Appendix Figure 1. Analytic framework

Key Questions:
1. What is the efficacy of multivitamin supplement use on health outcomes in the general adult population?
2. What is known about the safety of use of multivitamin supplements in the general adult population?
3. What is the efficacy of supplementation with single nutrients or functionally related nutrient pairs on health outcomes in the general adult population?
4. What is known about the safety of use of single nutrients in the general adult population?
Appendix Figure 2. Literature flow diagram

Number of citations identified through other sources (e.g., reference lists):
257

Number of citations identified through literature database searches:
16,023

Number of citations identified through supplementary diabetes prevention search:
1,346

Number of citations screened after duplicates removed:
12,766

Number of citations excluded at title/abstract stage:
12,489

Number of full-text articles assessed for eligibility:
277

Articles reviewed for Key Question 1:
33

Articles reviewed for Key Question 2:
28

Articles reviewed for Key Question 3:
222

Articles reviewed for Key Question 4:
162

Articles excluded for Key Question 1:

Relevance: 1
Setting: 5
Population: 5
Quality: 1
Design: 4
Outcomes: 4
Publication date: 0
Language: 0
Source only: 2
Non-RCT harms: 0
Intervention: 0

Articles included for Key Question 1:
11 (3 trials)

Articles excluded for Key Question 2:

Relevance: 3
Setting: 0
Population: 3
Quality: 0
Design: 3
Outcomes: 10
Publication date: 0
Language: 0
Source only: 0
Non-RCT harms: 1
Intervention: 2

Articles included for Key Question 2:
6 (5 studies)

Articles excluded for Key Question 3:

Relevance: 14
Setting: 5
Population: 17
Quality: 8
Design: 31
Outcomes: 37
Publication date: 0
Language: 1
Source only: 27
Non-RCT harms: 0
Intervention: 0

Articles included for Key Question 3:
82 (18 trials)

Articles excluded for Key Question 4:

Relevance: 14
Setting: 0
Population: 7
Quality: 3
Design: 27
Outcomes: 44
Publication date: 0
Language: 0
Source only: 9
Non-RCT harms: 1
Intervention: 2

