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Multivitamin/Mineral Supplements and Prevention of Chronic Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was funded by the National Institutes of Health Office of Medical Applications of Research (NIH OMAR). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objective. To review and synthesize published literature on the efficacy of multivitamin/mineral supplements and certain single nutrient supplements in the primary prevention of chronic disease in the general adult population, and on the safety of multivitamin/mineral supplements and certain single nutrient supplements, likely to be included in multivitamin/mineral supplements, in the general population of adults and children.

Data Sources. All articles published through February 28, 2006, on MEDLINE,® EMBASE,® and the Cochrane databases.

Review Methods. Each article underwent double reviews on title, abstract, and inclusion eligibility. Two reviewers performed data abstraction and quality assessment. Differences in opinion were resolved through consensus adjudication.

Results. Few trials have addressed the efficacy of multivitamin/mineral supplement use in chronic disease prevention in the general population of the United States. One trial on poorly nourished Chinese showed supplementation with combined β-carotene, vitamin E and selenium reduced gastric cancer incidence and mortality, and overall cancer mortality. In a French trial, combined vitamin C, vitamin E, β-carotene, selenium, and zinc reduced cancer risk in men but not in women. No cardiovascular benefit was evident in both trials. Multivitamin/mineral supplement use had no benefit for preventing cataract. Zinc/antioxidants had benefits for preventing advanced age-related macular degeneration in persons at high risk for the disease.

With few exceptions, neither β-carotene nor vitamin E had benefits for preventing cancer, cardiovascular disease, cataract, and age-related macular degeneration. β-carotene supplementation increased lung cancer risk in smokers and persons exposed to asbestos. Folic acid alone or combined with vitamin B12 and/or vitamin B6 had no significant effects on cognitive function. Selenium may confer benefit for cancer prevention but not cardiovascular disease prevention. Calcium may prevent bone mineral density loss in postmenopausal women, and may reduce vertebral fractures, but not non-vertebral fractures. The evidence suggests dose-dependent benefits of vitamin D with/without calcium for retaining bone mineral density and preventing hip fracture, non-vertebral fracture and falls.

We found no consistent pattern of increased adverse effects of multivitamin/mineral supplements except for skin yellowing by β-carotene.

Conclusion. Multivitamin/mineral supplement use may prevent cancer in individuals with poor or suboptimal nutritional status. The heterogeneity in the study populations limits generalization to United States population. Multivitamin/mineral supplements conferred no benefit in preventing cardiovascular disease or cataract, and may prevent advanced age-related macular degeneration only in high-risk individuals. The overall quality and quantity of the literature on the safety of multivitamin/mineral supplements is limited.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/multivit/multivit.pdf.

Executive Summary

Introduction

The Johns Hopkins University Evidence-based Practice Center (EPC) reviewed and synthesized the published literature on four Key Questions:

1. *What is the efficacy of multivitamin/mineral supplement use in the prevention of chronic disease for the general adult population?*
2. *What is the safety of multivitamin/mineral supplementation in the general population of adults and children?*
3. *What is the efficacy of single nutrients or functionally related nutrient pairs in preventing chronic disease in the general adult population?*
4. *What is the safety of single nutrients or functionally related nutrient pairs in the general population of adults and children?*

Multivitamin/mineral supplements are the most commonly used nutritional supplements in the United States. Most multivitamin/mineral supplements contain at least 10 vitamins or minerals with a wide range of doses. Many individuals use multivitamin/mineral supplements for prophylactic or disease-mitigating purposes.

Chronic disease is estimated to account for 35 million deaths worldwide. Cardiovascular disease and cancer comprise a major proportion of chronic diseases in both developed and developing countries. Other than cardiovascular disease and cancer, obesity-related diseases such as type 2 diabetes, end-stage renal disease, and osteoarthritis are also becoming significant public health problems. Many of these chronic diseases share common risk factors and underlying pathologic mechanisms that may be modified by nutrients. Examples include reduction of oxidative damage by antioxidants, DNA methylation regulated by folate and B vitamins, bone metabolism regulated by vitamin D and calcium, and cell differentiation, proliferation, and growth regulated by retinol, calcium, and vitamin D.

The biological effects of a nutrient are heavily dependent on its bioavailability. Key factors determining the bioavailability of micronutrients are the chemical form in which the nutrient is presented to the intestinal absorptive surface, the presence of other competing chemicals in the intestinal lumen, the concentration of food constituents (such as phytates and other chelating agents) that bind to the nutrient and make it unavailable for absorption, intestinal transit time, and enzyme activity. A nutrient may affect not only the absorption of other nutrients, but also the transport, tissue uptake, function and metabolism of other nutrients. Hence, concurrent ingestion of several nutrients may result in synergistic, antagonistic, or threshold effects as compared to a single nutrient. The efficacy of a single nutrient or multiple nutrients should be considered separately unless no interactive or threshold effects can be found.

The United States Food and Nutrition Board has established the tolerable upper intake levels (ULs) for several nutrients. By definition, a UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Since the time when ULs were determined, several large-scale randomized controlled trials of

vitamin/mineral supplementation have been completed. An update of the data on adverse effects/events will help to evaluate the appropriateness of the ULs.

Methodology

Our EPC established a team and a work plan to develop this evidence report. The project consisted of recruiting technical experts, formulating and refining the specific questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence into a report, and submitting the report for peer review. The investigative team has strong expertise in nutrition, medicine, chronic disease epidemiology, clinical trial methodology, HIV infection, ophthalmology, and gerontology. In addition, the investigators have extensive experience in conducting research projects specific to vitamins and minerals in the general population, children, and the elderly.

We defined multivitamin/mineral supplements as any supplements containing 3 or more vitamins and/or minerals without herbs, hormones, or drugs, each at a dose less than the UL determined by the Food and Nutrition Board. The general population is defined as community-dwelling individuals who do not have special nutritional need (e.g., not institutionalized, hospitalized, pregnant, or clinically deficient in nutrients). For efficacy, we considered data from randomized controlled trials. For safety, we considered data from randomized controlled trials and observational studies.

We used a systematic approach for searching the literature to minimize the risk of bias in selecting articles for inclusion in the review. In this systematic approach, we had to be very specific about defining the eligibility criteria for inclusion in the review. The systematic approach was intended to help identify gaps in the published literature."

To enhance our understanding of the efficacy of multivitamin/mineral supplements in preventing chronic disease, we also considered evidence on the efficacy and the safety of individual vitamins and minerals that are often included in multivitamin/mineral supplements. The individual or functionally-related paired nutrients considered for efficacy issues were calcium, folic acid, vitamin B6, vitamin B12, vitamin D, vitamin E, vitamin C, vitamin A, iron, zinc, magnesium, vitamin B1, vitamin B2, niacin, calcium/vitamin D, calcium/magnesium, folic acid/vitamin B12, and folic acid/vitamin B6. The nutrients considered for safety issues were calcium (with or without vitamin D), folic acid, vitamin D, vitamin E, vitamin A, iron, selenium, and β-carotene.

The following chronic diseases were considered: (a) breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric cancer, or any other malignancy; (b) myocardial infarction, stroke; (c) type 2 diabetes mellitus; (d) Parkinson's disease, dementia; (e) cataracts, macular degeneration, hearing loss; (f) osteoporosis, osteopenia, rheumatoid arthritis, osteoarthritis; (g) non-alcoholic steatorrheic hepatitis, non-alcoholic fatty-liver disease; (h) chronic renal insufficiency, chronic nephrolithiasis; and (i) HIV infection, hepatitis C, tuberculosis, and (j) chronic obstructive pulmonary disease.

Literature Sources

We searched for articles published from 1966 through February 2006 using MEDLINE,® EMBASE,® and the Cochrane database. Additional articles were identified by searching references in pertinent articles, querying experts, and hand-searching the tables of content of 15 journals published from January 2005 through February 2006.

Eligibility Criteria

An article was included if it had data from a randomized controlled trial that assessed the efficacy of multivitamin/mineral supplement use in preventing one or more of the chronic diseases listed above. An article was excluded if it met any of the following exclusion criteria: (1) not written in English; (2) contained no human data; (3) included only pregnant women; (4) only infants; (5) only subjects of age less than or equal to 18 years (if a study included only subjects of age less than or equal to 18 years, we included it only if it presented data on the safety of a vitamin/mineral supplement) (6) included only patients with particular chronic diseases; (7) included only patients receiving treatment for chronic disease or included only patients in long-term care facilities; (8) only studied clinical nutritional deficiency; (9) contained no useful information applying to the Key Questions; (10) did not address the use of supplements; (11) did not address the use of supplements separately from dietary intake; (12) did not cover the defined disease endpoints or; (13) was an editorial, commentary, or letter. Additionally, an article could be excluded if it applied to Key Question 1 and/or 3 but was not a randomized controlled trial or a systematic review and did not address safety issues. However, we included observational studies for the Key questions about the safety of vitamin/mineral supplements. Differences in opinions regarding abstract inclusion or exclusion were resolved through consensus adjudication.

Article Inclusion/exclusion

Each article underwent title review, abstract review, and inclusion/exclusion review by paired reviewers. Differences in opinions at abstract and inclusion/exclusion review were resolved through consensus adjudication.

Assessment of Study Quality

Each eligible article was reviewed by paired reviewers who independently rated the quality of each study with respect to the categories: representation of study participants (4 items), bias and confounding (12 items), descriptions of study supplements and supplementation (2 items), adherence and follow up (6 items), statistical analysis (6 items), and conflict of interest (1 item). Reviewers assigned a score of zero (criterion not met), one (criterion partially met), or two (criteria fully met) to each item. The score for each quality category was the percentage of the total score available in each category and could range from 0 to 100 percent. The overall quality score was the average of the six categorical scores.

Data Extraction

Paired reviewers abstracted data on study design, geographical location, study period, participants' eligibility, sample size, recruitment settings, demographic and lifestyle factors of participants, prior supplement use, intervention (type, dose, and chemical forms of study supplements, and duration, frequency, and timing of study supplement use), and results. Data abstraction forms were completed by a primary reviewer, and verified for completeness and accuracy by a second reviewer. Differences in opinions were resolved through adjudication. We used a systematic approach for extracting data from the studies to minimize the risk of bias in how we extracted data from eligible studies. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Results

The literature search process identified 11,324 citations potentially relevant to the Key Questions. We excluded 849 duplicate citations. In the title review process, we excluded 6,863 citations because they clearly did not pertain to the Key Questions. In the abstract review process, we excluded 3,163 citations that did not meet one or more of the eligibility criteria. Using the article inclusion/exclusion form, we then excluded an additional 386 articles that did not meet one or more of the eligibility criteria. That left a total of 63 articles eligible for inclusion in the review of one or more of the Key Questions.

