert. (REML)	0.94 (0.41 to 2.11)	3	5,051	49.2	0.04

Abbreviations: CI = Confidence interval; CVD = Cardiovascular disease; Full ascert. = Full ascertainment; MH = Mantel-Haenszel common effects model; MI = Myocardial infarction; NA = Not applicable; No. = Number; Peto odds ratio random effects REML model; REML-KH = Random effects restricted maximum likelihood model with the Knapp-Hartung adjustment

Appendix F Table 45. Summary of Results for Studies of Calcium Use

Author, Year (Study)	Final Quality Rating	Study Design	N	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Avenell, 2012 (RECORD)[88]	Fair	RCT	5292	Calcium (1000 mg)	↔	↔	↔	↔ Fractures ↑ GI sx
Baron, 2005 (CPPS)[84]	Fair	RCT	930	Calcium (1200 mg)	↔	↔	Prostate: ↓?	↔ AE WD ↑? GI hosp
Baron, 2015 (VCPPS)[90]	Good	RCT	2259	Calcium (1200 mg)*	↔	?	↔	↔ Fractures, kidney stones
Bolland, 2008 (ACS)[81]	Fair	RCT	1471	Calcium (1000 mg)	↔	↑?	NR	↑ Constipation ? Fractures
Fedirko, 2009[113]	Fair	RCT	92	Calcium (2000 mg)	NR	NR	NR	? Any AE
Lappe, 2007[82]	Fair	RCT	1180	Calcium (1500 mg)	NR	NR	↓?	? Serious AE, kidney stones
Lewis, 2011 (CAIFOS)[104]	Good	RCT	1460	Calcium (1200 mg)	↔	↔	NR	↑ Constipation, fractures ? Kidney stones
Reid, 2008[105]	Fair	RCT	323	Calcium (1200 mg) Calcium (600 mg)	?	?	NR	? AE WD, constipation, fractures, kidney stones
Feskanich, 2002 (NHS-I)[140]	Fair	Cohort	121700	Vitamin D (4 dose levels)	NA	NA	NA	↑? Kidney stones

*Only provided calcium vs. no calcium comparison in factorial design with concomitant vitamin D use in some participants

Abbreviations: ACM = All-cause mortality; ACS = Auckland calcium study; AE = Adverse event; CAIFOS = Calcium Intake Fracture Outcome Study; CPPS = Calcium Polyp Prevention Study; CVD = Cardiovascular disease; GI = Gastrointestinal; hosp = Hospitalization; mg = Milligrams; NA = Not applicable; NHS – I = Nurses' Health Study; NR = Not reported; RECORD = Randomized Evaluation of Calcium OR vitamin D; RCT = Randomized controlled trial; sx = Symptoms; VCPPS = Vitamin D/Calcium Polyp Prevention Study; WD = Withdrawal; WHI = Women's Health Initiative

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])

↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side CIs)

↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and CIs minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and CIs minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)

Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 46. Calcium Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	All-cause mortality	6.2	All	1.07 (0.91 to 1.26)	447/1311 (34.1)	434/1332 (32.6)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	All-cause mortality	6.2	All	HR=1.03 (0.94 to 1.13)	862/2617 (32.9)	855/2675 (32.0)	0.460
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	All-cause mortality	4	All	1.15 (0.64 to 2.07)	25/464 (5.4)	22/466 (4.7)	NR, NS
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	All-cause mortality	3.8	All	1.08 (0.49 to 2.38)	13/840 (1.5)	12/835 (1.4)	0.85
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	All-cause mortality	5	All	RR=1.18 (0.73 to 1.92)	34/732 (4.6)	29/739 (3.9)	0.52
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	All-cause mortality	5	All	0.75 (0.46 to 1.24)	29/730 (4.0)	38/730 (5.2)	NR
Reid, 2008[105]	Calcium vs. placebo	1200 mg	All-cause mortality	2	All	0.99 (0.06 to 16.05)	1/108 (0.9)	1/107 (0.9)	NR
Reid, 2008[105]	Calcium vs. placebo	600 mg	All-cause mortality	2	All	0.99 (0.06 to 16.05)	1/108 (0.9)	1/107 (0.9)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Any cancer deaths	6.2	All	1.18 (0.87 to 1.59)	95/1311 (7.2)	83/1332 (6.2)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Any cancer deaths	6.2	All	HR=1.13 (0.91 to 1.40)	173/2617 (6.6)	156/2675 (5.8)	0.249
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Arrhythmia deaths	5	All	0.33 (0.03 to 3.20)	1/730 (0.1)	3/730 (0.4)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Arrhythmia deaths	9.5	All	0.62 (0.28 to 1.38)	10/730 (1.4)	16/730 (2.2)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Breast cancer deaths	6.2	All	2.29 (0.70 to 7.47)	9/1311 (0.7)	4/1332 (0.3)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Breast cancer deaths	6.2	All	1.49 (0.69 to 3.22)	16/2617 (0.6)	11/2675 (0.4)	NR
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Cerebrovascular death	5	All	0.75 (0.26 to 2.17)	6/730 (0.8)	8/730 (1.1)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Cerebrovascular death	9.5	All	0.91 (0.49 to 1.68)	20/730 (2.7)	22/730 (3.0)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Colorectal cancer deaths	6.2	All	1.19 (0.40 to 3.54)	7/1311 (0.5)	6/1332 (0.5)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Colorectal cancer deaths	6.2	All	1.58 (0.78 to 3.18)	20/2617 (0.8)	13/2675 (0.5)	NR

Appendix F Table 46. Calcium Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	CVD deaths	6.2	All	1.10 (0.88 to 1.37)	194/1311 (14.8)	182/1332 (13.7)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	CVD deaths	6.2	All	HR=1.07 (0.92 to 1.24)	371/2617 (14.2)	355/2675 (13.3)	0.333
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	CVD deaths	5	All	RR=0.51 (0.13 to 2.01)	3/732 (0.4)	6/739 (0.8)	0.51
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	CVD deaths	5	All	0.74 (0.40 to 1.38)	18/730 (2.5)	24/730 (3.3)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	CVD deaths	9.5	All	0.80 (0.56 to 1.15)	59/730 (8.1)	72/730 (9.9)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Heart failure deaths	5	All	0.66 (0.24 to 1.87)	6/730 (0.8)	9/730 (1.2)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Heart failure deaths	9.5	All	0.50 (0.26 to 0.97)	14/730 (1.9)	27/730 (3.7)	0.040
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Ischemic heart disease deaths	5	All	1.45 (0.62 to 3.42)	13/730 (1.8)	9/730 (1.2)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Ischemic heart disease deaths	9.5	All	0.94 (0.58 to 1.52)	34/730 (4.7)	36/730 (4.9)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Lung cancer deaths	6.2	All	0.63 (0.31 to 1.25)	13/1311 (1.0)	21/1332 (1.6)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Lung cancer deaths	6.2	All	0.89 (0.53 to 1.49)	27/2617 (1.0)	31/2675 (1.2)	NR
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Peripheral artery disease deaths	5	All	1.00 (0.06 to 16.02)	1/730 (0.1)	1/730 (0.1)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Peripheral artery disease deaths	9.5	All	0.25 (0.03 to 2.23)	1/730 (0.1)	4/730 (0.5)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Prostate cancer deaths	6.2	All	1.02 (0.20 to 5.04)	3/1311 (0.2)	3/1332 (0.2)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Prostate cancer deaths	6.2	All	0.73 (0.23 to 2.30)	5/2617 (0.2)	7/2675 (0.3)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: ACS = Auckland calcium study; CAIFOS = Calcium Intake Fracture Outcome Study; CG = Control group; CVD = Cardiovascular disease; g = Gram; HR = Hazard ratio; IG = Intervention group; IU = International units; mg = Milligram; NR = Not reported; NS = Not significant; RECORD = Randomized Evaluation of Calcium OR vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study