Articles included for Key Question 4:
55 (23 studies)
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<tr>
<th>Study</th>
<th>Country</th>
<th>Study aim(s)</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention arm</th>
<th>N randomized</th>
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</thead>
<tbody>
<tr>
<td>ACS (45, 92, 93)</td>
<td>New Zealand</td>
<td>Assess the long-term effects of calcium on bone density and fracture incidence; determine effect of calcium supplementation on CVD and death</td>
<td>RCT</td>
<td>Women aged &gt; 55 years, more than 5 years postmenopausal, and life expectancy &gt; 5 years</td>
<td>Women receiving therapy for osteoporosis or taking calcium supplements; any other major ongoing disease, creatinine &gt; 1.8 mg/dL, untreated hypo- or hyperthyroidism, liver disease, serum 25-hydroxyvitamin D below 10 mcg/liter, malignancy, metabolic bone disease; regular users of hormone replacement therapy, anabolic steroids, glucocorticoids, or bisphosphonates in the previous 1 year; lumbar spine bone density was not below the age-appropriate normal levels</td>
<td>Calcium 1,000 mg bid</td>
<td>732</td>
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<td>AFPPS (39, 94)</td>
<td>United States and Canada</td>
<td>Assess the safety and efficacy of folic acid supplementation for preventing colorectal cancer adenomas</td>
<td>RCT</td>
<td>Aged 21-80 years old, had at least 1 of the following criteria: at least 1 histologically confirmed adenoma removed within the 3 months before recruitment, at least 1 histologically confirmed adenoma removed within 16 months before recruitment, lifetime history of 2 or more confirmed adenomas, or a histologically confirmed adenoma of at least 1 cm in diameter before recruitment; complete colonoscopy with removal of all known polyps within 3 months of enrollment.</td>
<td>History of familial polyposis syndromes, invasive large intestine cancer, malabsorption syndromes, any condition that could be worsened by supplemental aspirin or folic acid, or any condition commonly treated with aspirin, NSAIDS, or folate.</td>
<td>Folic acid 1 mg qd</td>
<td>516</td>
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<tr>
<td>ASAP (30)</td>
<td>Finland</td>
<td>Determine efficacy of vitamin E and vitamin C supplementation on</td>
<td>RCT, 2x2 factorial design*</td>
<td>Patients with hypercholesterolemia (serum cholesterol 5.0 mmol/L or higher) aged 45-69 years</td>
<td>Premenopausal, had regular oral estrogen substitution therapy, regular intake of antioxidants, ASA or any other drug with anti-</td>
<td>Vitamin E 91 mg bid</td>
<td>130</td>
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<td></td>
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<td></td>
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<td>Vitamin C 250 mg bid</td>
<td>130</td>
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<td>Study Country</td>
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<td>Study design</td>
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<tr>
<td>Fair USPSTF</td>
<td>Fair</td>
<td>progression of carotid atherosclerosis</td>
<td>RCT, 2x2 factorial design</td>
<td>Male smokers (5 or more cigarettes per day) aged 50-69 years living in southwestern Finland</td>
<td>oxidative properties, severely obese (BMI &gt; 32), type 1 diabetes, uncontrolled hypertension (DBP &gt; 105 mmHg), any condition limiting mobility making study visits impossible, severe disease shortening life expectancy or other disease/condition worsening the adherence to the measurements or treatment</td>
<td>Vitamin E 91 mg bid + vitamin C 250 mg bid Placebo</td>
<td>130</td>
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<tr>
<td>ATBC (24, 95–107) Finland Good</td>
<td>Reduce the incidence of lung cancer with vitamin E and/or β-carotene supplementation; reduce the incidence of other cancer, CVD and other chronic diseases</td>
<td>RCT, 2x2 factorial design</td>
<td>Male smokers (5 or more cigarettes per day) aged 50-69 years living in southwestern Finland</td>
<td>History of cancer (other than NMSC or CIS) or serious disease that would prevent (or limit) participation (severe angina on exertion - Rose criteria grade 2, chronic renal insufficiency, cirrhosis of liver, chronic alcoholism, psychiatric disorder, physical disability); taking supplements of vitamin E (&gt; 20 mg), A (&gt; 20,000 IU) or β-carotene (&gt; 6 mg) in excess of predefined doses; treated with anticoagulants; non-smokers</td>
<td>Vitamin E 50 mg qd β-carotene 20 mg qd Placebo</td>
<td>7,286</td>
<td></td>
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<tr>
<td>CARET (29, 108–113) Finland Good</td>
<td>Determine the effect of β-carotene plus vitamin A on</td>
<td>RCT</td>
<td>Asbestos exposed participants: Men aged 45-69 years; exposed to asbestos on the job 15 years</td>
<td>NR</td>
<td>β-carotene 30 mg qd + vitamin A 25,000 IU qd</td>
<td>9,420</td>
<td></td>
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<tr>
<td>United States</td>
<td>preventing lung cancer in high risk populations</td>
<td>RCT</td>
<td>prior to randomization; chest x-ray positive for asbestos related lung disease (fibrosis) or have worked in high-risk trades for 5 years; current smokers or have smoked in the last 15 years.*</td>
<td>Heavy smokers: Men and women 50-69 years of age; had at least 20-pack years of smoking; either currently smoking or had quit smoking within the previous 6 years†</td>
<td>Placebo</td>
<td>8,894</td>
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<td>CPPS (46, 88)</td>
<td>Determine if calcium intake increases the risk of prostate cancer; impacts the recurrence of colorectal adenomas</td>
<td>RCT</td>
<td>Less than 80 years old; in good health; no history of familial polyposis, invasive large-bowel cancer, malabsorption syndromes, or any condition that might be worsened by supplemental calcium; men without a history of prostate cancer for prostate cancer publication only</td>
<td>NR</td>
<td>Calcium 1,200 mg bid</td>
<td>464</td>
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<td>United States</td>
<td>Assess whether vitamin D</td>
<td>RCT</td>
<td>Healthy volunteers at least 18 years of age with sufficient</td>
<td>Current use of vitamin D or calcium supplements; history of</td>
<td>Vitamin D 5,000 IU qd</td>
<td>63</td>
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<tr>
<td>Australia</td>
<td>Good</td>
<td>supplementation would lead to improvement in cognitive and emotional functioning</td>
<td>English language skills required to complete study protocol</td>
<td>adverse reactions to vitamin supplements; current or past diagnosis of a mood or psychotic disorders; history of neurologic illnesses including cerebrovascular accident, CNS tumors, head trauma, multiple sclerosis, epilepsy, movement disorders or migraine treatment; current or recent (12 months) history of alcohol or illicit drug dependence; intellectual disability; pregnancy or current breast feeding or potential to become pregnant during the trial; history of severe renal impairment</td>
<td>Placebo</td>
<td>65</td>
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<td>Graat 2002 (22) Netherlands Good</td>
<td>Determine if long-term supplementation of a multivitamin and/or vitamin E reduces the incidence and severity of acute respiratory tract infections</td>
<td>RCT, 2x2 factorial design*</td>
<td>Men and women older than 60 years, noninstitutionalized</td>
<td>Used immunosuppressive treatment, anticoagulants interfering with vitamin K metabolism, dietary supplement in the previous 2 months or if they had a history of cancer, liver disease or fat malabsorption during the 5 years prior to randomization</td>