Results from this systematic review indicated a paucity of data from randomized controlled trials that specifically address the efficacy of multivitamin/mineral supplement use in the prevention of chronic disease in the general population of the United States. The data were on the efficacy of designed combinations of vitamins and minerals; none of the trials used one-a-day multivitamins prevailing on the market in the United States. Data on cancer and cardiovascular outcomes came from the Linxian General Population Trial in China and the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) trial in France. The Linxian trial documented that supplementation with combined β-carotene, vitamin E and selenium supplements at doses 1 to 2 times the United States Recommended Daily Allowance (RDA) for 5 years had 13 percent to 21 percent reductions in gastric cancer incidence, gastric cancer mortality, and total cancer mortality in a poorly nourished Chinese population. The reduction in cancer mortality was stronger in women than in men. There were no significant effects on total cancer incidence and cerebrovascular mortality. The SU.VI.MAX study in a French population documented a 31 percent reduction in overall cancer risk by use of vitamin C, vitamin E, β-carotene, selenium, and zinc at doses 1-2 times the RDAs for 8 years in men but not in women. A 12 percent reduction in prostate cancer risk, particularly a 48 percent risk reduction in those with normal prostate specific antigen levels at baseline, was found in men receiving active supplements compared to men receiving placebo. There was no significant effect of the combined antioxidants on ischemic cardiovascular disease incidence. In this trial, men had lower serum levels of vitamin C and β-carotene than women at baseline.

Multivitamin/mineral supplement use for 3 to 6 years had no significant benefits in preventing cataract in 3 trials in the United States (also in the United Kingdom in one trial) and the Linxian trial. In the Age-Related Eye Disease Study (AREDS), high-dose zinc (10 times the RDA) alone or combined with antioxidants (5 to 15 times the RDAs) had beneficial effects on age-related macular degeneration only in those with intermediate age-related macular

degeneration in one or both eyes, or those with advanced age-related macular degeneration in one eye.

Overall, data on total mortality rates pointed to either no increased risk or lower risk in the groups with multivitamin/mineral supplement use. Total mortality was 9 percent lower among those who received β-carotene, selenium, and vitamin E in the Linxian trial; there was no sex- or age-difference in the relative risks. In AREDS, total mortality was 6 percent higher in the group receiving antioxidants compared to the group receiving no antioxidants, but the increase was not statistically significant. Among the participants at high risk for age-related macular degeneration, total mortality was 13 percent to 20 percent lower in the groups receiving zinc alone or zinc combined with antioxidants. In the SU.VI.MAX study, a sex-difference was documented for the relative risk of total mortality among those receiving antioxidants and zinc compared to those receiving placebo. In the REACT, the total mortality rate was not calculated. There were 9 deaths in the antioxidant group, whereas 3 deaths occurred in the placebo group.

Daily supplementation with β-carotene of 20 mg, 30 mg or 50 mg was not protective against malignancies, cardiovascular disease outcomes, diabetes mellitus, cataract or age-related maculopathy. Supplementation with β-carotene with or without vitamin A increased the incidence of lung cancer in persons with asbestos exposure or in smokers, and was associated with increased mortality. To date, there has been no randomized controlled trial that assessed the efficacy of vitamin A alone in preventing chronic disease. Studies in selected populations (nutritionally inadequate, smokers, or asbestos exposure) showed no benefit of combinations of vitamin A and zinc or vitamin A and β-carotene for the prevention of stroke mortality, esophageal or gastric cancer incidence, cardiovascular mortality, or all-cause mortality.

Vitamin E supplements (synthetic α-tocopherol 50 mg or 300 IU per day, natural vitamin E 500 IU, or natural source vitamin E, 600 IU per day) have been studied for primary prevention of cancer, cardiovascular disease, cataract, and age-related eye disease. The evidence predominantly comes from the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) study and the Women's Health Study (WHS). There was a lack of effects of vitamin E in the prevention of these diseases, except for a 32 percent reduction in prostate cancer incidence, a 41 percent reduction in the prostate cancer mortality, and a 22 percent reduction in colorectal cancer in smokers in the ATBC study, and decreased cardiovascular deaths (primarily sudden death) in the WHS participants, particularly in those aged 65 years or older. The findings on hemorrhagic stroke were conflicting between the ATBC trial and the WHS; the former found a higher risk with use of low-dose α-tocopherol supplements but the latter found a lower risk with use at a high dose.

Two previous systematic reviews reported that supplementation with folic acid at a daily dose of 0.75 mg or 30 mg, alone or in combination with vitamin B12 and/or vitamin B6 for 5-12 weeks, had no significant effects on cognitive function in 5 small randomized controlled trials. Combined vitamin B2 and niacin supplement use for 5 years had no significant effects on cerebrovascular mortality, total mortality, total cancer incidence, esophageal or gastric dysplasia/cancer incidence, or esophageal or gastric cancer mortality in a poorly nourished population in China.

In a study in persons with a history of non-melanoma skin cancer, supplementation with selenium of 200 mcg per day had no effect on cardiovascular outcomes, but had protective effects on total mortality and incidence of lung, colorectal, and prostate cancers. Another study in China found a significantly reduced risk for liver cancer in those who used selenium supplements of 200 mcg/day for two years.

Due to the substantial amount of efficacy data on calcium/vitamin D and osteoporosis, we reviewed systematic review articles supplemented with updated data from recent randomized controlled trials and data from randomized controlled trials that met our inclusion criteria, but were not included in previous systematic reviews. The previous systematic reviews reported that supplementation with calcium has short-term (particularly within one year) benefit on retaining bone mineral density in postmenopausal women, and a possible effect in preventing vertebral fractures. The reviews also indicated that combined vitamin D_3 (700-800 IU/day) and calcium (1000 mg/day) may reduce the risk of hip and other non-vertebral fractures in populations with low levels of vitamin D and/or calcium. Recent published data from the Women's Health Initiative (WHI) trial were consistent with these systematic reviews in showing a 1.06 percent higher hip bone density ($p<0.02$) and a 12 percent non-significant lower risk for hip fracture in postmenopausal women after receiving calcium carbonate (500 mg twice a day) and vitamin D_3 (200 IU twice a day) for an average of 7 years as compared to women receiving a placebo. In this trial, participants were allowed to have self-selected use of multivitamin supplements as well as calcium and vitamin D supplements up to 1000 mg and 600 IU per day, respectively, and thus the WHI participants had higher intake of calcium (an average of 1150 mg per day) than the general population (761 mg per day). The WHI trial found no benefit of calcium and vitamin D supplementation in preventing colorectal cancer incidence.

For data on safety, we identified 10 studies using multivitamin/mineral preparations and 24 studies using single nutrients. Doses were usually 2 to 10 times the RDA. Overall, there was no consistent pattern of increased adverse effects in the active group compared with the placebo group, with the exception of changes in skin color, which was common in studies in which β-carotene was part of the multivitamin preparation. In the few studies where mortality was compared between active and control groups, no significant adverse effect of multivitamin/mineral supplementation on this outcome was found.

Supplementation with β-carotene with or without vitamin A increased the incidence of lung cancer in persons with asbestos exposure or in smokers. Vitamin A supplementation moderately increased serum triglyceride levels. Calcium supplementation increased the risk of kidney stones. Vitamin E supplementation was associated with an increased incidence of epistaxis but was not associated with an increased risk of more serious bleeding events, such as hemorrhagic stroke. Iron supplementation was found to reduce weight gain in iron-sufficient, non-anemic children in a small randomized controlled trial. More recent trials have not clarified this issue because they targeted deficient populations and/or included other micronutrients in the intervention formulation.

Future Research

In vitro studies and animal models have helped us to understand the function of nutrients under a controlled environment. However, these types of studies often have over-simplified the sophistication of the human body. There is a gap in our knowledge of how specific nutrients work in vivo to prevent disease. Future research should be directed toward filling the gap by developing valid in vivo biomarkers and applying them in the settings of randomized controlled trials to examine how nutrients influence the body's physiological function and pathological processes, and how multiple nutrients work in concert to do so. Identifying an optimal dose in dose-response studies is critical to guide the design of future large-scale randomized controlled trials when the conduct of the trials is considered worthwhile.

Nutritional research has adopted a reductionist approach that emphasizes the role of individual nutrients in physiologic function or disease process. In view of the complex pathological processes of chronic diseases, the idea of using a single nutrient or a few nutrients to modify disease risk carries considerable optimism. The design and conduct of several large-scale randomized controlled trials on antioxidants was derived from epidemiological data that showed a lower risk of chronic disease (predominantly cancer and cardiovascular disease) in those who had higher circulating levels or dietary intake of some micronutrients. Because of residual confounding and measurement errors in dietary assessment, dietary data from observational studies can be better examined by patterns of food consumption with a multivariate approach, rather than by ranking of specific nutrient intake with a univariate approach.

We have found that many studies did not report study participants' self-selected supplement use before and during the trial participation, and allowed self-selected supplement use during the trial. Similarly, there was a lack of information on other variables that might have modified the effects of study supplements. Furthermore, collective study findings also may not apply to every individual. Additional research should be done, particularly in existing randomized controlled trials, to examine how efficacy may vary by age, time since trial enrollment to diagnosis, self-selected supplement use, dietary patterns, disease history, medication use, and/or genetic polymorphisms.

With many food products being fortified with several nutrients, Americans' dietary intake of certain nutrients may well be above the RDAs. Hence, it is important to study the level of intake among consumers and assess how nutrient fortification may influence the public's health. An adverse event reporting system needs to be in place to facilitate this type of research.

For policy making, research should be conducted to estimate the cost-effectiveness and the risk/benefit profile of multivitamin/mineral supplement use or more generally, dietary supplement use, in the general population. Such research should also consider subpopulations for which these parameters may differ.

Chapter 1. Introduction

Purpose

Multivitamin/mineral supplements are the most commonly used nutritional supplements in the United States.[1] Scientific evidence on the efficacy and safety of supplement use will serve as the basis for us to identify knowledge gaps and inform the general public's practice and future research. This report synthesizes the published literature on the efficacy and the safety of multivitamin/mineral supplements in the prevention of chronic disease for the general population of adults, and on the efficacy and the safety of certain commonly-used single vitamin or mineral supplements in the general population of adults and children. The content of this report will be used by the National Institutes of Health (NIH) in preparing a State-of-the-Science Statement for health care providers and the general public.

Specific Aims

The specific aims of this review are to synthesize evidence in the literature for addressing the following Key Questions:

1. What is the efficacy determined in randomized controlled trials of multivitamin/mineral supplements (defined as 3 or more vitamins and/or minerals without herbs, hormones, or drugs), each at a dose less than the tolerable upper intake level (UL) determined by the Food and Nutrition Board, in the general adult population* for prevention† against the development of one or more of the following chronic diseases or conditions‡?
   a. Oncologic: breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric cancer, or any other malignancy (including colorectal polyps)
   b. Cardiovascular: myocardial infarction, stroke
   c. Endocrine: type 2 diabetes mellitus
   d. Neurologic: Parkinson's disease, cognitive decline, memory loss, dementia
   e. Age-related sensory loss: cataracts, macular degeneration, hearing loss
   f. Musculoskeletal: osteoporosis, osteopenia, rheumatoid arthritis, osteoarthritis
   g. Gastroenterologic: non-alcoholic steatorrheic hepatitis, non-alcoholic fatty-liver disease
   h. Renal: chronic renal insufficiency, chronic nephrolithiasis
   i. Infectious: HIV infection, hepatitis C, tuberculosis
   j. Pulmonary: chronic obstructive pulmonary disease

* General population is defined as community-dwelling individuals who do not have special nutritional need such as those who are institutionalized, hospitalized, pregnant or clinically deficient in nutrients."