Appendix F Table 47. Calcium Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Cerebrovascular events	5	All	1.21 (0.70 to 2.08)	30/730 (4.1)	25/730 (3.4)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Cerebrovascular events	9.5	All	0.78 (0.52 to 1.16)	45/730 (6.2)	57/730 (7.8)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg	Congestive heart failure	6.2	All	HR=0.75 (0.58 to 0.97)	102 events/ 2649 (3.8)	136 events/ 2643 (5.1)	0.027
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg	CVD events	6.2	All	HR=0.92 (0.80 to 1.08)	339 events/ 2649 (12.8)	363 events/ 2643 (13.7)	0.32
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	CVD events	4	All	1.10 (0.72 to 1.68)	50/464 (10.8)	46/466 (9.9)	NR, NS
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	CVD events	5	All	RR=1.21 (0.84 to 1.74)	60/732 (8.2)	50/739 (6.8)	0.32
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	CVD events	5	All	IRR=1.43 (1.01 to 2.04)	23.3/1000 p-y	16.3/1000 p-y	0.043
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	CVD events	5	All	HR=0.94 (0.69 to 1.27)	104/730 (14.2)	103/730 (14.1)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	CVD events	9.5	All	HR=0.92 (0.74 to 1.15)	195/730 (26.7)	200/730 (27.4)	NR, NS
Reid, 2008[105]	Calcium vs. placebo	1200 mg	CVD events	2	All	7.13 (0.36 to 139.77)	3/108 (2.8)	0/107 (0.0)	NR, NS
Reid, 2008[105]	Calcium vs. placebo	600 mg	CVD events	2	All	5.05 (0.24 to 106.37)	2/108 (1.9)	0/107 (0.0)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Heart failure	5	All	0.78 (0.29 to 2.09)	7/730 (1.0)	9/730 (1.2)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Heart failure	9.5	All	0.78 (0.44 to 1.37)	22/730 (3.0)	28/730 (3.8)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Ischemic heart disease	5	All	0.92 (0.62 to 1.37)	50/730 (6.8)	54/730 (7.4)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Ischemic heart disease	9.5	All	1.00 (0.72 to 1.37)	85/730 (11.6)	85/730 (11.6)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg	MI	6.2	All	HR=0.97 (0.75 to 1.26)	114 events/ 2649 (4.3)	117 events/ 2643 (4.4)	0.84
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	MI	3.8	All	0.22 (0.05 to 1.02)	2/840 (0.2)	9/835 (1.1)	0.03
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	MI	5	All	IRR=1.67 (0.98 to 2.87)	11.1/1000 p-y	6.6/1000 p-y	0.058

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	MI	5	All	RR=1.49 (0.86 to 2.57)	31/732 (4.2)	21/739 (2.8)	0.16
Reid, 2008[105]	Calcium vs. placebo	1200 mg	MI	2	All	5.05 (0.24 to 106.37)	2/108 (1.9)	0/107 (0.0)	NR, NS
Reid, 2008[105]	Calcium vs. placebo	600 mg	MI	2	All	3.00 (0.12 to 74.47)	1/108 (0.9)	0/107 (0.0)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Nonfatal CVD events	5	All	1.00 (0.73 to 1.36)	91/730 (12.5)	91/730 (12.5)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Nonfatal CVD events	9.5	All	0.93 (0.73 to 1.19)	160/730 (21.9)	169/730 (23.2)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Other CVD	5	All	1.32 (0.68 to 2.55)	21/730 (2.9)	16/730 (2.2)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Other CVD	9.5	All	0.97 (0.62 to 1.53)	39/730 (5.3)	40/730 (5.5)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Peripheral artery disease	5	All	0.83 (0.36 to 1.94)	10/730 (1.4)	12/730 (1.6)	NR, NS
Lewis, 2011 (CAIFOS)[104]	Calcium vs. placebo	1200 mg	Peripheral artery disease	9.5	All	1.06 (0.55 to 2.03)	19/730 (2.6)	18/730 (2.5)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg	Stroke	6.2	All	HR=1.06 (0.85 to 1.32)	160 events/ 2649 (6.0)	149 events/ 2643 (5.6)	0.61
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	Stroke	4	All	1.10 (0.48 to 2.51)	12/464 (2.4)	11/466 (2.6)	NR, NS
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	Stroke	3.8	All	0.59 (0.14 to 2.50)	3/840 (0.4)	5/835 (0.6)	0.51
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	Stroke	5	All	RR=1.37 (0.83 to 2.28)	34/732 (4.6)	25/739 (3.4)	0.23
Bolland, 2008 (ACS)[81]	Calcium vs. placebo	1 g	Stroke	5	All	IRR=1.45 (0.88 to 2.49)	11.4/1000 p-y	7.8/1000 p-y	0.15
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	Transient ischemic attack	3.8	All	0.14 (0.01 to 2.74)	0/840 (0.0)	3/835 (0.4)	0.12
Reid, 2008[105]	Calcium vs. placebo	1200 mg	Transient ischemic attack	2	All	0.99 (0.06 to 16.05)	1/108 (0.9)	1/107 (0.9)	NR, NS
Reid, 2008[105]	Calcium vs. placebo	600 mg	Transient ischemic attack	2	All	0.33 (0.01 to 8.12)	0/108 (0.0)	1/107 (0.9)	NR, NS

*Studies providing estimates other than ORs display effect type

Abbreviations: ACS = Auckland calcium study; CAIFOS = Calcium Intake Fracture Outcome Study; CG = Control group; CPPS = Calcium Polyp Prevention Study; CVD = Cardiovascular disease; g = Gram; HR = Hazard ratio; IG = Intervention group; IRR = Incidence rate ratio; IU = International units; mg = Milligram; NR = Not reported; NS = Not significant; p-y = Person-years; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study