<td>Multivitamin qd (vitamin A 600 mcg, β-carotene 1.2 mg, vitamin C 60 mg, vitamin E 10 mg, vitamin D₃ 5 mcg, vitamin K 30 mcg, vitamin B₁ 1.4 mg, vitamin B₂ 1.6 mg, vitamin B₃ 18 mg, vitamin B₆ 6 mg, vitamin B₉ 2.0 mg, biotin 150 mcg, folic acid 200 mcg, vitamin B₁₂ 1 mcg, zinc 10 mg, selenium 25 mcg, iron 4.0 mg, Mg 30 mg, Cu 1.0 mg, iodine 100 mcg, calcium 74 mg, phosphor 49 mg, Mn 1.0 mg, Cr 25 mcg, Mo 25 mcg, and silicium 2 mcg) + Vitamin E 200 mg</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>IWHS (38)</td>
<td>Examine the</td>
<td>Prospective</td>
<td>Women aged 55 to 69 years</td>
<td>Premenopausal at the time of</td>
<td>Vitamin A†</td>
<td>12,293</td>
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<tr>
<td>United States</td>
<td>Good</td>
<td>association between various lifestyle factors (e.g., supplement use) and morality, incidence of cancer, diabetes mellitus, hypertension and fracture</td>
<td>cohort study</td>
<td>with a valid Iowa driver's license</td>
<td>the baseline questionnaire; had an implausible energy intakes of &lt; 600 kcal or &gt; 5,000 kcal; failed to complete a substantial portion (greater than 29 missing items) of the food frequent questionnaire; history of cancer other than skin cancer</td>
<td>Non-users of vitamin A</td>
<td>22,410</td>
</tr>
<tr>
<td>Lappe 2007 (43, 114)</td>
<td>United States</td>
<td>Good</td>
<td>To determine the effect of calcium with or without vitamin D on skeletal status; determine efficacy in reducing incidence of cancer</td>
<td>RCT</td>
<td>&gt; 55 years of age, absence of known cancers, both mental and physical status sufficiently good to allow for 4-year participation in study; women only</td>
<td>Calcium 1,400-1,500 mg qd§ Calcium 1,400 mg qd + vitamin D₃ 25 mcg qd Placebo</td>
<td>NR</td>
</tr>
<tr>
<td>NHS (23)</td>
<td>United States</td>
<td>Good</td>
<td>Assess relationship between vitamin A supplementation and risk of hip fractures</td>
<td>Prospective cohort study</td>
<td>Postmenopausal (via natural or surgical menopause) registered nurses who responded to questionnaire in 1980</td>
<td>Previous hip fracture or diagnosis of cancer, heart disease, stroke, or osteoporosis</td>
<td>Supplement users (vitamin A, multivitamin, or β-carotene)‡ Non-users of supplements NR</td>
</tr>
<tr>
<td>NPC (34, 87, 115–118)</td>
<td>United States</td>
<td>Fair</td>
<td>Determine if selenium supplementation reduces the incidence of basal cell carcinoma and squamous cell carcinoma of the skin; reduces the incidence of other cancers</td>
<td>RCT</td>
<td>A history of 2 or more BCC or 1 SCC of the skin with one of these carcinomas occurring within the previous 1 year; a 5-year life expectancy; no reported internal malignancies treated within the previous 5 years</td>
<td>Selenium 200 mcg qd Brewer’s yeast</td>
<td>NR</td>
</tr>
<tr>
<td>NSCPS (28, 119)</td>
<td>Australia</td>
<td>Good</td>
<td>Determine if β-carotene can prevent skin cancer</td>
<td>RCT</td>
<td>Resident of Nambour, southeast Queensland; aged 20-69 years when they took part in the skin cancer prevalence study</td>
<td>β-carotene 30 mg qd Placebo</td>
<td>NR</td>
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<th>Intervention arm</th>
<th>N randomized</th>
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<tbody>
<tr>
<td>PHS-I (25, 90, 120, 121)</td>
<td>Assess the impact of β-carotene supplementation on the incidence of cancer and CVD</td>
<td>RCT, 2x2 factorial design*§</td>
<td>Male physicians residing in the US; no history of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, or transient cerebral ischemia</td>
<td>A history of the above conditions; current liver or renal disease, peptic ulcer, or gout; contraindications to aspirin consumption; current use of aspirin, other platelet-active drugs, or nonsteroidal antiinflammatory agents; current use of vitamin A supplement</td>
<td>β-carotene 50 mg qod No β-carotene</td>
<td>11,036 11,035</td>
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<tr>
<td>PHS-II (vitamin C and E arms) (31, 55, 85)</td>
<td>Evaluate whether long-term vitamin E or vitamin C supplementation decreases the risk of major cardiovascular events and cancer</td>
<td>RCT, 2x2x2x2 factorial design*</td>
<td></td>
<td>Male physicians aged 55 yrs and older; men from PHS I with a history of MI, stroke or cancer were eligible for PHS II (new participants were not eligible if they had a history of CVD or cancer)</td>
<td>Those unwilling to avoid using outside supplements; a history of cirrhosis or active liver disease in the past 6 months, cancer (except non-melanoma skin cancer) (new participants), CVD (new participants), current renal disease, peptic ulcer, or gout; currently on anticoagulants</td>
<td>Vitamin E 400 IU qd Vitamin C 500 mg qd Vitamin E 400 IU qd + vitamin C 500 mg qd Placebo 3,653</td>
</tr>
<tr>
<td>PHS-II (multivitamin arm) (54)</td>
<td>Evaluate whether long-term multivitamin supplementation decreases the risk of major cardiovascular events and cancer</td>
<td>RCT, 2x2x2x2 factorial design*</td>
<td></td>
<td>Male physicians aged 55 yrs and older; men from PHS I with a history of MI, stroke or cancer were eligible for PHS II (new participants were not eligible if they had a history of CVD or cancer)</td>
<td>Those unwilling to avoid using outside supplements; a history of cirrhosis or active liver disease in the past 6 months, cancer (except non-melanoma skin cancer) (new participants), CVD (new participants), current renal disease, peptic ulcer, or gout; currently on anticoagulants</td>
<td>Multivitamin tid</td>
</tr>
<tr>
<td>REACT (20)</td>
<td>Determine if multivitamin use would impact the progression of age-related cataract</td>
<td>RCT</td>
<td>At least 40 years old; at least 1 eye met the following criteria: cataract extraction unlikely within 2 years, immature idiopathic “senile” cataract</td>
<td>Pregnant; history of diabetes mellitus, severe renal failure or kidney stones, fat malabsorption syndrome, major intestinal surgery, chronic diarrhea,</td>
<td>Multivitamin tid (vitamin C 250 mg, vitamin E 200 mg, and β-carotene 6 mg)</td>
<td>149</td>
</tr>
<tr>
<td>Study Country</td>
<td>Study aim(s)</td>
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<td>Inclusion criteria</td>
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<tr>
<td>USPSTF Quality</td>
<td>Investigate whether vitamin D or calcium supplementation affects mortality, vascular disease and cancer in older people</td>
<td>RCT, 2x2 factorial design*</td>
<td>Older adults aged 70 years or older with a fragility fracture</td>
<td>Cancer likely to metastasize to bone within the previous 10 years; bed- or chair-bound before fracture, abbreviated mental test &lt; 7, fracture associated with preexisting local bone abnormality, known</td>
<td>Calcium 1,000 mg qd Vitamin D3 800 IU qd Calcium 1,000 mg qd + vitamin D 800 IU qd</td>
<td>1,311</td>
</tr>
<tr>
<td>RECORD (40, 122)</td>
<td>Study</td>
<td>Study design</td>
<td>Inclusion criteria</td>
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<td>Intervention arm</td>
<td>N randomized</td>
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- Study aim(s): Investigate whether vitamin D or calcium supplementation affects mortality, vascular disease and cancer in older people.
- Study design: RCT, 2x2 factorial design.
- Inclusion criteria: Older adults aged 70 years or older with a fragility fracture.
- Exclusion criteria: Cancer likely to metastasize to bone within the previous 10 years; bed- or chair-bound before fracture, abbreviated mental test < 7, fracture associated with preexisting local bone abnormality, known.
- Intervention arm: Calcium 1,000 mg qd, Vitamin D3 800 IU qd, Calcium 1,000 mg qd + vitamin D 800 IU qd.
- N randomized: 1,311.
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<tr>
<th>Study Country</th>
<th>Study aim(s)</th>
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<tbody>