† This review focused on primary prevention using the following definition as a guide. Primary prevention denotes an action taken to prevent the development of a disease in a person who is well and does not have the disease in question.[185] Using this definition, we included studies of supplements that were used in patients with risk factors for disease (e.g., type 2 diabetes mellitus or hypertension) to prevent one or more of the listed chronic diseases or conditions (e.g., cardiovascular disease). We also included studies of supplements that were used in patients with selected precursors of disease (e.g., polyps) to prevent a malignant disorder (e.g., colon cancer). We did not include studies of supplements that were used in patients with carcinoma-in-situ or similar malignant conditions.

2. What is known about the safety of use of multivitamin/mineral supplements (as defined in question 1) in the general population of adults and children, based primarily on data from randomized controlled trials and observational studies?

3. What is the efficacy determined in randomized controlled trials of supplementation with the single nutrients or functionally related nutrient pairs listed below, each at a dose less than the UL determined by the Food and Nutrition Board, in the general adult population for prevention against the development of one or more of the chronic diseases or conditions listed above for question 1?

a. calcium	b. folic acid	c. vitamin B6	d. vitamin B12
e. vitamin D	f. vitamin E	g. vitamin C	h. vitamin A
i. iron	j. zinc	k. magnesium	l. vitamin B1
m. vitamin B2	n. niacin	o. calcium/vitamin D	
p. calcium/magnesium		q. folic acid/vitamin B12	
r. folic acid/vitamin B6			

4. What is known about the safety of use of the following single nutrients in the general population of adults and children, based primarily on data from randomized controlled trials and observational studies?

a. calcium (with or without vitamin D)		b. folic acid
c. vitamin D	d. vitamin E	e. vitamin A
f. iron	g. selenium	h. β-carotene

Use of Multivitamin/mineral Supplements in the United States

Multivitamins are the most commonly used dietary supplements in the United States.[1] Multivitamin/mineral pills typically include at least 10 vitamins, and 10 minerals. They generally contain 100 percent of the Recommended Daily Allowance (RDA) for those micronutrients for which there are recommendations, except for calcium and certain other minerals, which are too bulky to include more than a fraction of the RDA. Recently, variation in the formulation of multivitamin/mineral supplements has occurred. Many of these supplements contain two to six times the RDA. Often, formulations of B vitamins are 10 to 20 times the RDA. According to the National Health and Nutrition Examination Survey (NHANES) 1999-2000, 35 percent of adults reported use of multivitamin/mineral supplements in the month prior to the survey.[1] Commercials have widely promoted dietary supplements. In 2005, 20.3 billion dollars were spent on purchases of dietary supplements in the United States.[2] Many individuals use vitamins/minerals supplements for prophylactic or disease-mitigating purposes. Whether long-term use is efficacious and safe warrants rigorous scientific evaluation.

Chronic Disease

Chronic disease is estimated to account for 35 million deaths worldwide.[3] Cardiovascular disease and cancer comprise a major proportion of chronic diseases in both developed and developing countries.[4] Other than cardiovascular disease and cancer, obesity-related diseases such as type 2 diabetes, end-stage renal disease, osteoarthritis and non-alcoholic steatorrheic hepatitis are also becoming significant public health problems.[5,6] The prevalence and incidence of these diseases may rapidly increase in the near future in the United States because the prevalence of obesity has increased from 23 percent to 30 percent during the 1990s.[7] At the same time, the population is gradually aging, and age-related degenerative diseases/conditions claim enormous health and economic tolls. Age-related cataract is the leading cause of blindness, accounting for about 42 percent of all blindness globally.[8] Approximately one in five people over age 65 live with age-related macular degeneration, and adults with advanced macular degeneration have a markedly reduced quality of life and need for assistance with activities of daily living.[9] The incidence of dementia also increases exponentially with age.[10] Alzheimer disease accounts for more than half of dementia cases.[11]

Common Pathologic Mechanisms of Chronic Diseases

The etiology of most chronic diseases is multifaceted. However, many chronic diseases share common risk factors and underlying pathologic mechanisms. Cigarette smoking/tobacco use, sedentary lifestyle, unhealthy (high calorie, low fruit/vegetable intake) diet, and obesity are well established as major risk factors of several chronic diseases. Cigarette smoke is a rich source of oxidants (free radicals and reactive oxygen, nitrogen and chlorine species), whereas a diet low in fruits and vegetables contains a low amount of antioxidants. Substantial evidence from *in vitro* experiments, animal models and epidemiological observational studies suggests that oxidative stress, a result of an imbalance between oxidative and reductive potential in favor of the former, may play an important role in the initiation, promotion, and progression of cardiovascular disease (in particular, ischemic heart disease and stroke), cancer, and several degenerative diseases/conditions, such as age-related cataract, age-related macular degeneration and cognitive decline.[12-19] Oxidative damage to lipids by free radicals initiates and propagates chain reactions that may be intercepted by antioxidants or otherwise lead to development of atherosclerosis and mutagenesis.[12,20] Oxidative damage to DNA causes formation of DNA adducts, double strand breaks, single strand breaks, aberrations and instability of chromosomes, and genomic instability, all of which may result in mutagenesis and carcinogenesis.[21] Oxidative damage to proteins may affect enzyme expression and impair critical cellular signaling, leading to alterations in cell function.[22]

It is well known that sedentary lifestyle, excessive caloric intake, and lack of physical activities lead to obesity, and obese individuals have higher levels of inflammation, a key process of host responses to infections and an important risk factor of cardiovascular disease and many cancers and chronic conditions.[23,24] Inflammatory responses can induce the generation of free radicals and reactive species that cause oxidative stress and further exacerbate disease processes.[25]

In addition to oxidative damage and inflammation, one-carbon metabolism has been implicated to be important in several chronic diseases, particularly cardiovascular disease, renal failure, neurological dysfunction, and cancer. An important step in one-carbon metabolism is the

synthesis/metabolism of methionine. Methionine is a precursor of S-adenosylmethionine (SAM), a universal methyl donor to DNA, RNA, protein, phospholipids, neurotransmitters and hormones. Hypermethylation in the promoter regions of tumor suppressor genes and chromosome aberrations due to global hypomethylation may lead to oncogenesis.[26,27] In methionine synthesis, an intermediate molecule is homocysteine, which has been found to be associated with increased risk of coronary artery disease, stroke, peripheral vascular disease, cognitive impairment, dementia, depression, osteoporotic fractures, and functional decline.[28]

Other pathways by which chronic disease develops may or may not be modifiable by vitamins/minerals. Examples of these factors include but are not limited to genetic susceptibility, growth factors, and capacity of detoxification.

Possible Mechanisms of Action of Vitamins and Minerals in Chronic Disease Prevention

Multivitamin/mineral supplements often contain vitamin A, β-carotene, vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B6 (pyridoxine), vitamin B12 (cyanocobalamin), vitamin C, vitamin D, vitamin E, folic acid, niacin, calcium, iron, zinc, magnesium, and selenium. These nutrients have numerous biological effects and have garnered considerable research interest in their potential as chemo-preventive agents for the prevention of chronic disease.

As described previously, a common process of chronic disease is oxidative damage by free radicals or reactive species. Multiple systems work in concert to protect the human body from oxidative damage. Endogenous enzymatic antioxidants, such as copper- and zinc-, or manganese-containing superoxide dismutase, selenium-dependent glutathione peroxidase, and catalase, can catalyze radical- and peroxide-quenching reactions. Nonenzymatic antioxidants include but are not limited to vitamin C, vitamin E, bilirubin, urate, flavanoids, and certain carotenoids (e.g., β-carotene and lycopene). In addition, metal-binding proteins can quench iron and copper ions which, if free, can catalyze oxidative reactions.[29]

Folate, vitamin B6, and vitamin B12 influence methylation by supplying methyl groups and are essential for nucleotide synthesis, DNA synthesis, and DNA repair.[30] Folate and B vitamins maintain normal brain function through the methylation of neurotransmitters, phospholipids and myelin.[31] They are also essential in homocysteine metabolism because irreversible transsulfuration and the re-methylation of homocysteine rely on coenzymes derived from vitamin B6, vitamin B12, and folate. A previous meta-analysis indicated that daily supplementation with folic acid of 0.5-5 mg and vitamin B12 of approximately 0.5 mg would reduce blood homocysteine concentrations by up to one-third, whereas vitamin B6 did not have a significant additional effect.[32] However, whether a reduction in homocysteine leads to decreased risk for clinical outcomes awaits evidence from randomized controlled trials.

In addition to anti-oxidation and regulation of methylation, vitamins and minerals may have inhibitory effects on inflammation (γ-tocopherol, zinc, and vitamin A) and angiogenesis (α-tocopherol, vitamin A, vitamin C, vitamin D). Some may also regulate cell differentiation, proliferation, and apoptosis (vitamin A, α-tocopherol, vitamin D, calcium) and enhance immunity (vitamin A, zinc, vitamin E, vitamin C, calcium).[33-40] Vitamin C may be useful in the prevention or management of osteoarthritis through collagen synthesis,[41] and vitamin D may prevent the progression of osteoarthritis by impairing bone's response to the pathophysiological

process of the disease.[42] Magnesium and calcium are important in regulating blood pressure.[43,44] Calcium may also have beneficial effects on cholesterol levels and body weight, and may shield the contact of carcinogen with bowel mucosa by forming insoluble chemical complexes with bile acid and fat.[45,46] Several meta-analyses have addressed the effects of calcium and/or vitamin D supplementation on bone density, osteoporosis, fractures, and falls.[47-52] The evidence has led the Food and Drug Administration (FDA) to authorize health claims in the labeling of calcium supplements for the benefits in osteoporosis prevention. The 2004 United States Surgeon General's Report on Bone Health and Osteoporosis has clearly stated the importance of calcium and vitamin D in maintaining healthy bones and preventing osteoporosis.[53] However, intake of vitamin D and calcium from food source has been generally inadequate in American adults; only 4 percent of individuals of age greater than 51 years meet the Adequate Intake level of vitamin D,[54] and the average calcium intake in American adults was estimated to be 761mg per day, below the Recommended Dietary Allowance for adults (1,000-1,200 mg).[55]

Factors that Affect the Efficacy and Safety of Vitamin/mineral Supplement Use in Chronic Disease Prevention

Perturbation of metabolism and other physiologic function often occurs in persons with established chronic disease. Accordingly, evaluation of the efficacy and safety of multivitamin/mineral supplement use should be made separately for primary versus secondary prevention. In addition to individuals' health status, several factors may affect the efficacy and the safety of vitamin and/or mineral supplement use in chronic disease prevention, such as individuals' nutritional status, bioavailability of nutrients, nutrient-nutrient interaction, chemical forms and doses of supplements, timing and duration of supplement use, among others.