Appendix F Table 48. Calcium Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	Adenomas	4	All	RR=0.85 (0.74 to 0.98)	195/454 (43.0)	234/459 (51.0)	0.03
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Any cancer incidence	6.2	All	1.10 (0.87 to 1.39)	163/1311 (12.4)	152/1332 (11.4)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Any cancer incidence	6.2	All	. (. to .)	371 events/2617	352 events/2675	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Any cancer incidence	6.2	All	HR=1.06 (0.91 to 1.23)	329/2617 (12.6)	324/2675 (12.1)	0.485
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	Any cancer incidence	3.8	All	0.99 (0.65 to 1.51)	46/840 (5.5)	46/835 (5.5)	0.98
Lappe, 2007[82]	Calcium vs. placebo	1500 mg	Any cancer incidence	4	All	RR=0.53 (0.27 to 1.03)	17/445 (3.8)	20/288 (6.9)	0.063
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Breast cancer	6.2	All	. (. to .)	21 events/1311	16 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Breast cancer	6.2	All	. (. to .)	41 events/2617	39 events/2675	NR
Lappe, 2007[82]	Calcium vs. placebo	1500 mg	Breast cancer	4	All	0.48 (0.16 to 1.39)	6/445 (1.3)	8/288 (2.8)	NR, NS
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Colorectal cancer	6.2	All	. (. to .)	22 events/1311	8 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Colorectal cancer	6.2	All	. (. to .)	46 events/2617	25 events/2675	NR
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	Colorectal cancer	3.8	All	4.98 (0.24 to 103.93)	2/840 (0.2)	0/835 (0.0)	0.50
Lappe, 2007[82]	Calcium vs. placebo	1500 mg	Colorectal cancer	4	All	0.13 (0.01 to 2.69)	0/445 (0.0)	2/288 (0.7)	NR
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	Invasive large-bowel cancer	4	All	0.33 (0.03 to 3.22)	1/464 (0.2)	3/466 (0.6)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Lung cancer	6.2	All	. (. to .)	14 events/1311	18 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Lung cancer	6.2	All	. (. to .)	24 events/2617	32 events/2675	NR
Lappe, 2007[82]	Calcium vs. placebo	1500 mg	Lung cancer	4	All	0.64 (0.13 to 3.22)	3/445 (0.7)	3/288 (1.0)	NR
Lappe, 2007[82]	Calcium vs. placebo	1500 mg	Lymph, leukemia, myeloma	4	All	0.64 (0.16 to 2.60)	4/445 (0.9)	4/288 (1.4)	NR

Appendix F Table 48. Calcium Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Baron, 2015 (VCPPS)[90]	Calcium vs. no calcium	1200 mg + 1000 IU Vitamin D	Non-CRC cancer incidence	3.8	All	0.95 (0.62 to 1.45)	44/840 (5.2)	46/835 (5.5)	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. placebo	1000 mg	Prostate cancer	6.2	All	. (. to .)	4 events/1311	8 events/1332	NR
Avenell, 2012 (RECORD)[88]	Calcium vs. no calcium	1000 mg + 800 IU Vitamin D	Prostate cancer	6.2	All	. (. to .)	12 events/2617	17 events/2675	NR
Baron, 2005 (CPPS)[84]	Calcium vs. placebo	1200 mg	Prostate cancer	6	All	RR=0.52 (0.28 to 0.98)	15/345 (4.3)	27/327 (8.3)	<0.05

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; CG = Control group; CPPS = Calcium Polyp Prevention Study; CRC = Colorectal cancer; IG = Intervention group; IU = International units; mg = Milligram; NR = Not reported; NS = Not significant; HR = Hazard ratio; RECORD = Randomized Evaluation of Calcium OR vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study

Appendix F Table 49. Calcium Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Fedirko, 2009[113]	2 g	Calcium vs. placebo	Any AE	0.5	All	1.00 (0.02 to 52.53)	0/23 (0.0)	0/23 (0.0)
Bolland, 2008 (ACS) [81]	1 g	Calcium vs. placebo	Constipation	5	All	1.76 (1.31 to 2.37)	132/732 (18.0)	82/739 (11.1)
Lewis, 2011 (CAIFOS)[104]	1200 mg	Calcium vs. placebo	Constipation	5	All	1.56 (1.12 to 2.17)	98/730 (13.4)	66/730 (9.1)
Reid, 2008[105]	1200 mg	Calcium vs. placebo	Constipation	2	All	1.50 (0.25 to 9.16)	3/108 (2.8)	2/107 (1.9)
Reid, 2008[105]	600 mg	Calcium vs. placebo	Constipation	2	All	0.99 (0.14 to 7.16)	2/108 (1.9)	2/107 (1.9)
Avenell, 2012 (RECORD)[88]	1000 mg	Calcium vs. placebo	Fractures	3.75	All	0.98 (0.78 to 1.21)	185/1311 (14.1)	192/1332 (14.4)
Avenell, 2012 (RECORD)[88]	1000 mg + 800 IU Vitamin D	Calcium + vitamin D vs. placebo	Fractures	3.75	All	0.94 (0.76 to 1.17)	179/1306 (13.7)	192/1332 (14.4)
Avenell, 2012 (RECORD)[88]	1000 mg + 800 IU Vitamin D	Calcium vs. no calcium	Fractures	3.75	All	HR=0.99 (0.86 to 1.15)	364/2617 (13.9)	400/2675 (15.0)
Baron, 2015 (VCPPS)[90]	1200 mg + 1000 IU Vitamin D	Calcium vs. no calcium	Fractures	3.8	All	0.85 (0.54 to 1.33)	37/840 (4.4)	43/835 (5.1)
Bolland, 2008 (ACS)[81]	1 g	Calcium vs. placebo	Fractures	5	All	HR=3.55 (1.31 to 9.63)	17/732 (2.3)	5/739 (0.7)
Lewis, 2011 (CAIFOS)[104]	1200 mg	Calcium vs. placebo	Fractures	5	All	HR=0.87 (0.67 to 1.12)	./730 (.)	./730 (.)
Reid, 2008[105]	1200 mg	Calcium vs. placebo	Fractures	2	All	0.48 (0.14 to 1.63)	4/108 (3.7)	8/107 (7.5)
Reid, 2008[105]	600 mg	Calcium vs. placebo	Fractures	2	All	0.60 (0.19 to 1.90)	5/108 (4.6)	8/107 (7.5)
Wactawski-Wende, 2006 (WHI)[78]	1000 mg + 400 IU Vitamin D	Calcium + vitamin D vs. placebo	Fractures	11.9	All	HR=0.99 (0.94 to 1.03)	4013/18176 (22.1)	4018/18106 (22.2)
Avenell, 2012 (RECORD)[88]	1000 mg + 800 IU Vitamin D	Calcium vs. no calcium	Gastrointestinal symptoms	3.75	All	1.44 (1.24 to 1.69)	428/2617 (16.4)	319/2675 (11.9)
Baron, 2005 (CPPS)[84]	1200 mg	Calcium vs. placebo	GI disease-related hospitalization	4	All	1.21 (0.74 to 1.97)	38/464 (8.2)	32/466 (6.9)