<tr>
<td>USPSTF Quality</td>
<td>Determine if β-carotene supplementation increases the time to occurrence of first skin cancer</td>
<td>RCT</td>
<td>At least one biopsy-proven BCC or SCC since January 1, 1980; aged &lt; 85 years; no potential childbearing; agree not to take vitamin supplements containing vitamin A or β-carotene; not a vegan vegetarian</td>
<td>Active cancer other than skin cancer; xerodermapigmentosum; basal cell nevus syndrome; significant known arsenic exposure; other major medical problems that might limit participation (e.g., disabling CVD, active liver disease, alcohol or drug dependence)</td>
<td>Placebo</td>
<td>1,332</td>
</tr>
<tr>
<td>SCPS (27, 83, 123)</td>
<td>Reduce the risk of prostate cancer with selenium and/or vitamin E as well as other cancers and cardiovascular events</td>
<td>RCT, 2x2 factorial design</td>
<td>Healthy men aged 50 years or older (African-Americans) or 55 years or older (all other races); normal blood pressure; ≥4 ng/mL serum PSA; DRE not suspicious for cancer; willing to restrict off-study supplement use; SWOG performance status equals zero.</td>
<td>Prior history of prostate cancer or high-grade prostatic intraepithelial neoplasia; anticoagulation therapy other than ≥175 mg/day ASA or ≥81 mg/day ASA with clopidogrel bisulfate; history of hemorrhagic stroke</td>
<td>Vitamin E 400 IU qd + selenium 200 mcg qd</td>
<td>8,863</td>
</tr>
<tr>
<td>SELECT (33, 86, 124–127)</td>
<td>Determine the efficacy of vitamin A</td>
<td>RCT</td>
<td>21-85 years of age; ambulatory and capable of self-care; no</td>
<td>NR</td>
<td>Vitamin A 25,000 IU qd</td>
<td>1,157</td>
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<td><strong>USPSTF Quality</strong></td>
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<td>United States</td>
<td>supplementation on the incidence of first NMSC in moderate-risk patients</td>
<td>RCT</td>
<td>diagnosis of a life-threatening condition or internal cancer in the past year; normal or near normal lab values in a routine screening panel of tests; planning to live within travel distance of SKICAP clinic for at least 5 years; willing to limit non-study vitamin A supplementation to no more than 10,000 IU/day; history of 10 or more pathologically confirmed actinic keratoses (most recent of which had to be diagnosed within the preceding year) and a pathologically confirmed record of at most 1 prior SCC or BCC</td>
<td>Placebo</td>
<td>1,140</td>
<td></td>
</tr>
<tr>
<td>SKICAPS-SB (37, 128)</td>
<td>Determine the effect of vitamin A and isotretinoin on the incidence of NMSC in high-risk patients</td>
<td>RCT</td>
<td>21-85 years of age; ambulatory and capable of self-care; no diagnosis of a life-threatening condition or internal cancer in the past year; normal or near normal lab values in a routine screening panel of tests; planning to live within travel distance of SKICAP clinic for at least 5 years; history of 4 or more pathologically confirmed BCCs or cutaneous SCCs; triglyceride level below the 95% UL of normal; no childbearing potential or breastfeeding</td>
<td>Patients with a diagnosis of basal cell nevus syndrome or xerodermapigmentosum</td>
<td>Vitamin A</td>
<td>173</td>
</tr>
<tr>
<td>SU.VI.MAX (19, 47–53)</td>
<td>Reduce the incidence of cancer and ischemic heart disease with multivitamin supplementation</td>
<td>RCT</td>
<td>Men (aged 45-60 years) and women (aged 35-60 years), free of any severe pathology that might limit participation, not be taking supplements containing any of the study vitamins or minerals, express no ambiguous</td>
<td>NR</td>
<td>Multivitamin qd (vitamin C 120 mg, vitamin E 30 mg, β-carotene 6 mg, selenium 100 mcg, and zinc 20 mg)</td>
<td>6,481</td>
</tr>
<tr>
<td>Study</td>
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<td>Study design</td>
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<td>Exclusion criteria</td>
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<td>--------------------------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>USPSTF Quality</td>
<td></td>
<td></td>
<td>motivations or obsessional behavior concerning diet and health; manifest no qualms about complying with protocol constraints</td>
<td>Placebo</td>
<td>6,536</td>
<td></td>
</tr>
<tr>
<td>Trivedi 2003 (41)</td>
<td>Determine the effect of vitamin D supplementation on rate of fractures</td>
<td>RCT</td>
<td>Men and women aged 65-85 years</td>
<td>Already taking vitamin D supplements, conditions that were contraindications to vitamin D supplements (e.g., renal stones, sarcoidosis, or malignancy)</td>
<td>Vitamin D₃</td>
<td>1,345</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100,000 IU every 4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK PRECISE (35)</td>
<td>Determine the effect of selenium supplementation on cancer prevention</td>
<td>RCT</td>
<td>Elderly volunteers aged 60-74 years</td>
<td>Southwest Oncology Group performance score &gt; 1, active liver or kidney disease, prior diagnosis of cancer (excluding NMSC), diagnosed HIV infection, on immunosuppressive therapy, diminished mental capacity, taking ≥ 50 mcg/d of selenium supplements in the previous 6 months</td>
<td>Selenium 100 mcg qd</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selenium 200 mcg qd</td>
<td></td>
<td>127</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selenium 300 mcg qd</td>
<td></td>
<td>126</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td>121</td>
</tr>
<tr>
<td>WHI (44, 76, 77, 129–138)</td>
<td>Evaluate the efficacy of calcium with vitamin D supplementation on preventing colorectal cancer; evaluate the efficacy of preventing hip and other fractures</td>
<td>RCT</td>
<td>Participants enrolled in the WHI Dietary Modification trial, Hormone Therapy trials, or both; women aged 50-79 years of age at initial screening; no evidence of a medical condition associated with a predicted survival of &lt; 3 years; no safety, adherence, or retention risks</td>
<td>Hypercalcemia; renal calculi; corticosteroid or calcitriol use; intention to continue to take ≥ 600 IUs of vitamin D per day of personal supplements</td>
<td>Vitamin D₃ 200 IU bid + calcium 500 mg bid</td>
<td>18,176</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td>18,106</td>
</tr>
<tr>
<td>WHS (26, 32, 139)</td>
<td>Prevent cancer and CVD with vitamin E or β-carotene supplementation</td>
<td>RCT, 2x2x2 factorial design¶</td>
<td>Females aged 45 years or older; postmenopausal or had no intention of becoming pregnant; without previous history of CHD, cerebrovascular disease, cancer</td>
<td>Participants in the ongoing Nurses’ Health Study (an observational cohort study of registered nurses).</td>
<td>Vitamin E 600 IU qod</td>
<td>19,937</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No vitamin E β-carotene 50 mg qod</td>
<td></td>
<td>19,939</td>
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<tr>
<td>Study Country</td>
<td>Study aim(s)</td>
<td>Study design</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention arm</td>
<td>N randomized</td>
</tr>
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<td>---------------</td>
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<td>-------------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>USPSTF Quality</td>
<td></td>
<td></td>
<td>(except NMSC), or any serious illness that might preclude participation; without reported history of serious side effects to any study treatment; not currently taking ASA, ASA-containing medications, or NSAID more than once a week or were willing to forgo the use of these medications; not currently taking anticoagulants or corticosteroids; and not taking vitamin A or E or β-carotene supplements more than once a week.</td>
<td>No β-carotene</td>
<td>19,937</td>
<td></td>
</tr>
</tbody>
</table>