Age, sex, race, genetic susceptibility, geographic location, smoking, diet, physical activity, obesity, and sunlight exposure are important factors because they affect individuals' baseline nutritional levels and may modify the efficacy and safety of supplement use. Geographical location is also relevant because dietary intake of selenium depends on the selenium content of the soil where plants are grown or animals are raised. In addition, ecological studies have linked areas with increased selenium levels to lower rates of lung, colorectal, bladder, esophageal, pancreas, breast, ovarian, and cervical cancers.[56]

After a nutrient is ingested, its biological effects are heavily determined by the bioavailability, i.e., the absorbable fraction that affects the biological effects of the nutrient by modulating the amount of the nutrient entering the body. Key factors determining the bioavailability of a micronutrient are the chemical form in which the nutrient is presented to the intestinal absorptive surface, the presence of other competing chemicals the concentration of food constituents (such as phytates and other chelating agents) that bind to the nutrient and make it unavailable for absorption, intestinal transit time, and enzyme activity. For example, synthetic vitamin E has approximately 50 percent the bioavailability of natural vitamin E, and use of α-tocopherol can reduce the bioavailability of other forms of vitamin E,[57] after competing for the uptake into very low-density lipoproteins (VLDL) by α-tocopherol transfer protein in the liver. Hence, factors influencing the bioavailability of a nutrient are important to consider when assessing the effects of multiple micronutrient preparations.

One nutrient may affect the absorption, transport, tissue uptake, function and metabolism of other nutrients. Accordingly, the concurrent ingestion of several nutrients may result in synergistic, antagonistic, or threshold effects as compared to a single nutrient. Hence, the

efficacy of a single nutrient vs. multiple nutrients should be considered separately unless no interactive or threshold effects can be found. Examples of nutrient-nutrient interactions include vitamin B12 and selenium modification of host's responses to inadequate dietary intake of folic acid. An excessive intake of folic acid may obscure vitamin B12 deficiency.[58] Zinc regulates the absorption, transport and utilization of vitamin A.[59] Calcium and vitamin D are inter-related metabolically in bone and intestine.

The chemical form of a nutrient may also determine its effects. For example, rather than an antioxidant effect, α-tocopheryl succinate has anti-proliferative effects in in vitro settings. Doses of supplements and duration of use are directly relevant to the efficacy, particularly for lipid soluble vitamins that can be accumulated in the tissue for a long-term.

The Tolerable Upper Intake Levels of Daily Nutrient Intake

The United States Food and Nutrition Board established tolerable ULs for several nutrients. By definition, a UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.[60] A UL is determined by the following steps: (1) hazard identification based on in vitro experiments, animal studies, and/or human studies, (2) dose-response assessment to identify the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse- effect level (LOAEL), which is then weighed with an uncertainty factor (UF) to derive the UL. In the case where toxicity data are unavailable from children, an extrapolation from the ULs determined for adults is made based on body weight difference. The strength of the evidence for determining a UF varies and therefore the choice of a UF has leeway of subjectivity. The UL of vitamin E for adults is determined primarily based upon its hemorrhagic effects in rats.[60] The UL of iron, zinc, and selenium was determined based on gastrointestinal symptoms, reduced copper status, and hair and nail brittleness and loss, respectively.[60] Since the time when ULs were determined, several large-scale randomized controlled trials of vitamin/mineral supplementation have been completed. An update on the data regarding adverse effects will help to evaluate the appropriateness of ULs.

Federal Regulation of Vitamin/mineral Supplements

The United States FDA regulates dietary supplements under the Dietary Supplement Health and Education Act (DSHEA) of 1994 which states that supplements containing ingredients marketed prior to the enactment of DSHEA are not subject to pre-market burden on proof of safety. Many vitamins and minerals, such as vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, calcium, and magnesium, with established nutritional function, fall into this category and have been grandfathered as Generally Recognized As Safe (GRAS).[61,62] However, the determination of GRAS was primarily based on experts' opinions or a history of safe use before January 01, 1958 when the Food Additives Amendment to Food, Drug, and Cosmetic Act was enacted. A lack of high-quality data before 1958 is conceivable when an adverse event reporting system was not in place.

Conceptual Framework

Figure 1 demonstrates the conceptual framework used to guide this systematic review, focusing on primary prevention of chronic disease. Chronic disease endpoints are the outcomes of interest. A biomarker endpoint is considered if the biomarker is a marker of disease progression or the biomarker is reported as an adverse effect of supplement use. Bone mineral density, cognitive function, and fasting glucose were considered as biomarker endpoints for efficacy in this review. The framework acknowledges that vitamin and mineral supplements have many biologic effects that could help to prevent chronic disease outcomes. The framework also acknowledges potential adverse effects of vitamin and mineral supplements.

Chapter 2: Methods

The NIH Office of Medical Applications of Research (OMAR) requested an evidence report to review and synthesize the evidence on multivitamin/mineral supplements and prevention of chronic disease. Our Evidence-based Practice Center established a team and a work plan to develop the evidence report. The project consisted of recruiting technical experts, formulating and refining the specific questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence and submitting the report for peer review.

Recruitment of Technical Experts and Peer Reviewers

At the beginning of the project, we recruited a panel of internal and external technical experts to give input on key steps including the selection and refinement of the questions to be examined. The panel included two internal technical experts from the Johns Hopkins University who have strong expertise in various aspects of the efficacy and/or safety of multivitamins/minerals and evidence-based medicine, and external experts who have strong expertise in nutritional research (see Appendix A[a]). In addition to this panel of technical experts, we recruited a few additional experts to serve as peer reviewers of the evidence report, as described further in the section on Peer Review.

Key Questions

We worked with the technical experts and representatives of OMAR and the Agency for Healthcare Research and Quality (AHRQ) to develop the Key Questions that are presented in the Specific Aims section of Chapter 1 (Introduction). We expanded the preliminary questions to include functionally related nutrient pairs, tuberculosis, hepatitis C, and pulmonary disease, and limited the questions involving efficacy to randomized controlled trials. The Key Questions focus on the efficacy of multivitamins/minerals (and specific single nutrients and functionally related pairs) in the prevention of chronic diseases and conditions as well as the safety of multivitamin/minerals and specific nutrients.

Literature Search Methods

Searching the literature included the steps of identifying reference sources, formulating a search strategy for each source, and executing and documenting each search. Additionally, we searched for medical subject heading (MeSH) terms that were relevant to the specific nutrients and diseases specified in Key Question 1 to help develop the search strategy. We used a systematic approach for searching the literature to minimize the risk of bias in selecting articles for inclusion in the review. In this systematic approach, we had to be very specific about defining the eligibility criteria for inclusion in the review. The systematic approach was intended to help

[a] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/multivittp.htm

identify gaps in the published literature. We used a systematic approach for extracting data from the studies to minimize the risk of bias in how we extracted data from eligible studies. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Sources

Our comprehensive search plan included electronic and hand searching. Beginning in August of 2005 we ran searches of the following databases: MEDLINE®, EMBASE,® and the Cochrane database including Cochrane Reviews and The Cochrane Central Register of Controlled Trials (CENTRAL). These searches were updated to include all articles published up until November 1, 2005. The FDA Adverse Event Reporting System (AERS) was researched. AERS covers drug adverse events and does not include reports on supplements. A similar reporting system exists for reporting adverse events associated with supplements; the Center for Food Safety and Applied Nutrition (CFSAN). CFSAN does not have a searchable database.

Hand searching for possibly relevant citations took several forms. Our experts identified 15 journals that were thought to be most likely to contain relevant studies (see Appendix B[a]). We scanned the table of contents of each issue of these journals for relevant citations from January 2005 through February 2006. For the second form of hand searching, reviewers received eligible articles and flagged references of interest for the team to compare to the existing database. We used SRS® 3.0 (TrialStat! Corporation, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management, to track the article flagging.

Search terms and strategies

Search strategies, specific to each database, were designed to enable the team to focus available resources on articles most likely to be relevant to the Key Questions, given that an enormous body of literature exists on vitamins and minerals. Initially, we developed a core strategy for MEDLINE, accessed via PubMed, based on an analysis of the MeSH terms and text words of key articles identified a priori. The PubMed strategy formed the basis for the strategies developed for the other electronic databases (see Appendix C[a]).

Organization and tracking of literature search

The results of the searches were downloaded and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). From ProCite, the articles were uploaded to SRS 3.0. We used the duplication check feature in SRS 3.0. This feature allowed us to scan for exact article duplicates, author/title duplicates, and title duplicates. Additionally, this database was used to store citations in portable document format (PDF) and to track the search results at title review, abstract review, article inclusion/exclusion, and data abstraction levels (Figure 2). A list of excluded articles is presented in Appendix D[a].

[a] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/multivittp.htm

Title Review

After the electronic databases were searched, citations were downloaded into ProCite, and uploaded to the SRS 3.0 tracking system. The study team scanned all titles. Two independent reviewers conducted title scans in a parallel fashion. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible. If the two reviewers did not agree on the eligibility of an article, it was automatically promoted to the next level (see Appendix E[a], Title Review Form). The title review phase was designed to capture as many studies as possible reporting on the efficacy of single nutrients, related nutrient pairs, and multivitamins/minerals in the primary prevention of chronic diseases and conditions as well as the safety of multivitamins/minerals and a specified set of nutrients. All titles that were thought to address the above efficacy and or safety issues were promoted to the abstract review phase.

Abstract Review

Inclusion and exclusion criteria

The abstract review phase was designed to identify studies reporting on the efficacy of single nutrients, related nutrient pairs, and multivitamins/minerals in the primary prevention of chronic diseases and conditions as well as the safety of multivitamins/minerals and a specified set of nutrients. Investigators determined whether studies involving efficacy were randomized controlled trials and applied to primary prevention as previously defined in the Specific Aims section of Chapter 1. Investigators were instructed that articles relating to safety did not need to be randomized controlled trials. This review was primarily interested in safety studies on multivitamin/mineral supplements as well as a defined set of single nutrients for which reasonable concerns exist regarding potential adverse effects in the doses used. All articles with abstracts meeting these criteria were kept for further review. Abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one of the following exclusion criteria: (1) not written in English; (2) contained no human data; (3) included only pregnant women; (4) only infants; (5) only subjects of age less than or equal to 18 years (if a study included only subjects of age less than or equal to 18 years, we included it only if it presented data on the safety of a vitamin/mineral supplement) (6) included only patients with particular chronic diseases; (7) included only patients receiving treatment for chronic disease or included only patients in long-term care facilities; (8) only studied clinical nutritional deficiency; (9) contained no useful information applying to the Key Questions; (10) did not address the use of supplements; (11) did not address the use of supplements separately from dietary intake; (12) did not cover the defined disease endpoints or; (13) was an editorial, commentary, or letter. Additionally, an article could be excluded if it applied to Key Question 1 and/or 3 but was not a randomized controlled trial or a systematic review and did not address safety issues. (see Appendix E, Abstract Review Form). Differences in opinions regarding abstract inclusion or exclusion were resolved through consensus adjudication. At this level of inclusion/exclusion, the reviewers were also asked to identify which

[a] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/multivittp.htm

nutrient(s) each article addressed as well as the Key Questions the article might apply to if the article was eligible.