Appendix F Table 49. Calcium Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Baron, 2015 (VCPPS)[90]	1200 mg + 1000 IU Vitamin D	Calcium vs. no calcium	Kidney stones	3.8	All	1.33 (0.68 to 2.62)	20/840 (2.4)	15/835 (1.8)
Feskanich, 2002 (NHS-I)[140]	NR	Calcium vs. no Calcium	Kidney stones	12	All	RR=1.20 (1.02 to 1.41)	227 events/.	331 events/.
Feskanich, 2002 (NHS-I)[140]	mg/d	Calcium 1-100 mg/d vs. no Calcium	Kidney stones	12	All	RR=1.26 (0.79 to 2.00)	19 events/.	331 events/.
Feskanich, 2002 (NHS-I)[140]	mg/d	Calcium 101-500 mg/d vs. no Calcium	Kidney stones	12	All	RR=1.18 (0.98 to 1.43)	160 events/.	331 events/.
Feskanich, 2002 (NHS-I)[140]	mg/d	Calcium ≥500 mg/d vs. no Calcium	Kidney stones	12	All	RR=1.21 (0.96 to 1.52)	98 events/.	331 events/.
Lappe, 2007[82]	1500 mg	Calcium vs. placebo	Kidney stones	4	All	1.95 (0.20 to 18.82)	3/445 (0.7)	1/288 (0.3)
Lappe, 2007[82]	1500 mg + 1000 IU Vitamin D	Calcium + vitamin D vs. placebo	Kidney stones	4	All	0.64 (0.04 to 10.35)	1/446 (0.2)	1/288 (0.3)
Lappe, 2017[92]	1500 mg + 2000 IU Vitamin D	Calcium + vitamin D vs. placebo	Kidney stones	4	All	1.60 (0.72 to 3.54)	16/1102 (1.4)	10/1095 (0.9)
Lewis, 2011 (CAIFOS)[104]	1200 mg	Calcium vs. placebo	Kidney stones	5	All	1.00 (0.14 to 7.12)	2/730 (0.3)	2/730 (0.3)
Reid, 2008[105]	1200 mg	Calcium vs. placebo	Kidney stones	2	All	0.33 (0.01 to 8.12)	0/108 (0.0)	1/107 (0.9)
Reid, 2008[105]	600 mg	Calcium vs. placebo	Kidney stones	2	All	0.33 (0.01 to 8.12)	0/108 (0.0)	1/107 (0.9)
Wactawski-Wende, 2006 (WHI)[78]	1000 mg + 400 IU Vitamin D	Calcium + vitamin D vs. placebo	Kidney stones	7	All	HR=1.17 (1.02 to 1.34)	449/18176 (0.3)	381/18106 (0.3)
Baron, 2005 (CPPS)[84]	1200 mg	Calcium vs. placebo	Non-serious: Cancer-related hospitalization (NS)	4	All	. (. to .)	./464 (.)	./466 (.)
Baron, 2005 (CPPS)[84]	1200 mg	Calcium vs. placebo	Non-serious: Hospitalization (all-cause) (NS)	4	All	. (. to .)	./464 (.)	./466 (.)
Lappe, 2017[92]	1500 mg + 2000 IU Vitamin D	Calcium + vitamin D vs. placebo	Non-serious: Hypercalcemia (NS)	4	All	. (. to .)	./1102 (.)	./1095 (.)
Lappe, 2007[82]	1500 mg	Calcium vs. placebo	Serious AEs	4	All	0.65 (0.01 to 32.73)	0/445 (0.0)	0/288 (0.0)

Appendix F Table 49. Calcium Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Lappe, 2007[82]	1500 mg + 1000 IU Vitamin D	Calcium + vitamin D vs. placebo	Serious AEs	4	All	0.65 (0.01 to 32.65)	0/446 (0.0)	0/288 (0.0)
Lappe, 2017[92]	1500 mg + 2000 IU Vitamin D	Calcium + vitamin D vs. placebo	Serious AEs	4	All	0.99 (0.02 to 50.12)	0/1102 (0.0)	0/1095 (0.0)
Baron, 2005 (CPPS)[84]	1200 mg	Calcium vs. placebo	Withdrawals due to AEs	4	All	0.93 (0.42 to 2.05)	12/464 (2.6)	13/466 (2.8)
Lappe, 2017[92]	1500 mg + 2000 IU Vitamin D	Calcium + vitamin D vs. placebo	Withdrawals due to AEs	4	All	1.24 (0.90 to 1.69)	93/1102 (8.4)	76/1095 (6.9)
Reid, 2008[105]	1200 mg	Calcium vs. placebo	Withdrawals due to AEs	2	All	3.09 (0.61 to 15.66)	6/108 (5.6)	2/107 (1.9)
Reid, 2008[105]	600 mg	Calcium vs. placebo	Withdrawals due to AEs	2	All	1.50 (0.25 to 9.16)	3/108 (2.8)	2/107 (1.9)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; ACS = Auckland calcium study; AE = Adverse event; CAIFOS = Calcium Intake Fracture Outcome Study; CG = Control group; CPPS = Calcium Polyp Prevention Study; g = Grams; GI = Gastrointestinal; HR = Hazard ratio; IG = Intervention group; IU = International units; mg/d = Milligrams per day; NHS – I = Nurses' Health Study; NR = Not reported; NS = Not significant; RECORD = Randomized Evaluation of Calcium OR vitamin D; RR = Risk ratio; VCPPS = Vitamin D/Calcium Polyp Prevention Study; WHI = Women's Health Initiative

Appendix F Table 50. Summary of Results for Studies of Selenium Use

Author, Year (Study)	Quality Rating	Study Design	Study N*	Supplement (daily dose)	ACM	CVD	Cancer	Harms
Clark, 1996 (NPC)[77]	Fair	RCT	1312	Selenium (200 mcg)	↔	↔	↓	↑? (AE WD)
Lippman, 2009 (SELECT)[79]	Good	RCT	25,984	Selenium (200 mcg)	↔	↔	↔	↑? (Dermatitis)
				Selenium (200 mcg) + Vitamin E (400 IU)	↔	↔	↔	↔? (Dermatitis)
Rayman, 2012 (UK-PRECISE)[89]	Fair	RCT	501	Selenium (100 mcg)	NR	NR	NR	↔? (Serious, AE WD)
				Selenium (200 mcg)	NR	NR	NR	
				Selenium (300 mcg)	NR	NR	NR	
Rayman, 2018 (DK-PRECISE)[97]	Fair	RCT	491	Selenium (100 mcg)	↔	?	?	↑? (ACM, 300 mg/d only) ↔? (AE WD)
				Selenium (200 mcg)	↔	?	?	
				Selenium (300 mcg)	↔	?	?	
Thompson, 2016 (Sel/Cel)[98]	Fair	RCT	1621	Selenium (200 mcg)	↔	NR	?	↔? (Serious, non-serious)

* Includes only participants randomized to an intervention group assigned to take selenium

Abbreviations: ACM = All-cause mortality; AE = Adverse events; CVD = Cardiovascular disease; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; mcg = Micrograms; mg/d = Milligrams per deciliter; NPC = Nutritional Prevention of Cancer; NR = Not reported; RCT = Randomized controlled trial; Sel = Selenium; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial; UK-PRECISE = United Kingdom PREvention of Cancer by Intervention with Selenium; WD = Withdrawal

↑ Likely non-trivial increase in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and Cis minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

↑? Possible non-trivial increase in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and Cis minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↔ Evidence of no to minimal group differences (e.g., few to no statistically significant findings with reasonably precise estimates [e.g., >~20 events in all treatment arms])