*Factorial design studies may have reported outcomes by original randomized arms and/or by factorial design – i.e., participants who were randomized to receive a specific supplement (e.g., vitamin C with or without vitamin E) vs. participants not randomized to receive the aforementioned specific supplement (e.g., vitamin E alone or placebo).

†IWHS: Prospective cohort study among women taking vitamin A compared to non-users of vitamin A; dosage not reported.

‡ NHS: Prospective cohort study among women taking one of the following supplements: multivitamin, vitamin A or β-carotene compared to non-users; dosage or number of participants by supplement not reported.

§PHS-I: Participants randomized to receive β-carotene, β-carotene + aspirin, aspirin, or placebo; numbers of participant allocated to original randomized arms not reported.

¶PHS-II: Participants randomized to receive vitamin E, vitamin C, multivitamin, β-carotene (discontinued), or placebo.

‖WHS: Participants randomized to receive vitamin E, β-carotene, aspirin or placebo; numbers of participants allocated to original randomized arms not reported.

**Abbreviations:** ASA = acetylsalicylic acid; bid = twice daily; BCC = basal cell carcinoma; BMI = body mass index; CHD = coronary heart disease; CIS = carcinoma in situ; cm = centimeter(s); CNS = central nervous system; Cr = chromium; Cu = copper; CVD = cardiovascular disease; DBP = diastolic blood pressure; DRE = digital rectal exam; HRT = hormone replacement therapy; IU = international unit(s); kcal = kilocalorie(s); mcg = microgram(s); mg = milligram(s); Mg = magnesium; MI = myocardial infarction; mmHg = millimeter of mercury; Mn = manganese; Mo = molybdenum; NMSC = non-melanoma skin cancer; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drugs; PSA = prostate serum antigen; qd = once daily; qod = every other day; RCT = randomized controlled trial; SCC = squamous cell carcinoma; SERMs = selective estrogen receptor modulators; SWOG = Southwest Oncology Group; UL = upper limit.
<table>
<thead>
<tr>
<th>Study</th>
<th>Supplement(s)</th>
<th>N randomized</th>
<th>Mean age (years)</th>
<th>Female (%)</th>
<th>Non-white (%)</th>
<th>Mean BMI (kg/m²)</th>
<th>Current smokers (%)</th>
<th>Alcohol use</th>
<th>Prior supplement use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS (45, 92, 93)</td>
<td>Calcium</td>
<td>1,471</td>
<td>74.3</td>
<td>100</td>
<td>NR</td>
<td>26.4</td>
<td>3.0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AFPPS (39, 94)</td>
<td>Folic acid</td>
<td>1,021</td>
<td>57</td>
<td>36.3</td>
<td>14.4</td>
<td>27.4</td>
<td>14.4</td>
<td>0.6 drinks/day</td>
<td>MVI: 35.9</td>
</tr>
<tr>
<td>ASAP (30)</td>
<td>Vitamin E, vitamin C</td>
<td>520</td>
<td>59.8</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>58.6 grams/week</td>
<td>NR</td>
</tr>
<tr>
<td>ATBC (24, 84, 95–107)</td>
<td>β-carotene, vitamin E</td>
<td>29,133</td>
<td>57.2</td>
<td>0</td>
<td>NR</td>
<td>26.3</td>
<td>100</td>
<td>18.0 grams/day</td>
<td>NR</td>
</tr>
<tr>
<td>CARET (29, 108–113)</td>
<td>β-carotene + vitamin A</td>
<td>18,314</td>
<td>57.5</td>
<td>34.3</td>
<td>6.8</td>
<td>NR</td>
<td>60.1</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CPPS (46, 88)</td>
<td>Calcium</td>
<td>930</td>
<td>61.9</td>
<td>28</td>
<td>5.4 (men only)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Calcium: 3</td>
</tr>
<tr>
<td>Dean 2011 (42)</td>
<td>Vitamin D</td>
<td>128</td>
<td>21.8</td>
<td>57</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Graat 2002 (22)</td>
<td>Multivitamin, vitamin E</td>
<td>652</td>
<td>73.2</td>
<td>50</td>
<td>NR</td>
<td>27.4</td>
<td>9</td>
<td>NR</td>
<td>39</td>
</tr>
<tr>
<td>IWHS (38)</td>
<td>Vitamin A</td>
<td>34,703</td>
<td>61</td>
<td>100</td>
<td>0.7</td>
<td>27.0</td>
<td>NR</td>
<td>3.8 grams/day</td>
<td>Vitamin A: 35</td>
</tr>
<tr>
<td>Lappe 2007 (43, 114)</td>
<td>Calcium, vitamin D</td>
<td>1,180</td>
<td>66.7</td>
<td>100</td>
<td>0</td>
<td>29.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NHS (23)</td>
<td>Multivitamin, vitamin A, β-carotene</td>
<td>72,337</td>
<td>58.3</td>
<td>100</td>
<td>NR</td>
<td>26.0</td>
<td>26</td>
<td>7.4 grams/day</td>
<td>MVI: 17 Vitamin A: 0.6 β-carotene: 0.8</td>
</tr>
<tr>
<td>NPC (34, 87, 91, 115–118, 140)</td>
<td>Selenium</td>
<td>1,312</td>
<td>63</td>
<td>0</td>
<td>NR</td>
<td>26</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NSCPS (28, 119)</td>
<td>β-carotene</td>
<td>1,621</td>
<td>48.7</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PHS-I (25, 90, 120, 121)</td>
<td>β-carotene</td>
<td>22,071</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>MVI: 20</td>
</tr>
<tr>
<td>PHS-II (21, 31, 54, 55, 85)</td>
<td>Vitamin E, vitamin C, multivitamin</td>
<td>14,641</td>
<td>64.3</td>
<td>0</td>
<td>NR</td>
<td>26.0</td>
<td>3.6</td>
<td>80.7% consume ≥1 drink per month</td>
<td>NR</td>
</tr>
<tr>
<td>REACT (20)</td>
<td>Multivitamin</td>
<td>297</td>
<td>66.2</td>
<td>59.3</td>
<td>NR</td>
<td>NR</td>
<td>18.8</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Study</td>
<td>Supplement(s)</td>
<td>N randomized</td>
<td>Mean age (years)</td>
<td>Female (%)</td>
<td>Non-white (%)</td>
<td>Mean BMI (kg/m²)</td>
<td>Current smokers (%)</td>