Article Inclusion/Exclusion

Because of the broad array of potentially eligible articles obtained at the abstract review phase, full articles initially selected for review underwent another independent parallel review by investigators to determine if they should be included for full data abstraction. At this phase of review, investigators determined which of the Key Questions each article addressed, and what type of protocol was used in the study (see Appendix E, Article Inclusion/Exclusion Form). If articles were still deemed to have applicable information, they were included in the final article review. Differences in opinions regarding article inclusion or exclusion were resolved through consensus adjudication.

Article Review/Data Abstraction

The purpose of the article review was to confirm the relevance of each article to the research questions, to determine methodological characteristics pertaining to study quality, and to collect evidence that addressed the research questions. Articles eligible for full review could address one or more of the Key Questions. If reviewers determined that an article addressed both efficacy and safety, multiple data abstraction forms were used. We used a systematic approach for extracting data from the studies to minimize the risk of bias in how we extracted data from eligible studies. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Each article underwent double review by study investigators for full data abstraction and assessment of study quality. For all data abstracted from studies, we used a sequential review process. In this process, the primary reviewers completed all data abstraction forms. The second reviewer confirmed the first reviewer's data abstraction forms for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer re-reviewed a random sample of articles marked as "ineligible" by the first two reviewers to ensure consistency in the classification of the articles. Reviewers were not masked to the articles' authors, institution, or journal. In most instances, data were directly abstracted from the article. If possible, relevant data were also abstracted from figures. Differences in opinion were resolved through consensus adjudication. For assessments of study quality, each reviewer independently judged study quality and rated items on quality assessment forms. (see Appendix E, Data Abstraction Review Forms)

For all articles containing original data, reviewers extracted information on general study characteristics such as study design, study period and follow up, study participants, sample size, and prior supplement use (see Appendix E, Data Abstraction Review Forms). Data abstracted to the "Arm" forms (see Appendix E, Data Abstraction Review Forms) included: placebo or intervention; nutrients studied; chemical form; dose; units; frequency of use; timing of use; and duration of use.

For studies addressing efficacy (Key Question 1 and/or 3), an outcomes form for efficacy (see Appendix E, Data Abstraction Review Forms) was filled out to obtain the information on study outcomes and adverse effects, and the results from subgroup analyses. Additionally, a

specific study quality form was filled out (quality forms were filled out independently) to assess: representativeness of the study population; bias and confounding; description of study supplements/supplementation; adherence and completeness of follow up; statistical analysis; and conflict of interest (see Appendix E, Data Abstraction Review Forms).

Reviewers used an outcomes form to abstract data from articles addressing safety (Key Questions 2 and/or 4) on adverse effects/events and criteria for causality (see Appendix E, Data Abstraction Review Forms).

We also abstracted data from systematic reviews that specifically applied to our Key Questions. This included systematic reviews of calcium and/or vitamin D only, and reviews of studies other than calcium and/or vitamin D only (see Appendix E, Data Abstraction Review Forms).

All information from the article review process was entered into the TrialStat database by the individual completing the review. Reviewers entered comments into the system whenever applicable. The TrialStat database was used to maintain and clean the data, as well as to create detailed evidence tables and summary tables (see Appendix F and Summary Tables).

Data abstracted to assess the efficacy of multivitamin/mineral supplements and single nutrients (and related pairs of nutrients) in the primary prevention of chronic diseases/conditions (Key Questions 1 and 3)

Articles were reviewed to obtain information on (1) study characteristics, (2) study participants, (3) study supplements, and (4) study results. Specific abstracted data on study characteristics were: study name and abbreviation (if available), types of study design, study period, chronological follow up period, median/mean follow up duration, eligibility criteria for trial enrollment, sample size, study site, and recruitment setting. The inclusion of the item on recruitment setting was intended to capture the source population from which the study population was established. Specific abstracted data on participants' characteristics were: age, sex, race, smoking, alcohol, and body mass index (BMI). These factors were considered by the team members to be important confounding variables. Other characteristics reported in the article were also abstracted. Specific abstracted data on study supplements were: control (placebo, no dietary supplements or no standard care, standard care, nutritional/dietary education) and intervention arms (list of nutrients). The chemical form, total dose per ingestion, dose unit, and frequency, timing and duration of use of study supplements were abstracted. For clinical endpoints, data abstracted were: outcome measures, number of events, person years, incidence rates, and estimates of efficacy (relative risk, odds ratio, hazard ratio) along with the corresponding 95% confidence intervals. For biomarker endpoints such as bone mineral density, central and dispersion statistics of the biomarker measurements were abstracted.

Data abstracted to assess the safety of multivitamins/minerals and single nutrients (selenium, iron, β-carotene, vitamin A, vitamin E, folic acid, and calcium (with or without vitamin D)) (Key Questions 2 and 4)

Articles with safety data were reviewed to obtain information on (1) study characteristics, (2) study participants, (3) randomized groups, and (4) study results. Specific abstracted data on study

characteristics, study participants and study supplements were the same as those for Key Questions 1 and 3. Specific abstracted data on study results were: the types of adverse effects/events, whether the adverse effects/events occurred, numbers of adverse events, and estimates of associations along with the corresponding 95% confidence intervals. For biomarker endpoints, central and dispersion statistics of the biomarker measurements were abstracted. Plausibility of causality was considered using the following criteria: temporal relationship, lack of alternative causes, dose-response, relationship, evidence of increased circulating levels of the nutrient under investigation, and response to re-challenge.

Data abstracted from previous systematic reviews on vitamin D and calcium

Several systematic reviews have been published to address the efficacy of vitamin D and/or calcium in the prevention of bone loss, osteoporosis and fractures. The most recent review article was published in 2005. In addition, the University of Ottawa Evidence-based Practice Center will soon release a systematic review that focuses on vitamin D, including the effect of supplemental doses of vitamin D on bone density and fracture and fall risk. Since the studies on vitamin D and/or calcium have been reviewed so recently, we reviewed the available systematic reviews on this subject. Data from systematic review articles were abstracted regarding: (1) the aim of the review, (2) exclusion criteria, (3) search strategies (databases, search terms), (4) range of publication dates of reviewed articles, (5) number of trials in the review, (6) total numbers of trial participants in vitamin D and/or calcium group and in the placebo groups, (7) range of follow up periods, (8) range of proportions of participants lost to follow up, (9) trial participants' characteristics (age, women, race/ethnicity groups), (10) inclusion of primary prevention trials alone or a mixture of primary and secondary prevention trials, (11) chemical forms of vitamin D and calcium, and (12) aggregate results of bone mineral density/content.

Data abstracted from previous systematic reviews on nutrients other than vitamin D and calcium

We also abstracted the following data from published systematic reviews on nutrients other than vitamin D and calcium: (1) the aim of the review, (2) exclusion criteria, (3) search strategies (databases, search terms), (4) range of publication dates of reviewed articles, (5) number of trials in the review, (6) total numbers of trial participants in vitamin/mineral group and in the placebo groups, (7) range of follow up periods, (8) range of proportions of participants lost to follow up, (9) trial participants' characteristics (age, women, race/ethnicity groups), (10) inclusion of primary prevention trials alone or a mixture of primary and secondary prevention trials, (11) chemical forms of nutrients included in the review, and (12) aggregate estimates of efficacy along with the corresponding 95% confidence intervals and p-values. Efforts were made to abstract data from primary prevention trials included in systematic reviews that reviewed evidence from both primary and secondary prevention trials.

Quality Assessment

Article quality was assessed differently for different types of studies: efficacy studies (randomized controlled trials only); safety studies; and systematic reviews. The dual, independent review of article quality judged articles on several aspects of each study type's external and internal validity. Quality assessment of studies addressing efficacy included: (1) the representativeness of the study population (description of the study population and where it was drawn, and how well the participants' characteristics were described); (2) bias and confounding (whether this was controlled for in the study design and reported on in the study); (3) description of supplements/supplementation; (4) description of adherence to study protocols and follow up (flow of patients through the study over time, loss to follow up, and participant withdrawal); (5) statistical analysis; and (6) conflict of interest.

Quality assessment of studies addressing safety considered: (1) temporal relationships between timing of supplement use and adverse events (how this was reported); (2) dose-response relationship; (3) whether adverse effects disappeared after supplement use ceased; (4) serum levels of supplements; (5) whether an alternative cause for the adverse event was investigated: and (6) whether the adverse event re-occurred if the supplement was used again.

The quality of each systematic review was assessed using a different set of criteria: (1) whether the question being addressed by the review was clearly stated; (2) comprehensiveness of search methods used and described in the report; (3) whether inclusion/exclusion criteria were clearly defined and appropriate; (4) whether analyses were conducted to measure variability in efficacy; (5) whether study quality was assessed and done appropriately (using validated instruments); (6) whether differences in how outcomes were reported and analyzed across studies were taken into consideration; (7) whether the study methodology was reproducible; and (8) whether conclusions were supported by the data presented.

For each study, we assigned a rating of high, medium or low quality for each domain of study quality based on whether the score for that domain was designated High (80-100%), Medium (50-79%), or Low (0-49%) quality.

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies. The investigators reviewed the tables and eliminated items that were rarely reported. Investigators used the resulting versions of the evidence tables to prepare the text of the report and selected summary tables.