↔? Limited evidence of no to minimal group differences (e.g., few to no statistically significant findings, but imprecise estimates/side Cis)

↓? Possible non-trivial decrease in events (e.g., statistically significant effects of questionable clinical importance, or moderate to large effect size and Cis minimally overlap line of no effect or inconsistency of effects where multiple related effects are reported)

↓ Likely non-trivial decrease in events (e.g., magnitude of effect size likely to be clinically important with statistically significant effect, or large effect size and Cis minimally overlap the line of no effect; and with reasonable consistency of effects where multiple related effects are reported)

? Insufficient evidence to evaluate (e.g., very few [e.g., <10] events)

Judgement for symbols based on totality of evidence for each study, considering statistical and clinical significance

Appendix F Table 51. Selenium Meta-Analysis Results: Results of Meta-Analyses by Outcome, Primary Analysis Listed First for Each Outcome, Followed by Sensitivity Analyses

Outcome	Model/Analysis	Pooled OR (95% CI)	No. studies	N analyzed	I^2, %	Tau^2
All-cause mortality	MH	0.94 (0.83 to 1.07)	4	20,832	NA	NA
	Peto	0.94 (0.82 to 1.08)	4	20,832	4.7	.00
	REML-KH	0.94 (0.79 to 1.12)	4	20,832	26.4	.01
CVD mortality	MH	0.93 (0.75 to 1.14)	3	19,008	NA	NA
	Peto	0.93 (0.75 to 1.14)	3	19,008	0	.00
	REML-KH	0.93 (0.74 to 1.18)	3	19,008	14.4	.01
Cancer mortality	MH	0.86 (0.69 to 1.06)	3	19,008	NA	NA
	Peto	0.74 (0.42 to 1.30)	3	19,008	71.6	.15
	REML-KH	0.74 (0.26 to 2.08)	3	19,008	59.4	.10
Colorectal cancer	Peto	0.82 (0.44 to 1.51)	3	20,584	53.8	.16
	MH	0.91 (0.67 to 1.25)	3	20,584	NA	NA

Abbreviations: CI = Confidence interval; CVD = Cardiovascular disease; MH = Mantel-Haenszel common (fixed) effects model; NA = Not applicable; No. = Number; OR = Odds ratio; Peto = Peto odds ratio random effects REML model; REML-KH = Random effects restricted maximum likelihood model with the Knapp-Hartung adjustment.

Appendix F Table 52. Selenium Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	All-cause mortality	6.3	All	HR=0.79 (0.61 to 1.02)	108/653 (16.5)	129/659 (19.6)	0.07
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	All-cause mortality	7.6	All	HR=0.95 (0.73 to 1.24)	110/504 (21.8)	111/500 (22.2)	0.71
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	All-cause mortality	5.5	All	HR=0.99 (0.82 to 1.19)	378/8752 (4.3)	382/8696 (4.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	All-cause mortality	7.1	All	HR=0.98 (0.84 to 1.14)	551/8752 (6.3)	564/8696 (6.5)	0.67
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	All-cause mortality	5.5	All	HR=0.94 (0.77 to 1.13)	359/8703 (4.1)	382/8696 (4.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	All-cause mortality	7.1	All	HR=0.96 (0.82 to 1.12)	542/8702 (6.2)	564/8696 (6.5)	0.47
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	All-cause mortality	5	All	HR=1.62 (0.66 to 3.96)	12/119 (10.1)	8/126 (6.3)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	All-cause mortality	15.9	All	HR=1.59 (1.02 to 2.46)	47/119 (39.5)	35/126 (27.8)	<0.05
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	All-cause mortality	15.9	Females	HR=1.52 (0.74 to 3.14)	17 events/60	13 events/66	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	All-cause mortality	15.9	Males	HR=1.64 (0.95 to 2.84)	30 events/59	22 events/60	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	All-cause mortality	5	All	HR=0.64 (0.21 to 1.94)	5/122 (4.1)	8/126 (6.3)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	All-cause mortality	15.9	All	HR=0.99 (0.62 to 1.59)	35/122 (28.7)	35/126 (27.8)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	All-cause mortality	15.9	Females	HR=0.78 (0.34 to 1.84)	9 events/56	13 events/66	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	All-cause mortality	15.9	Males	HR=1.02 (0.58 to 1.79)	26 events/66	22 events/60	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	All-cause mortality	5	All	HR=0.75 (0.26 to 2.16)	6/124 (4.8)	8/126 (6.3)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	All-cause mortality	15.9	All	HR=1.15 (0.73 to 1.80)	41/124 (33.1)	35/126 (27.8)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	All-cause mortality	15.9	Females	HR=1.38 (0.65 to 2.89)	15 events/54	13 events/66	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	All-cause mortality	15.9	Males	HR=0.94 (0.53 to 1.67)	26 events/70	22 events/60	NR, NS

Appendix F Table 52. Selenium Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Thompson, 2016 (Sel/Cel)[98]	Selenium vs. placebo	200 mcg	All-cause mortality	3	All	1.07 (0.54 to 2.13)	17/910 (1.9)	16/914 (1.8)	NR
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer deaths	6.3	All	HR=0.48 (0.31 to 0.76)	29/653 (4.4)	57/659 (8.6)	0.001
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer deaths	7.4	All	HR=0.59 (0.39 to 0.87)	40/621 (6.4)	66/629 (10.5)	0.008
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Any cancer deaths	5.5	All	HR=1.02 (0.74 to 1.41)	128/8752 (1.5)	125/8696 (1.4)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer deaths	5.5	All	HR=0.93 (0.67 to 1.30)	117/8703 (1.3)	125/8696 (1.4)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	Any cancer deaths	5	All	HR=2.17 (0.65 to 7.21)	8/119 (6.7)	4/126 (3.2)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	Any cancer deaths	15.9	All	HR=1.78 (0.94 to 3.34)	24/119 (20.2)	16/126 (12.7)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	Any cancer deaths	5	All	HR=0.77 (0.17 to 3.46)	3/122 (2.5)	4/126 (3.2)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	Any cancer deaths	15.9	All	HR=0.94 (0.46 to 1.90)	15/122 (12.3)	16/126 (12.7)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	Any cancer deaths	5	All	HR=0.75 (0.17 to 3.36)	3/124 (2.4)	4/126 (3.2)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	Any cancer deaths	15.9	All	HR=1.22 (0.63 to 2.36)	20/124 (16.1)	16/126 (12.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Bladder cancer deaths	7.1	All	0.50 (0.12 to 1.99)	3/8752 (0.0)	6/8696 (0.1)	NR
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Bladder cancer deaths	7.1	All	0.50 (0.12 to 2.00)	3/8703 (0.0)	6/8696 (0.1)	NR
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Colorectal cancer deaths	5.5	All	HR=1.00 (0.32 to 3.16)	10/8752 (0.1)	10/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer deaths	5.5	All	HR=1.49 (0.52 to 4.28)	15/8703 (0.2)	10/8696 (0.1)	NR, NS
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	CVD deaths	6.3	All	HR=0.96 (0.64 to 1.44)	47/653 (7.2)	46/659 (7.0)	0.83
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	CVD deaths	7.6	All	HR=1.22 (0.76 to 1.95)	40/504 (7.9)	31/500 (6.2)	0.41
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	CVD deaths	5.5	All	HR=0.91 (0.66 to 1.24)	129/8752 (1.5)	142/8696 (1.6)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD deaths	5.5	All	HR=0.82 (0.60 to 1.13)	117/8703 (1.3)	142/8696 (1.6)	NR, NS