<td>Alcohol use</td>
<td>Prior supplement use (%)</td>
</tr>
<tr>
<td>-------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>RECORD (40, 122)</td>
<td>Calcium, vitamin D</td>
<td>5,292</td>
<td>77</td>
<td>84.7</td>
<td>0.8</td>
<td>NR</td>
<td>11.7</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SCPS (27, 83, 123)</td>
<td>β-carotene</td>
<td>1,805</td>
<td>63.0</td>
<td>30.7</td>
<td>NR</td>
<td>NR</td>
<td>18.7</td>
<td>NR</td>
<td>Daily: 23.9</td>
</tr>
<tr>
<td>SELECT (33, 86, 124–127)</td>
<td>Vitamin E, selenium</td>
<td>35,533</td>
<td>62.5</td>
<td>0</td>
<td>21</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>Occasionally: 15.6</td>
</tr>
<tr>
<td>SKICAP-AK (36, 128)</td>
<td>Vitamin A</td>
<td>2,297</td>
<td>63</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>NR</td>
<td>Sometimes: 28.5</td>
</tr>
<tr>
<td>SKICAP-SB (37, 128)</td>
<td>Vitamin A</td>
<td>347</td>
<td>NR</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Sometimes: 27</td>
</tr>
<tr>
<td>SU.VI.MAX (19, 47–53)</td>
<td>Multivitamin</td>
<td>13,017</td>
<td>49.0</td>
<td>59.0</td>
<td>NR</td>
<td>24.3</td>
<td>15.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Trivedi 2003 (41)</td>
<td>Vitamin D, calcium</td>
<td>2,686</td>
<td>74.8</td>
<td>24.2</td>
<td>NR</td>
<td>24.4</td>
<td>4.2</td>
<td>71.7% regular users</td>
<td>Vitamin D: 0</td>
</tr>
<tr>
<td>UK PRECISE (35)</td>
<td>Selenium</td>
<td>501</td>
<td>67.5</td>
<td>47.4</td>
<td>NR</td>
<td>27.5</td>
<td>9.5</td>
<td>86.9% current users</td>
<td>NR</td>
</tr>
<tr>
<td>WHI (44, 76, 77, 129–138)</td>
<td>Vitamin D + calcium</td>
<td>36,282</td>
<td>62.4</td>
<td>100</td>
<td>16.9</td>
<td>29.1</td>
<td>7.6</td>
<td>71.3% current users</td>
<td>Calcium: 29.0</td>
</tr>
<tr>
<td>WHS (26, 32, 139)</td>
<td>Vitamin E, β-carotene</td>
<td>39,876</td>
<td>54.6</td>
<td>100</td>
<td>NR</td>
<td>26.0</td>
<td>13.1</td>
<td>54.9% consume alcohol ≥1 once per month</td>
<td>MVI: 38.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI = body mass index; kg = kilogram(s); m = meter(s); MVI = multivitamin/multi-mineral; NR = not reported.
<table>
<thead>
<tr>
<th>Study Quality</th>
<th>Study design</th>
<th>Follow up</th>
<th>Supplement and dose</th>
<th>N</th>
<th>Mean age (y)</th>
<th>% Female</th>
<th>CVD incidence</th>
<th>Cancer incidence</th>
<th>Mortality</th>
<th>Harms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-carotene studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>16 years (max)</td>
<td>β-carotene 20 mg qd (alone or in combination with vitamin E 50 mg qd)</td>
<td>29,133</td>
<td>57</td>
<td>0</td>
<td>NR</td>
<td>Any: ↔</td>
<td>Lung: ↑* CRC: ↔† Prostate Breast: NA Other: ↔</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>12 years</td>
<td>β-carotene 50 mg qod (alone or in combination with ASA)</td>
<td>22,071</td>
<td>NR</td>
<td>0</td>
<td>Any: ↔ MI: ↔ Stroke: ↔</td>
<td>Any: ↔</td>
<td>Lung: ↔ CRC: ↔ Prostate: ↔ NA Breast: NA Other: ↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Good</td>
<td>2x2x2 RCT</td>
<td>4.1 years</td>
<td>β-carotene 50 mg qod (alone or in combination with vitamin E 600 IU qod and/or ASA)</td>
<td>39,876</td>
<td>55</td>
<td>100</td>
<td>Any: ↔ MI: ↔ Stroke: ↔</td>
<td>Any: ↔</td>
<td>Lung: ↔ CRC: ↔ Prostate: ↔ NA Breast: ↔ Other: ↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Good</td>
<td>RCT</td>
<td>8.2 years</td>
<td>β-carotene 50 mg qd</td>
<td>1,805</td>
<td>63</td>
<td>31</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>4.5 years</td>
<td>β-carotene 30 mg qd (alone or in combination with topical sunscreen)</td>
<td>1,621</td>
<td>49</td>
<td>56</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Study Quality</td>
<td>Study Design</td>
<td>Follow up</td>
<td>Supplement and Dose</td>
<td>N</td>
<td>Mean age (y)</td>
<td>% Female</td>
<td>CVD incidence</td>
<td>Cancer incidence</td>
<td>Mortality</td>
<td>Harms</td>
<td>Comments</td>
</tr>
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<td>----------</td>
</tr>
<tr>
<td>Good</td>
<td>RCT</td>
<td>11 years</td>
<td>β-carotene 30 mg qd + vitamin A 25,000 IU qd</td>
<td>18,314</td>
<td>58</td>
<td>34</td>
<td>NA</td>
<td>Any: ↔ Lung: ↑* CRC: ↔ Prostate: ↔ Breast: ↔ Other: ↔</td>
<td>↑</td>
<td>↔</td>
<td>Baseline population at high-risk for lung cancer (smokers or asbestos-exposed workers)</td>
</tr>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>16 years</td>
<td>Vitamin E 50 mg qd (alone or in combination with β-carotene 20 mg qd)</td>
<td>29,133</td>
<td>57</td>
<td>0</td>
<td>NA</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↓‡ Breast: NA Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>2x2 factorial RCT</td>
<td>3 years</td>
<td>Vitamin E 91 mg bid (alone or in combination with vitamin C 250 mg bid)</td>
<td>520</td>
<td>60</td>
<td>51</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>2x2x2x2 factorial RCT</td>
<td>8 years</td>
<td>Vitamin E 400 IU qd (alone or in combination with β-carotene, vitamin C, and/or MVI)</td>
<td>14,641</td>
<td>64</td>
<td>0</td>
<td>Any: ↔ Stroke: ↔ MI: ↔</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↔ Breast: NA Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td>Hemorrhagic stroke (↑)</td>
</tr>
</tbody>
</table>