Data Entry and Quality Control

Initial data were abstracted by investigators and entered directly into Web-based data collection forms using; SRS® 3.0 (TrialStat! Corporation, Ottawa, Ontario, Canada). After a second reviewer reviewed data, adjudicated data were re-entered into Web-based data collection forms by the second reviewer. Second reviewers were generally more experienced members of the research team, and one of their main priorities was to check the quality and consistency of the first reviewers' answers. In addition to the second reviewers checking the consistency and accuracy of the first reviewers, a senior investigator examined all reviews to identify problems

with the data abstraction. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Grading of the Evidence

At the completion of our review, we graded the quantity, quality and consistency of the best available evidence addressing Key Questions 1 and 3 by adapting an evidence grading scheme recommended by the GRADE Working Group.[63] We applied evidence grades to bodies of evidence on each type of nutrient for each major type of outcome. We considered the strength of the study designs with randomized controlled trials considered best, followed by non-randomized controlled trials, observational studies, and case reports. We considered at least two randomized controlled trials reporting on a specific outcome to constitute a body of evidence pertaining to that outcome. If an outcome was evaluated by at least two randomized controlled trials as well as observational studies and case reports, our evidence grade was based only on the randomized controlled trials evaluating that outcome. If an outcome was evaluated by one or no randomized controlled trials, our evidence grade was based on the single randomized controlled trial in addition to the best available non-randomized controlled trial or the best available observational studies (cohort studies considered best, followed by cross-sectional studies and studies with pre-post observational design). We reported the number of studies within the category of best available evidence to assess the quantity of evidence. We also assessed the quality and consistency of the best available evidence, including assessment of limitations to individual study quality (using individual quality scores), certainty regarding the directness of the observed effects in studies, precision and strength of findings, and availability (or lack thereof) of data to answer the Key Question. We classified evidence bodies pertaining to each Key Question into four basic categories: (1) "high" grade (indicating confidence that further research is very unlikely to change our confidence in the estimated effect in the abstracted literature); (2) "moderate" grade (indicating that further research is likely to have an important impact on our confidence in the estimates of effects and may change the estimates in the abstracted literature); (3) "low" grade (indicating further research is very likely to have an important impact on confidence in the estimates of effects and is likely to change the estimates in the abstracted literature); and 4) "very low" grade (indicating any estimate of effect is very uncertain).

Peer Review

Throughout the project, feedback was sought from the technical experts through ad hoc and formal requests for guidance. A draft of the completed report was sent to the technical experts and peer reviewers, as well as to the representatives of the NIH and AHRQ. In response to the comments of the technical experts and peer reviewers, revisions were made to the evidence report, and a summary of the comments and their disposition has been submitted to AHRQ.

Chapter 3. Results

Overall Results of the Literature Search

The literature search process identified 11,324 citations potentially relevant to the Key Questions (see Figure 2). We excluded 849 duplicate citations. In the title review process, we excluded 6,863 citations because they clearly did not pertain to the Key Questions. In the abstract review process, we excluded 3,163 citations that did not meet one or more of the eligibility criteria (see the list in the Methods chapter). Using the article inclusion/exclusion form, we then excluded an additional 386 articles that did not meet one or more of the eligibility criteria. That left a total of 63 articles eligible for inclusion in the review of one or more of the Key Questions.

Key Question 1

What is the Efficacy Determined in Randomized Controlled Trials of Multivitamin/mineral Supplement Use (Defined as 3 or More Vitamins and/or Minerals Without Herbs, Hormones, or Drugs), Each at a Dose Less Than the UL Determined by the Food and Nutrition Board, in the General Adult Population for Prevention Against the Development of one or More Chronic Diseases or Conditions?

Introduction

Multivitamin/mineral supplements have been used by many as a simple means to ensure adequate intake of several essential micronutrients in the hope for prophylactic benefits. Typical multivitamin/mineral supplements on the market contain about 10 vitamins and 10 minerals, such as vitamin A, vitamin C, B vitamins, vitamin E, folic acid, vitamin D, calcium, magnesium, zinc, iron among others. The following section summarizes the evidence from randomized controlled trials on the efficacy of multivitamin/mineral supplement use in the prevention of chronic disease.

Results of literature search for Key Question 1

Our literature search identified 11 articles from randomized controlled trials that addressed the efficacy of multivitamin/mineral supplements in the primary prevention of cancer, cardiovascular disease, cataract and age-related macular degeneration. Data for other diseases were lacking (Table 1). These studies used designed vitamin/mineral combinations, but not the one-a-day type of multivitamin supplements available on the United States market.

The 11 articles documented results from 5 randomized controlled trials published from 1993 to 2005, including (1) the Linxian General Population Trial in China,[64 65 66 67 68], (2) the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study in France,[69 70] (3) the Multi-center Ophthalmic and Nutritional Eye-Related Macular Degeneration Study (MONMD) in United States veterans,[71] (4) the Roche European American Cataract Trial

(REACT) in the United States and United Kingdom,[72] and (5) the Age-Related Eye Disease Study (AREDS) in the United States.[73]

Design of randomized controlled trials

The Linxian General Population Trial (referred to as "Linxian Trial" henceforth) was a fractional factorial trial designed to determine the efficacy of 8 vitamin/mineral combinations in cancer prevention in 29,584 adults of ages 40 to 69 years from 4 Linxian communes[64] where the rates of esophageal cancer were high. Users of any vitamins were ineligible for trial participation. Vitamin/mineral supplements were combinations of the following: (A) retinol 5000 IU and zinc 22 mg, (B) riboflavin 3 mg and niacin 40 mg, (C) vitamin C 120 mg and molybdenum 30 µg, and (D) β-carotene 15 mg, α-tocopherol 30 mg, and selenium 50 µg. The combinations were AB, AC, AD, BC, BD, CD, ABCD, and placebo. The dose of each nutrient ranged from 1 to 2 times the United States RDAs. The follow up period was 1986 to 1991. At the end of the trial, 3,249 participants had eye exams,[65] and 391 participants had esophageal/gastric endoscopy examinations[68] (Appendix F[a], Evidence Tables 1a-1c).

The SU.VI.MAX study was designed to determine the efficacy of a daily supplement of antioxidants (vitamin C 120 mg, vitamin E 30 mg, β-carotene 6 mg, selenium 100 µg, and zinc 20 mg) for the primary prevention of cancer and ischemic cardiovascular disease in 13,017 French adults (7,876 women of age 35 to 60 years, and 5,141 men of age 45 to 60 years).[69] Regular users of any of the vitamins/minerals provided in the study were ineligible for trial participation. The follow up period was 1994 to 2002. Women had higher baseline serum β-carotene levels than men. Women also had slightly higher baseline serum levels of vitamin C but lower levels of zinc and selenium. Information on self-selected supplement use was not provided (Appendix F, Evidence Tables 1a-1c).

The MONMD study was aplacebo-controlled trial conducted in 1992 to evaluate nutritional status in 71 United States veterans with dry age-related macular degeneration (AMD) and to assess the efficacy of multivitamin/mineral supplement use for 18 months on the progression of AMD and potential side effects. The daily multivitamin/mineral supplements included β-carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin 50 mg, biberry extract 5 mg, rutin 50 mg, zinc picolinate 12.5 mg, selenium 50 mcg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, and chromium 100 mcg. The study excluded people who had used vitamins in the year prior to enrollment.[74] The instruments used to measure cataract transparence were changed during the study period, but the examiners were not well instructed on how to use the new instruments[71] (Appendix F, Evidence Tables 1a-1c).

REACT assessed the efficacy of a mixture of antioxidant supplements in preventing cataract progression among 297 individuals in Boston, United States and Oxford and Bradford, United Kingdom.[72] Regular users of any vitamin supplement were also excluded. Participants took a placebo or combined β-carotene (6 mg, in the form of beadlets), vitamin C (250 mg), and all-rac α-tocopherol acetate (200 mg) 3 times per day with meals. The follow up period was 1990 to 1995. (Appendix F, Evidence Tables 1a-1c).

The AREDS study was an 11-center trial that assessed the efficacy of zinc (80 mg zinc oxide and 2 mg cupric oxide) and antioxidants (vitamin C 500 mg, vitamin E 400 IU, and β-carotene

[a] Appendices cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/multivittp.htm

15 mg) in the development and progression of age-related lens opacities and visual acuity loss in the United States.[73,75] Participants were classified into 4 AMD categories according to the size and the extent of drusen and retinal pigment abnormality in each eye, the presence of manifestations of advanced AMD, and visual acuity. Persons in AMD category 1 (n= 1,117) were assigned to antioxidant or placebo, whereas persons in AMD categories 2 to 4 (n=3,640) were assigned to placebo, antioxidants, zinc, or combined antioxidants and zinc. The follow up period was 1992 to 2001. The major limitations were the option of multivitamin use (by 66% of the participants) and self-selected use of non-study supplements (20% of participants) that contain at least one of the study nutrients (Appendix F, Evidence Tables 1a-1c).

Similarity and heterogeneity in study design among trials

The Linxian trial was conducted in a Chinese population that was nutritionally inadequate whereas SU.VI.MAX was conducted in an apparently healthy French population. The Linxian trial and the REACT study excluded any vitamin use without specifying how recent the use was. The MONMD study excluded persons with supplement use during the year prior to enrollment. In contrast, AREDS provided Centrum® to 66 percent of the study participants, in addition to study supplements, and SU.VI.MAX allowed use of supplements other than those under study. The Linxian trial and the SU.VI.MAX study used doses of 1-2 times RDAs. In contrast, MONMD used vitamins C and B2 at doses that were more than 10 times the RDAs; AREDS used high doses of vitamin E and zinc (10 times the RDA), and a moderate dose of vitamin C (6 times the RDA); REACT used a high dose of vitamin E. All trials employed a parallel-arm design except for the Linxian trial that used a fractional factorial design. A total of 47,289 individuals were included in this review section (Appendix F, Evidence Tables 1a-1c; Table 2).

Study quality

Inclusion/exclusion criteria were clearly defined in most trials. Quality of these trials was good in terms of randomization, double masking, ascertainment of trial endpoints, adherence, and use of intention-to treat approach in statistical analyses. However, there was a lack of descriptions as to whether concealment of allocation sequence was done, and whether observers independently evaluated trial outcomes. There was a paucity of data on prior supplement use, concomitant supplement use, and medication use that may have had effects on the efficacy of study supplements. None of the trials reported success of blinding and the extent of unintended crossover. Only the AREDS and REACT studies provided information on numbers and reasons for withdrawals and percents of loss-to-follow-up (Table 3).

Cancer

The Linxian trial examined incidence of and mortality for all cancer, esophageal cancer, stomach cancer (cardia and noncardia), esophageal/gastric cardia, and other cancers.[64] After 5.25 years of follow up, no significant risk reduction by supplement use was observed for these endpoints. The only exceptions were the reductions in gastric cancer incidence (relative risk (RR) 0.84, 95% confidence interval (CI) (0.71-1.00)), cancer mortality (RR 0.87, 95% CI 0.75-1.00), especially stomach cancer mortality (RR 0.79, 95% CI 0.64-0.99) in the groups receiving

β-carotene, vitamin E and selenium compared to the groups receiving other vitamin/mineral combinations,[64] and a lower non-cardia stomach cancer mortality in those receiving retinol and zinc (RR 0.59, 95% CI 0.37-0.93).[64] Reduction in cancer mortality was greater in women than in men and among those of age less than 55 years in this trial (RR 0.79, 95% CI 0.64-0.98) vs. RR 0.93, 95% CI 0.77-1.12), and (RR 0.71, 95% CI 0.55-0.92) vs. RR 0.94, 95% CI 0.80-1.11), respectively).[67] In the substudy where participants underwent endoscopy examination, there was no significant effect of β-carotene, vitamin E and selenium supplement use on worse overall diagnoses of esophageal and gastric cancer or combined cancer and dysplasia prevalence, although the odds ratios were in the protective direction [68] (Appendix F, Evidence Tables 1b-1e).