Appendix F Table 52. Selenium Mortality Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	CVD deaths	5	All	HR=2.17 (0.40 to 11.85)	4/119 (3.4)	2/126 (1.6)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	300 mcg	CVD deaths	15.9	All	HR=1.51 (0.69 to 3.33)	14/119 (11.8)	11/126 (8.7)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	CVD deaths	5	All	HR=0.52 (0.05 to 5.72)	1/122 (0.8)	2/126 (1.6)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	200 mcg	CVD deaths	15.9	All	HR=1.00 (0.44 to 2.31)	11/122 (9.0)	11/126 (8.7)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	CVD deaths	5	All	HR=1.00 (0.14 to 7.11)	2/124 (1.6)	2/126 (1.6)	NR, NS
Rayman, 2018 (DK-PRECISE)[97]	Selenium vs. placebo	100 mcg	CVD deaths	15.9	All	HR=0.62 (0.24 to 1.61)	7/124 (5.6)	11/126 (8.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Hemorrhagic stroke deaths	5.5	All	HR=1.12 (0.32 to 3.93)	9/8752 (0.1)	8/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Hemorrhagic stroke deaths	5.5	All	HR=1.49 (0.46 to 4.84)	12/8703 (0.1)	8/8696 (0.1)	NR, NS
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Lung cancer deaths	6.3	All	HR=0.47 (0.23 to 0.93)	12/653 (1.8)	25/659 (3.8)	0.03
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Lung cancer deaths	5.5	All	HR=1.10 (0.63 to 1.91)	45/8752 (0.5)	41/8696 (0.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer deaths	5.5	All	HR=0.95 (0.53 to 1.69)	39/8703 (0.4)	41/8696 (0.5)	NR, NS
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	MI, fatal	7.6	All	HR=1.08 (0.42 to 2.80)	9/504 (1.8)	8/500 (1.6)	0.88
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Prostate cancer deaths	5.5	All	2.98 (0.12 to 73.19)	1/8752 (0.0)	0/8696 (0.0)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer deaths	5.5	All	1.00 (0.02 to 50.36)	0/8703 (0.0)	0/8696 (0.0)	NR, NS

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CVD = Cardiovascular disease; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; mcg = Microgram; HR = Hazard ratio; IG = Intervention group; IU = International units; MI = Myocardial infarction; NPC = Nutritional Prevention of Cancer; NR = Not reported; NS = Not significant; OR = Odds ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial

Appendix F Table 53. Selenium Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Cerebrovascular events	7.6	All	HR=1.02 (0.65 to 1.59)	40/504 (7.9)	37/500 (7.4)	0.94
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	CHD events	7.6	All	HR=1.04 (0.73 to 1.49)	63/504 (12.5)	59/500 (11.8)	0.81
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Coronary artery bypass graft	7.6	All	HR=1.30 (0.59 to 2.84)	15/504 (3.0)	11/500 (2.2)	0.51
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	CVD events	7.6	All	HR=1.03 (0.78 to 1.37)	103/504 (20.4)	96/500 (19.2)	0.81
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	CVD events	5.5	All	RR=1.02 (0.92 to 1.13)	1080/8752 (12.3)	1050/8696 (12.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	CVD events	7.1	All	HR=0.97 (0.86 to 1.09)	939/8752 (10.7)	969/8696 (11.1)	0.45
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD events	5.5	All	RR=0.99 (0.89 to 1.10)	1041/8703 (12.0)	1050/8696 (12.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	CVD events	7.1	All	HR=0.97 (0.86 to 1.09)	943/8702 (10.8)	969/8696 (11.1)	0.51
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	MI	7.6	All	HR=0.94 (0.61 to 1.44)	41/504 (8.1)	43/500 (8.6)	0.77
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	MI, nonfatal	7.6	All	HR=0.91 (0.56 to 1.47)	32/504 (6.3)	35/500 (7.0)	0.69
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Other CVD	7.6	All	HR=0.98 (0.28 to 3.39)	5/504 (1.0)	5/500 (1.0)	0.87
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Percutaneous transluminal coronary angioplasty	7.6	All	HR=1.36 (0.43 to 4.31)	7/504 (1.4)	5/500 (1.0)	0.60
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Stroke	7.6	All	HR=1.02 (0.63 to 1.65)	35/504 (6.9)	32/500 (6.4)	0.92
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Stroke	5.5	All	0.92 (0.65 to 1.30)	62/8752 (0.7)	67/8696 (0.8)	
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke	5.5	All	1.18 (0.85 to 1.64)	79/8703 (0.9)	67/8696 (0.8)	
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Stroke, Hemorrhagic	5.5	All	RR=0.99 (0.33 to 2.98)	11/8752 (0.1)	11/8696 (0.1)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, Hemorrhagic	5.5	All	RR=1.09 (0.37 to 3.19)	12/8703 (0.1)	11/8696 (0.1)	NR, NS

Appendix F Table 53. Selenium Cardiovascular Disease Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)	p-value
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Stroke, Ischemic	5.5	All	RR=0.90 (0.55 to 1.49)	51/8752 (0.6)	56/8696 (0.6)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, Ischemic	5.5	All	RR=1.20 (0.75 to 1.90)	67/8703 (0.8)	56/8696 (0.6)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Stroke, nonfatal	5.5	All	0.79 (0.58 to 1.07)	73/8752 (0.8)	92/8696 (1.1)	NR
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Stroke, nonfatal	5.5	All	1.08 (0.81 to 1.43)	99/8703 (1.1)	92/8696 (1.1)	NR

*Studies providing estimates other than ORs display effect type

Abbreviations: CG = Control group; CHD = Coronary heart disease; CVD = Cardiovascular disease; HR = Hazard ratio; IG = Intervention group; IU = International units; mcg = Micrograms; MI = Myocardial infarction; NPC = Nutritional Prevention of Cancer; NR = Not reported; NS = Not significant; OR = Odds ratio; RR = Risk ratio; SELECT = Selenium and Vitamin E Cancer Prevention Trial