ATBC (24, 84, 95–107) | 2x2 factorial RCT | 16 years  | Vitamin E 50 mg qd (alone or in combination with β-carotene 20 mg qd) | 29,133| 57           | 0        | NA            | Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↓‡ Breast: NA Other: ↔ | ↔         | ↔     |          |

ASAP (30) | 2x2 factorial RCT | 3 years   | Vitamin E 91 mg bid (alone or in combination with vitamin C 250 mg bid) | 520   | 60           | 51       | NA            | NA               | ↔         | ↔     |          |

PHS-II (31, 55, 85) | 2x2x2x2 factorial RCT | 8 years   | Vitamin E 400 IU qd (alone or in combination with β-carotene, vitamin C, and/or MVI) | 14,641| 64           | 0        | Any: ↔ Stroke: ↔ MI: ↔ | Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↔ Breast: NA Other: ↔ | ↔         | ↔     | Hemorrhagic stroke (↑) |
<table>
<thead>
<tr>
<th>Study Quality</th>
<th>Study design</th>
<th>Supplement and dose</th>
<th>N</th>
<th>Mean age (y)</th>
<th>% Female</th>
<th>CVD incidence</th>
<th>Cancer incidence</th>
<th>Mortality</th>
<th>Harms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>Vitamin E 600 IU qod (alone or in combination with β-carotene 50 mg qod or ASA)</td>
<td>39,876</td>
<td>55</td>
<td>100</td>
<td>Any: ↔ Stroke: ↔ MI: ↔</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: NA Breast: ↔ Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Good</td>
<td>2x2 factorial RCT</td>
<td>Vitamin E 200 mg qd (alone or in combination with an MVI)</td>
<td>652</td>
<td>73</td>
<td>50</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>Respiratory infections (↔)</td>
</tr>
<tr>
<td>Good</td>
<td>RCT</td>
<td>Vitamin E 400 IU qd (alone or in combination with selenium 200 mcg qd)</td>
<td>35,533</td>
<td>63</td>
<td>0</td>
<td>Any: ↔ Stroke: NR MI: NR</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↑† Breast: NA Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Fair</td>
<td>RCT</td>
<td>Selenium 200 mcg qd</td>
<td>1,312</td>
<td>63</td>
<td>25</td>
<td>Any: ↔ MI: ↔ Stroke: ↔</td>
<td>Any: ↓ Lung: ↔ CRC: ↓ Prostate: ↓ Breast: ↔ Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
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</tbody>
</table>

**Selenium studies**

- **NPC (34, 87, 91, 115–118, 140)**
  - RCT
  - 7.6 years
  - Selenium 200 mcg qd
  - 1,312
  - 63
  - 25
  - Any: ↔ MI: ↔ Stroke: ↔
  - Any: ↓ Lung: ↔ CRC: ↓ Prostate: ↓ Breast: ↔ Other: ↔
  - ↔
  - ↔
  - Cancer-related mortality (↓)
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<thead>
<tr>
<th>Study Quality</th>
<th>Study Design</th>
<th>Follow up</th>
<th>Supplement and dose</th>
<th>N</th>
<th>Mean age (y)</th>
<th>% Female</th>
<th>CVD incidence</th>
<th>Cancer incidence</th>
<th>Mortality</th>
<th>Harms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>RCT</td>
<td>5 years with extended followup</td>
<td>Selenium 200 mcg qd (alone or in combination with vitamin E 400 IU qd)</td>
<td>35,533</td>
<td>63</td>
<td>0</td>
<td>Any: ↔ MI: NR Stroke: NR</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: ↔ Breast: NA Other: ↔</td>
<td>↔</td>
<td>↔</td>
<td>Mixed dermatological harms among arms: selenium alone (↑) and selenium + vitamin E (↔)</td>
</tr>
<tr>
<td>Fair</td>
<td>RCT</td>
<td>0.5 years</td>
<td>Selenium 100, 200 or 300 mcg qd</td>
<td>501</td>
<td>67</td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>No serious harms reported; stomach and abdominal discomfort (↔)</td>
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<tr>
<td>Vitamin A studies</td>
<td></td>
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<tr>
<td>SKICAP-AK (36, 128)</td>
<td>RCT</td>
<td>5 years</td>
<td>Vitamin A 25,000 IU qd</td>
<td>2,297</td>
<td>63</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>RCT</td>
<td>5 years</td>
<td>Sodium selenite 100 mcg qd</td>
<td>347</td>
<td>NR</td>
<td>28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>CARET (29, 108–113)</td>
<td>RCT</td>
<td>11 years</td>
<td>Vitamin A 25,000 IU qd + β-carotene 30 mg qd</td>
<td>18,314</td>
<td>58</td>
<td>34</td>
<td>NA</td>
<td>Any: ↔ Lung: ↑* CRC: ↔ Prostate: ↔ Breast: ↔ Other: ↔</td>
<td>↑</td>
<td>↔</td>
<td>Baseline population at high-risk for lung cancer (smokers or asbestos-exposed workers)</td>
</tr>
<tr>
<td>NHS (23)</td>
<td>Prospective cohort</td>
<td>18 years</td>
<td>Vitamin A users (dose NR)</td>
<td>72,337</td>
<td>58</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>↑</td>
<td>Hip fracture among current (↔) and past (↑) vitamin A supplement users</td>
<td></td>
</tr>
<tr>
<td>IWHS (38)</td>
<td>Prospective cohort</td>
<td>9.5 years</td>
<td>Vitamin A users (dose NR)</td>
<td>34,703</td>
<td>61</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>All fractures (↔) and hip fractures (↔)</td>
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</table>