The SU.VI.MAX study reports no benefit on overall cancer incidence by the antioxidant supplement use in women (RR 1.04, 95% CI 0.85-1.29), but a 31 percent risk reduction (RR 0.69, 95% CI 0.53-0.91) in men.[69] As a result, there was a statistically significant interactive effect of sex and randomized group on total cancer incidence (p=.02). Women were younger than men in this trial, and generally had a healthier lifestyle as evident by higher serum β-carotene and vitamin C and fewer smokers. Among men, a moderate reduction in prostate cancer risk was observed in the antioxidant supplement group (RR 0.88, 95% CI 0.60-1.29). Further stratification analysis showed differential efficacy by baseline prostate specific antigen (PSA) level with a risk reduction among men with normal baseline PSA (≤3 μg/L) (hazard ratio (HR) 0.52, 95% CI 0.29-0.92), but not among men with elevated PSA (HR 1.54, 95% CI 0.87-2.72)[70] (Appendix F, Evidence Table 1d, Figures 3 and 4).

Cardiovascular disease

The Linxian trial reported a non-significant lower risk of stroke mortality with the greatest risk reduction (RR 0.91, 95% CI 0.76-1.07) observed in those receiving β-carotene, selenium, and α-tocopherol with or without other study nutrients,[66] particularly in those receiving the combination of β-carotene, selenium, α-tocopherol, retinol and zinc (RR 0.71, 95% CI 0.50-1.00) as compared to the counterpart. There was no sex difference in the risk reduction. Hemorrhagic and ischemic stroke was not distinguished but other sources showed that approximately two-thirds of the strokes were ischemic in this population[76] (Appendix F, Evidence Tables 1b-1e).

In the SU.VI.MAX study, no significant difference in ischemic cardiovascular disease incidence was noted between randomized groups. There was no interaction between sex and randomized groups. The cardiovascular events in women were only 22.6 percent of the events in men[69] (Appendix F, Evidence Table 1d, Figure 5).

Total mortality

In the Linxian trial, total mortality was lower among those who received β-carotene, selenium, and vitamin E, but not other nutrient combinations (RR 0.91, 95% CI 0.84-0.99).[66] In the AREDS study, total mortality was 6 percent higher in the group receiving antioxidants compared to the group receiving no antioxidants, but the increase was not statistically significant.[64,73,75] When limited to those participants with AMD categories 2, 3, and 4, total mortality was 19 percent and 13 percent lower in the groups receiving zinc alone or zinc combined with antioxidants respectively.[73] A sex difference in the relative risk for total mortality was documented in the SU.VI.MAX study (RR 0.63, 95% CI 0.42-0.93 in men and RR 1.03, 95% CI 0.64-1.63 in women)[69], but no sex or age differences were noted in the Linxian trial[67] In

the REACT, 9 deaths occurred in the antioxidant group, whereas 3 deaths occurred in the placebo group. Further examination on the causes of death revealed that the deaths in the antioxidant group were due to esophagitis, sudden death, aneurysm, pulmonary fibrosis, cancer and coronary thrombosis (Appendix F, Evidence Table 1e, Figure 6).

Cataract and age-related macular degeneration

In the Linxian trial, there was no effect of combined vitamin E, selenium and β-carotene on nuclear cataract, cortical cataracts, or posterior subcapsular cataracts[65] (Appendix F, Evidence Table 1d).

In the MONMD study, distance acuity declined in the placebo group, but was unchanged in the multivitamin group (p=.03). The multivitamin group also had better M print acuity and fewer scotoma in left eyes in the multivitamin group (p=.07), after 12 months. There was no significant difference between randomized groups in refraction, metamorphopsia and Lens Opacities Classification System (LOCS) II readings on nuclear color, nuclear opalescence, and posterior subcapsular opacities. There was an unanticipated cortical cataractogenic effect for right eyes in the multivitamin group.[71] (Appendix F, Evidence Tables 1d).

In the REACT, the primary outcome was the difference between baseline and the last visit in percentage pixel opaque (IPO) in the anteriorly-focused, retroillumination image. Secondary outcomes were posterior subcapsular cataract, nuclear cataract, cortical cataract, and nuclear color. At the end of the second year, there was a small positive effect on percent IPO in both the United States and United Kingdom groups. After the third year, the positive effects were greater in the United States group (percent pixel opaque = 0.389 vs. 2.517 in the vitamin vs. placebo group, p=.0001), but not the United Kingdom group. Unfavorable changes in all secondary outcomes were smaller in the vitamin group than the placebo group, but none was statistically significantly different[72] (Appendix F, Evidence Table 1d).

In the AREDS study on cataract, outcome measures were cataract surgery, changes in photographic grade of nuclear, cortical and posterior subcapsular opacities, and visual acuity loss (≥15 letters). After 6 years of follow up, no appreciable difference was found in any of the outcomes between antioxidant and placebo groups[73] (Appendix F, Evidence Table 1d).

In the AREDS study, outcomes were rates of progression to advanced AMD and visual acuity. After an average follow up period of 6.3 years, the odds ratio (OR) (99% CI) of developing advanced AMD was 0.75 (0.55-1.03), 0.80 (0.59-1.09), and 0.72 (0.52-0.98) among individuals with zinc, antioxidants, and combined zinc and antioxidant supplementation as compared to individuals in the placebo group. Excluding individuals in AMD category 2 (extensive small drusen, nonextensive intermediate size drusen or pigment abnormalities), the OR (99% CI) of developing advanced AMD was 0.71 (0.52-0.99), 0.76 (0.55-1.05), and 0.66 (0.47-0.91) among individuals with zinc, antioxidants, and combined zinc supplementation and antioxidant supplementation, and the OR(99% CI) of having moderate visual acuity loss was 0.73 (0.54-0.99) in the group with antioxidants plus zinc, but not statistically significant for other supplementation groups[75] (Appendix F, Evidence Table 1d).

Summary

There is a paucity of data on the efficacy of multivitamin/mineral supplement use in the prevention of chronic disease in the general United States population. Limited data from the Linxian trial suggest 13 percent to 21 percent reductions in gastric cancer incidence, gastric cancer mortality, and cancer mortality by use of β-carotene, vitamin E and selenium supplements of doses 1 to 2 times RDAs. Results of total cancer incidence in the SU.VI.MAX trial in France were sex-dependent with a 31percent lower risk in men who received vitamin C, vitamin E, β-carotene, selenium, and zinc at doses near RDAs, but no risk reduction in women who appeared to have had higher fruit/vegetable intake. The antioxidants used in SU.VI.MAX did not confer benefit in preventing ischemic cardiovascular disease, whereas use of β-carotene, selenium, α-tocopherol, retinol, and zinc supplements in the Linxian trial had a moderate reduction (30%) in stroke mortality. Generalizability of these findings for the United States population is uncertain in view of the French paradox and the general nutritional inadequacy of the Linxian population. Multivitamin/mineral supplement use for 3 to 6 years had no significant benefits in preventing cataract. Zinc (of dose 10 times thhe RDA) alone or in combination with antioxidants had beneficial effects on AMD only in those with intermediate AMD in one or both eyes, or those with advanced AMD in one eye. Overall, the quality of individual articles was "medium" (Table 3). Taking into consideration the quantity, quality, and consistency of evidence, we concluded the strength of evidence on the efficacy of multivitamin/mineral supplementation was rated as "very low" for primary prevention of cancer and cardiovascular disease, and "low" for cataract and age-related macular degeneration (Table 4).

Key Question 2

What is Known About the Safety of Use of Multivitamin/mineral Supplements (As Defined In Key Question 1) in the General Population of Adults and Children, Based Primarily on Data From Randomized Controlled Trials and Observational Studies?

Issues to consider

Because the most recent revisions of recommended nutrient intakes, the 1997-2004 dietary reference intakes (DRIs), include for the first time an upper level of intake, this concept has been used as a benchmark to assess the 'safety' of micronutrient intake. However, it is important to point out that the UL was designed to identify risk, not safety. Risk is a probabilistic, biological, objective indicator of the potential adverse effect resulting from a defined intake level. The risk associated with a given intake level is expected to be similar for comparable human populations. Safety, on the other hand, is a social, cultural and intellectual construct, and reflects the risk that a given society is willing to tolerate. This threshold varies in different cultures and societies, and can change over time. The distinction is of relevance for our review since, in the absence of standardized methods to assess risk associated with nutrient intakes, studies report these adverse or unexpected events in a variety of ways, in some cases reflecting more a subjective self-assessment of 'safety', and in others a more specific assessment of risk based on objective indicators, such as laboratory tests.

Very few studies have been specifically designed to assess the risk associated with different intake levels of single or multiple micronutrients. Nevertheless, many randomized controlled trials include a data collection component aimed at monitoring safety, thus providing information on adverse events in active and control groups. These data typically include a variety of endpoints, from spontaneous or elicited self-reported symptoms or events, exit surveys in participants withdrawing from the study, or objective measurements such as blood or urine tests or clinical examination. It should be noted that most randomized controlled trials reviewed in this evidence report used one or more nutrients at doses above the UL defined by the current DRIs. Besides randomized controlled trials, additional insight on risk associated with specific nutrients can be obtained from other types of studies, including case series and case reports, usually of very small sample size (often single case reports). Not surprisingly, many case reports describe the effects of very high intake levels or of unusual host conditions, thus limiting their generalizability.

The basic conditions that enhance the quality of a study in terms of determining the main health effects also apply to adverse effects: temporal association, adequate exposure, dose-response relationship, biological plausibility, and specificity, etc. In the case of safety, reversal of effects upon withdrawal may also enhance the solidity of the findings.

Review of data on the safety/risk of multivitamin/mineral supplements

We identified 8 articles that reported the adverse effects of multivitamin/mineral preparations. The 8 articles were published from 4 randomized controlled trials and 3 case reports.[72-75,77-81] We considered the following criteria when assessing adverse effects: (1) randomized allocation of treatment, (2) adequate sample size, (3) well-defined population, (4) defined dose and total intake of the nutrient(s) of interest, and (5) adequate duration of exposure. We used the following criteria for assessing causality: temporal relationship, lack of alternative causes, dose-response relationship, evidence of increased circulating levels of the nutrient under investigation, and response to re-challenge.

Doses were usually 2 to 10 times the RDA. For example, typical daily dosage for vitamin E doses ranged from 200 to 600 IU, vitamin A from 10,000 to 20,000 IU, and vitamin C from 75 to 750 mg**.** Overall, we found no consistent pattern of increased adverse events in the active group compared with the placebo group, with the exception of changes in skin color, which was common in studies in which β-carotene was part of the multivitamin preparation (Appendix F, Evidence Tables 2a-2d).

The REACT study evaluated the effects of an antioxidant vitamin combination (750 mg vitamin C, 600 mg vitamin E, and 18 mg β-carotene), given daily for 3 years. The frequency of reported side effects did not differ between intervention and control groups[72] (Appendix F, Evidence Tables 2a-2d).