Appendix F Table 54. Selenium Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer incidence	6.3	All	HR=0.61 (0.46 to 0.82)	77/653 (11.8)	119/659 (18.1)	<0.001
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer incidence	7.4	All	HR=0.75 (0.58 to 0.97)	105/621 (16.9)	137/629 (21.8)	0.03
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer incidence	7.4	Females	HR=1.20 (0.66 to 2.20)	23/161 (14.3)	20/157 (12.7)	0.55
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Any cancer incidence	7.4	Males	HR=0.67 (0.50 to 0.89)	82/460 (17.8)	117/472 (24.8)	0.005
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Any cancer incidence	5.5	All	HR=1.01 (0.89 to 1.15)	837/8752 (9.6)	824/8696 (9.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Any cancer incidence	7.1	All	HR=1.02 (0.92 to 1.14)	1132/8752 (12.9)	1108/8696 (12.7)	0.59
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer incidence	5.5	All	HR=1.02 (0.90 to 1.16)	846/8703 (9.7)	824/8696 (9.5)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Any cancer incidence	7.1	All	HR=1.02 (0.92 to 1.14)	1149/8702 (13.2)	1108/8696 (12.7)	0.60
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Breast cancer	6.3	Females	HR=2.95 (0.80 to 10.90)	9/172 (5.2)	3/161 (1.9)	0.11
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Breast cancer	7.4	Females	HR=1.89 (0.69 to 5.14)	11/161 (6.8)	6/157 (3.8)	0.21
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Carcinomas	6.3	All	HR=0.54 (0.39 to 0.75)	59/653 (9.0)	104/659 (15.8)	<0.001
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Colorectal cancer	6.3	All	HR=0.39 (0.17 to 0.90)	8/653 (1.2)	19/659 (2.9)	0.03
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Colorectal cancer	7.4	All	HR=0.46 (0.21 to 1.02)	9/621 (1.4)	19/629 (3.0)	0.057
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Colorectal cancer	5.5	All	HR=1.05 (0.66 to 1.67)	63/8752 (0.7)	60/8696 (0.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Colorectal cancer	7.1	All	HR=0.96 (0.63 to 1.46)	74/8752 (0.8)	75/8696 (0.9)	0.79
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer	5.5	All	HR=1.28 (0.82 to 2.00)	77/8703 (0.9)	60/8696 (0.7)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Colorectal cancer	7.1	All	HR=1.21 (0.81 to 1.81)	93/8702 (1.1)	75/8696 (0.9)	0.22
Thompson, 2016 (Sel/Cel)[98]	Selenium vs. placebo	200 mcg	Colorectal cancer	3	All	1.26 (0.34 to 4.70)	5/910 (0.5)	4/914 (0.4)	NR

Appendix F Table 54. Selenium Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Esophageal cancer	6.3	All	HR=0.30 (0.06 to 1.49)	2/653 (0.3)	6/659 (0.9)	0.14
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Esophageal cancer	7.4	All	HR=0.40 (0.08 to 2.07)	2/621 (0.3)	5/629 (0.8)	0.28
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Head and neck cancer	6.3	All	HR=0.77 (0.27 to 2.24)	6/653 (0.9)	8/659 (1.2)	0.64
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Head and neck cancer	7.4	All	HR=1.27 (0.47 to 3.42)	9/621 (1.4)	7/629 (1.1)	0.63
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Leukemia/lymphoma	6.3	All	HR=1.50 (0.49 to 4.60)	8/653 (1.2)	5/659 (0.8)	0.48
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Leukemia/lymphoma	7.4	All	HR=1.25 (0.43 to 3.61)	8/621 (1.3)	6/629 (1.0)	0.68
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Lung cancer	6.3	All	HR=0.56 (0.31 to 1.01)	17/653 (2.6)	31/659 (4.7)	0.05
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Lung cancer	7.4	All	HR=0.74 (0.44 to 1.24)	25/621 (4.0)	35/629 (5.6)	0.26
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Lung cancer	5.5	All	HR=1.12 (0.73 to 1.72)	75/8752 (0.9)	67/8696 (0.8)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Lung cancer	7.1	All	HR=1.02 (0.70 to 1.50)	94/8752 (1.1)	92/8696 (1.1)	0.89
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer	5.5	All	HR=1.16 (0.76 to 1.78)	78/8703 (0.9)	67/8696 (0.8)	NR, NS
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Lung cancer	7.1	All	HR=1.11 (0.76 to 1.62)	104/8702 (1.2)	92/8696 (1.1)	0.48
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Melanoma skin cancer	6.3	All	HR=0.92 (0.34 to 2.45)	8/653 (1.2)	8/659 (1.2)	0.87
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Melanoma skin cancer	7.4	All	HR=1.18 (0.49 to 2.85)	11/621 (1.8)	9/629 (1.4)	0.71
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Noncarcinomas	6.3	All	HR=1.16 (0.60 to 2.27)	19/653 (2.9)	16/659 (2.4)	0.65
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Other carcinomas	6.3	All	HR=0.54 (0.18 to 1.62)	5/653 (0.8)	9/659 (1.4)	0.27
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Other carcinomas	7.4	All	HR=0.67 (0.24 to 1.88)	6/621 (1.0)	9/629 (1.4)	0.44
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Other noncarcinomas	6.3	All	HR=0.99 (0.20 to 4.94)	3/653 (0.5)	3/659 (0.5)	0.99
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Other noncarcinomas	7.4	All	HR=0.59 (0.14 to 2.47)	3/621 (0.5)	5/629 (0.8)	0.47

Appendix F Table 54. Selenium Cancer Results

Author, Year (Study)	Comparison	Supplement (daily dose)	Outcome	Followup, years	Group	Effect	IG n/N (%)	CG n/N (%)	p-value
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Prostate cancer	6.3	All	HR=0.35 (0.18 to 0.65)	13/481 (2.7)	35/498 (7.0)	0.001
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Prostate cancer	7.4	All	HR=0.48 (0.28 to 0.80)	22/457 (4.8)	42/470 (8.9)	0.005
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Prostate cancer	5.5	All	HR=1.04 (0.90 to 1.18)	432/8752 (4.9)	416/8696 (4.8)	0.62
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Prostate cancer	7.1	All	HR=1.09 (0.93 to 1.27)	575/8752 (6.6)	529/8696 (6.1)	0.18
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer	5.5	All	HR=1.05 (0.88 to 1.25)	437/8702 (5.0)	416/8696 (4.8)	0.52
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Prostate cancer	7.1	All	HR=1.05 (0.89 to 1.22)	555/8702 (6.4)	529/8696 (6.1)	0.46
Thompson, 2016 (Sel/Cel)[98]	Selenium vs. placebo	200 mcg	Squamous cell carcinoma	3	All	HR=1.34 (0.76 to 2.37)	10.9/1000 p-y	8.2/1000 p-y	0.32
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Urinary bladder cancer	6.3	All	HR=1.27 (0.44 to 3.67)	8/653 (1.2)	6/659 (0.9)	0.66
Clark, 1996 (NPC)[77]	Selenium vs. placebo	200 mcg	Urinary bladder cancer	7.4	All	HR=1.28 (0.50 to 3.25)	10/621 (1.6)	8/629 (1.3)	0.60
Lippman, 2009 (SELECT)[79]	Selenium vs. placebo	200 mcg	Urinary bladder cancer	7.1	All	HR=1.13 (0.78 to 1.63)	60/8752 (0.7)	53/8696 (0.6)	0.52
Lippman, 2009 (SELECT)[79]	Selenium + vitamin E vs. placebo	200 mcg + 400 IU Vitamin E	Urinary bladder cancer	7.1	All	HR=1.05 (0.71 to 1.51)	55/8703 (0.6)	53/8696 (0.6)	0.86