**Vitamin C studies**
<table>
<thead>
<tr>
<th>Study Quality</th>
<th>Study Design</th>
<th>Supplement and Dose</th>
<th>N</th>
<th>Mean Age (y)</th>
<th>% Female</th>
<th>CVD Incidence</th>
<th>Cancer Incidence</th>
<th>Mortality</th>
<th>Harms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>2x2x2x2 factorial RCT</td>
<td>Vitamin C 500 mg qd (alone or in combination with vitamin E, β-carotene and/or MVI)</td>
<td>14,641</td>
<td>64</td>
<td>0</td>
<td>Any: ↔</td>
<td>Any: ↔</td>
<td>↔</td>
<td>NR</td>
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<tr>
<td>ASAP (30)</td>
<td>2x2 factorial RCT</td>
<td>Vitamin C 250 mg bid (alone or combined with vitamin E 91 mg bid)</td>
<td>520</td>
<td>60</td>
<td>51</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
<td>↔</td>
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</tr>
<tr>
<td>Fair</td>
<td>3x2 factorial RCT</td>
<td>Folic acid 1 mg qd</td>
<td>1,021</td>
<td>57</td>
<td>36</td>
<td>Any: ↔</td>
<td>Any: ↑</td>
<td>↔</td>
<td>NR</td>
<td>Paradoxical effect for noncolorectal cancers (†)</td>
</tr>
<tr>
<td>Fair</td>
<td>2x2 factorial RCT</td>
<td>Vitamin D3 800 IU qd (alone or in combination with calcium 1,000 mg qd)</td>
<td>5,292</td>
<td>77</td>
<td>85</td>
<td>Any: ↔</td>
<td>Any: ↔</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>Trivedi 2003 (41)</td>
<td>RCT</td>
<td>Vitamin D3 100,000 IU q4m</td>
<td>2,686</td>
<td>75</td>
<td>24</td>
<td>Any: ↔</td>
<td>Any: ↔</td>
<td>↔†</td>
<td>NR</td>
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<tr>
<td>Study Quality</td>
<td>Study Design</td>
<td>Supplement and dose</td>
<td>N</td>
<td>Mean age (y)</td>
<td>% Female</td>
<td>CVD Incidence</td>
<td>Cancer Incidence</td>
<td>Mortality</td>
<td>Harms</td>
<td>Comments</td>
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<td>Dean, 2011 (42)</td>
<td>RCT</td>
<td>Vitamin D 5,000 IU qd</td>
<td>128</td>
<td>22</td>
<td>57</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Good</td>
<td>Follow up</td>
<td>0.1 years</td>
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<td>0.1 years</td>
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<td>Vitamin D and calcium combination studies</td>
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<tr>
<td>Lappe 2007 (43, 114)</td>
<td>RCT</td>
<td>Vitamin D3 25 mcg qd + calcium 1,400 mg qd</td>
<td>1,180</td>
<td>67</td>
<td>100</td>
<td>NR</td>
<td>Any: ↓ Lung: ↔ CRC: ↔ Prostate: NA Breast: ↔ Other: ↔</td>
<td>NR</td>
<td>↔</td>
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<tr>
<td>Fair</td>
<td>Follow up</td>
<td>4 years</td>
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<td>Good</td>
<td>Follow up</td>
<td>7 years</td>
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<td>ACS (45, 92, 93)</td>
<td>RCT</td>
<td>Calcium 1,000 mg qd</td>
<td>1,471</td>
<td>74</td>
<td>100</td>
<td>Any: ↔ MI: ↔ Stroke: ↔</td>
<td>NR</td>
<td>↔</td>
<td>↑ Constipation (↑) and hip fractures (↑)</td>
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<tr>
<td>Fair</td>
<td>Follow up</td>
<td>5 years</td>
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<td>5 years</td>
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<tr>
<td>Lappe 2007 (43)</td>
<td>RCT</td>
<td>Calcium 1,400 mg qd</td>
<td>1,180</td>
<td>67</td>
<td>100</td>
<td>NR</td>
<td>Any: ↔ Lung: ↔ CRC: ↔ Prostate: NA Breast: ↔ Other: ↔</td>
<td>NR</td>
<td>↔</td>
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<tr>
<td>Fair</td>
<td>Follow up</td>
<td>4 years</td>
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<td>Follow up</td>
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<tr>
<td>Study Quality</td>
<td>Study design</td>
<td>Follow up</td>
<td>Supplement and dose</td>
<td>N</td>
<td>Mean age (y)</td>
<td>% Female</td>
<td>CVD incidence</td>
<td>Cancer incidence</td>
<td>Mortality</td>
<td>Harms</td>
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<tr>
<td>RECORD (40, 122)</td>
<td>2x2 factorial RCT</td>
<td>6.2 years</td>
<td>Calcium 1,000 mg qd (alone or in combination with vitamin D3 800 IU qd)</td>
<td>5,292</td>
<td>77</td>
<td>85</td>
<td>Any: ↔*</td>
<td>Any: ↔</td>
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<td>MI: NR</td>
<td>Lung: ↔</td>
<td>Stroke: NR</td>
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<td>CRC: ↑</td>
<td>Prostate: ↔</td>
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<td>Prostate: ↔</td>
<td>Breast: ↔</td>
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<td>Other: ↔</td>
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Data Supplement References


142. Wyatt G. Vitamin E increases prostate cancer risk in middle-aged men relative to placebo: no significant association observed with selenium, either alone or in combination with vitamin E. Evid Based Nurs. 2012;15:90-1. [PMID: 22411161]