Abbreviation: CG = Control group; HR = Hazard ratio; IG = Intervention group; IU = International unit; mcg = Microgram; NPC = Nutritional Prevention of Cancer; NR = Not reported; NS = Not significant; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial

Appendix F Table 55. Selenium Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Lippman, 2009 (SELECT)[79]	200 mcg	Selenium vs. placebo	Dermatitis	5.5	All	RR=1.17 (1.00 to 1.35)	605/8752 (6.9)	516/8696 (5.9)
Lippman, 2009 (SELECT)[79]	200 mcg + 400 IU Vitamin E	Selenium + vitamin E vs. placebo	Dermatitis	5.5	All	RR=1.07 (0.92 to 1.25)	554/8703 (6.4)	516/8696 (5.9)
Lippman, 2009 (SELECT)[79]	200 mcg	Selenium vs. placebo	Non-serious: Fatigue (NS); Halitosis (NS); Nail changes (NS)	5.5	All	. (. to .)	./8737 (.)	./8696 (.)
Lippman, 2009 (SELECT)[79]	200 mcg + 400 IU Vitamin E	Selenium + vitamin E vs. placebo	Non-serious: Fatigue (NS); Halitosis (NS); Nail changes (NS)	5.5	All	. (. to .)	./8737 (.)	./8696 (.)
Thompson, 2016 (Sel/Cel)[98]	200 mcg	Selenium vs. placebo	Non-serious: Brittle hair and/or nails (NS)	3	All	HR=0.86 (0.53 to 1.39)	12.2/1000 p-y	13.8/1000 p-y
Rayman, 2012 (UK-PRECISE)[89]	100 mcg	Selenium vs. placebo	Serious AEs	0.5	All	0.93 (0.02 to 47.45)	0/120 (0.0)	0/112 (0.0)
Rayman, 2012 (UK-PRECISE)[89]	200 mcg	Selenium vs. placebo	Serious AEs	0.5	All	0.90 (0.02 to 45.92)	0/124 (0.0)	0/112 (0.0)
Rayman, 2012 (UK-PRECISE)[89]	300 mcg	Selenium vs. placebo	Serious AEs	0.5	All	0.96 (0.02 to 48.66)	0/117 (0.0)	0/112 (0.0)
Thompson, 2016 (Sel/Cel)[98]	200 mcg	Selenium vs. placebo	Serious AEs	3	All	HR=1.00 (0.83 to 1.21)	101.3/1000 p-y	100.3/1000 p-y
Clark, 1996 (NPC)[77]	200 mcg	Selenium vs. placebo	Withdrawals due to AEs	6.3	All	1.53 (0.77 to 3.04)	21/653 (3.2)	14/659 (2.1)
Rayman, 2012 (UK-PRECISE)[89]	100 mcg	Selenium vs. placebo	Withdrawals due to AEs	0.5	All	0.93 (0.13 to 6.73)	2/120 (1.7)	2/112 (1.8)
Rayman, 2012 (UK-PRECISE)[89]	200 mcg	Selenium vs. placebo	Withdrawals due to AEs	0.5	All	0.45 (0.04 to 5.00)	1/124 (0.8)	2/112 (1.8)
Rayman, 2012 (UK-PRECISE)[89]	300 mcg	Selenium vs. placebo	Withdrawals due to AEs	0.5	All	4.04 (0.84 to 19.44)	8/117 (6.8)	2/112 (1.8)
Rayman, 2018 (DK-PRECISE[97]	300 mcg	Selenium vs. placebo	Withdrawals due to AEs	5	All	1.17 (0.50 to 2.77)	12/119 (10.1)	11/126 (8.7)
Rayman, 2018 (DK-PRECISE)[97]	200 mcg	Selenium vs. placebo	Withdrawals due to AEs	5	All	1.93 (0.88 to 4.24)	19/122 (15.6)	11/126 (8.7)
Rayman, 2018 (DK-PRECISE)[97]	100 mcg	Selenium vs. placebo	Withdrawals due to AEs	5	All	1.78 (0.80 to 3.93)	18/124 (14.5)	11/126 (8.7)

*Studies providing estimates other than ORs display effect type

Abbreviations: . = not reported; AE = Adverse event; CG = Control group; DK-PRECISE = Denmark PREvention of Cancer by Intervention with Selenium; HR = Hazard ratio; IG = Intervention group; IU = International units; mcg = Microgram; NPC = Nutritional Prevention of Cancer; NS = Not significant; p-y = Person-years; RR = Risk ratio; Sel/Cel = Selenium and Celecoxib; SELECT = Selenium and Vitamin E Cancer Prevention Trial; UK-PRECISE = United Kingdom PREvention of Cancer by Intervention with Selenium

Appendix F Table 56. Zinc Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Hemila, 2020[137]	78 mg	Zinc vs. placebo	Any AE	0.03	All	3.81 (1.57 to 9.24)	29/46 (63.0)	13/42 (31.0)
Hemila, 2020[137]	78 mg	Zinc vs. placebo	Withdrawals due to AEs	0.03	All	2.8 (0.11 to 70.68)	1/46 (2.2)	0/42 (0.0)

*Studies providing estimates other than ORs display effect type

Abbreviations: AE = Adverse event; CG = Control group; IG = Intervention group; mg = Milligram; NHS-I = Nurses' Health Study; NR = Not reported; OR = Odds ratio

Appendix F Table 57. Magnesium Adverse Event Results

Author, Year (Study)	Dose	Comparison	Outcome	Followup, years	Group	Effect*	IG n/N (%)	CG n/N (%)
Alonso, 2020[136]	400 mg	Magnesium vs. placebo	Gastrointestinal symptoms	0.19	All	15.0 (3 to 74.96)	15/29 (50.0)	2/30 (7.0)
Alonso, 2020[136]	400 mg	Magnesium vs. placebo	Withdrawals due to AEs	0.19	All	3.21 (0.13 to 82.07)	1/29 (3.4)	0/30 (0.0)

*Studies providing estimates other than ORs display effect type

Abbreviations: AE = Adverse event; CG = Control group; IG = Intervention group; mg = Milligram; NHS-I = Nurses' Health Study; NR = Not reported; OR = Odds ratio

Appendix G. Ongoing Studies

Trial	Trial number	Location	N	Duration (years)	Intervention	Relevant endpoints	Estimated completion date
Finnish Vitamin D Trial (FIND)	NCT01463813	Finland	2,495	5	Vitamin D (1600 or 3200 IU/day)	Cancer, CVD	Publication late 2020 or early 2021
COcoa Supplement tamin Outcomes Study (COSMOS)	NCT03035201	US	21,445	5	Multivitamin (1/day) Other arms include Cocoa extract	CVD, cancer	Publication Fall 2021
D-Health	ACTRN12613000743763	Australia	21,315	5	Vitamin D (60,000 IU/month)	Mortality, cancer	2024

Abbreviations: CVD = Cardiovascular disease; IU = International units; US = United States