In the AREDS trial,[73] an antioxidant combination (400 IU vitamin E, 500 mg vitamin C, 15 mg β-carotene) and/or 80 mg zinc and 2 mg Cu, was given to healthy adults with early signs of lens opacity. The only significant effect of the antioxidant supplement was yellowing of the skin (Appendix F, Evidence Tables 2a-2d). A similar study enrolling patients with incipient macular degeneration,[75] and using a similar antioxidant combination, also found a higher percent of yellowing of the skin in the active group (8.3% vs. 6.0%, $p<0.008$).

The MONMD trial assigned 39 patients with macular degeneration to an antioxidant combination, with follow up of 18 months.[74] No adverse effects were reported, except for "a few

cases of diarrhea," which the authors attributed to the high ascorbic acid content of the preparation.

In a 2 by 4 factorial feasibility trial in Yunnan Province, China, where the incidence of lung cancer was extremely high, participants received combinations of retinol 25,000 IU, β-carotene 50 mg, α-tocopherol 800 IU and selenium 400 μg each day, and there were no excessive adverse effects reported for the active supplement groups. Symptoms such as broken nails and skin yellowing were generally improved in the groups receiving active supplements.[78]

In the 3 trials[66 73 69] of multivitamin supplements where mortality rates were compared between active and control groups, no adverse effects of supplementation on the outcomes were found. In fact, two trials reported lower mortality in the groups receiving multivitamin/mineral supplements. [66 69] Few if any studies met all or even a few of the causality criteria (Appendix F, Evidence Table 1e).

Key Question 3

What is the Efficacy Determined in Randomized Controlled Trials of Supplementation with Single Nutrients or Functionally Related Nutrient Pairs, Each at a Dose Less than the UL Determined by the Food and Nutrition Board, in the General Adult Population for Prevention Against the Development of One or More Chronic Diseases or Conditions

Our literature search identified data from randomized controlled trials that assessed the efficacy of β-carotene, vitamin A combined with β-carotene or zinc, vitamin E, folic acid with or without vitamin B12 or vitamin B6, selenium, and vitamin D with or without calcium in the primary prevention of cardiovascular disease, cancer, cataract, age-related macular degeneration, cognitive function, bone mineral density, falls or fractures. Using our search strategies, we did not identify data on the efficacy of vitamin C, iron, magnesium, vitamin B2, niacin, or calcium/magnesium supplement use in the primary prevention of chronic disease.

β-Carotene

Introduction

β-carotene is a major dietary carotenoid and the most abundant carotene found in nature. In the 1980s, several large clinical trials had been launched to determine the role of β-carotene in chronic disease prevention. The following section summarizes the evidence.

Results of the literature search

We identified 22 articles from randomized controlled trials that assessed the efficacy of β-carotene in the prevention of cancer, cardiovascular disease, diabetes mellitus, or age-related maculopathy. The 22 articles were published from 6 trials, the Alpha-tocopherol β-carotene Cancer Prevention Study (ATBC), the Beta-Carotene and Retinol Efficacy Trial (CARET), the Nambour Skin Cancer Prevention Trial (NSCP), the Skin Cancer Prevention Study (SCP), the Physician's Health Study (PHS), and the Women's Health Study (WHS).[82-87]

Design of randomized controlled trials

The ATBC was a 2 by 2 factorial trial of synthetic *all-rac*-α-tocopherol acetate (50% powder, 50 mg per day) and synthetic β-carotene (10% water-soluble beadlets, 20 mg per day)

supplementation in 29,133 Finnish smokers aged 50 to 69 years.[88] Users of vitamin E, vitamin A, and/or β-carotene in excess of predefined doses were excluded. The follow up period was 1985 to 1993. Post-intervention follow up of cancer incidence and cause-specific mortality was performed from 1993 to 1999 for cancer incidence and cause-specific mortality and up to 2001 for total mortality.[89] Gastrointestinal endoscopy was performed on 1,344 men with gastritis after a median supplementation time of 5.1 years[90] (Appendix F, Evidence Tables 3a-3c).

The CARET study consisted of two pilot studies conducted in 1985 to 1988 followed by a large trial conducted from 1988 to 1991 in the United States. The first pilot study, the Asbestos Workers Pilot Study for CARET, involved 816 men with a history of asbestos exposure. [91] The second pilot study, the Smokers Pilot Study, involved 1029 men and women with a history of cigarette smoking.[92] The full CARET study was conducted in 18,314 high-risk men and women who had a history of asbestos exposure or smoking. Participants were randomly assigned to receive either β-carotene 50 mg and retinyl palmitate 25,000 IU per day or placebo. Prior β-carotene supplement users were excluded.[93] The follow up period was 1985 to 1995. Post-trial follow up of cancer incidence and mortality was performed until the end of 2001[94] (Appendix F, Evidence Tables 3a-3c).

The NSCP trial was a 2 by 2-factorial trial of β-carotene 30 mg per day and daily sunscreen among 1,621 adult Australians of age 20 to 69 years.[84] No exclusion or prior supplement use was reported. The follow up period was 1992 to 1996 (Appendix F, Evidence Tables 3a-3c).

The SCP was a trial with a parallel-arm design conducted in 1,729 adults of age 85 years or less who had at least one biopsy-proven basal cell or squamous cell skin cancer at baseline. Participants were randomized to receive placebo or β-carotene (50 mg per day) during the trial.[85] No exclusion or prior supplement use was reported. The follow up period was 1983 to 1993 (Appendix F, Evidence Tables 3a-3c).

The PHS was a 2 by 2 factorial trial of β-carotene (50 mg every other day) and aspirin conducted among 22,071 apparently healthy male physicians, aged 40-84 years, in the United States. Vitamin A supplement users were ineligible for trial enrollment. The follow-up period was 1982 to 1995 [95] (Appendix F, Evidence Tables 3a-3c).

The WHS was a 2 by 2 by 2 factorial trial conducted in 39,876 female health professionals in the United States aged 45 years or older to determine whether alternate daily use of aspirin (100 mg), β-carotene (50 mg), and vitamin E (600 IU) can prevent cancer and cardiovascular disease.[87] β-carotene supplementation was terminated after a median treatment duration of 2.1 years (range 0 to 2.7 years), primarily because of the null findings from the PHS.[95] Users of vitamin A, β-carotene, or vitamin E were ineligible for trial enrollment. Nearly 40 percent of the trial participants reported to have multivitamin supplement use at baseline. The follow up period of this trial was 1992 to 2004 (Appendix F, Evidence Tables 3a-3c).

Similarity and heterogeneity in study design among trials

Except for the ATBC and NSCP that were conducted in Finland and Australia, respectively, the 4 other trials included in this review were conducted in the United States. Except for the SCP and NSCP, prior users of β-carotene and/or vitamin A supplements were excluded. The range of follow up was 4 to 10 years. The range of daily doses was 20 mg to 50 mg. The ATBC, PHS, WHS, and NSCP used a factorial design with α-tocopherol, aspirin, aspirin with/without vitamin E, and sunscreen, respectively, as the other intervention, whereas SCP and CARET adopted a parallel-arm study design. A total of 112,564 individuals were included in this review section. They were heterogeneous populations that ranged from high-risk people with a history of

asbestos exposure and cigarette smoking (ATBC, CARET) to male physicians (PHS), female health professionals (WHS), and adults in a high sun exposure area in Australia (Appendix F, Evidence Tables 3a-3c).

Study quality

The general strengths of the randomized clinical trials were large sample size, double masking and randomization, high adherence to treatment, and ascertainment of clinical outcomes. Adherence was not reported in the CARET study, although β-carotene treatment was shown to raise the median serum β-carotene levels to 12 times the baseline levels.[93] The success of blinding the study was not reported in the NCSP,[84] WHS,[96] and SCP.[85] The study population was incompletely described in the SCP.[85] Most of these studies did not report on participants' prior use of supplements (Table 3).

Results

Cancer. In the ATBC study, compared to those who did not receive β-carotene, participants receiving β-carotene had a higher lung cancer incidence and lung cancer mortality (RR 1.18, 95% CI 1.03-1.36; RR 1.08, 95% CI 1.01-1.16, respectively),[97,98] but no increased risk for gastric cancer,[90] pancreatic cancer,[99] colorectal adenomas,[100] prostate cancer [101] or colorectal cancer [102] In the 6-year post-trial follow up, the relative risk of lung cancer was 1.06 (95% CI 0.94-1.20) for β-carotene recipients versus non-recipients. The supplementation had a late effect on colorectal cancer (RR 1.88; 95% CI 1.28-2.76) 4 years after the end of supplementation, but no late effect on other cancer outcomes.[103] (Appendix F, Evidence Tables 3b-3e, Table 5).

In the PHS, β-carotene supplementation increased the risk of thyroid cancer (RR 9.5, 95% CI 2.2-40.7), and bladder cancer (RR 1.5, 95% CI 1.0-2.2), but had no effect on other malignant neoplasms[95,104] or non-melanoma skin cancer[86] (Appendix F, Evidence Table 3d, Table 5).

In the CARET study, the combination of β-carotene and vitamin A supplementation increased the incidence of lung cancer (RR 1.28, 95% CI 1.04-1.57)[93,105] and the effects persisted 6 years after the trial terminated, especially among women.[94] β-carotene supplementation had no effects on cancers such as leukemia, mesothelioma, bladder cancer, breast cancer, prostate cancer, colorectal cancer, head and neck cancer, or lymphoma[105] (Appendix F, Evidence Table 3d, Table 5).

In the SCP, β-carotene supplementation had no effect on cancer deaths[85] (Appendix F, Evidence Table 3d, Table 5).

In the WHS, β-carotene supplementation had no impact on the incidence of cancer[96] (Appendix F, Evidence Table 3d, Table 5).

In the NSCP trial, β-carotene supplementation had no impact upon the incidence of basal cell carcinoma or squamous cell carcinoma after 4 years of follow up[84] (Appendix F, Evidence Table 3d, Table 5).

Cardiovascular disease. The ATBC study participants who received β-carotene had a non-significant higher incidence of angina and stroke mortality during the trial,[106,107] and had higher mortality for a wide spectrum of cardiovascular disease during the post-trial follow up[103] (Appendix F, Evidence Table 3d, Table 5).

Participants receiving β-carotene and vitamin A in CARET had a non-significant increased risk of cardiovascular death after a mean follow up of 4 years (RR 1.26, 95% CI 0.99-1.61),[93] but the risk was lower (RR 1.02) 6 years after supplementation was terminated.[94]

Participants in the WHS study had a non-significant higher risk for stroke (RR 1.42, 95% CI

0.96-2.10), but lower risk for myocardial infarction (RR 0.84, 95% CI 0.56-1.27)[96] (Appendix F, Evidence Table 3d, Table 5).

In the PHS, β-carotene supplementation had no effects on incidence of type 2 diabetes mellitus,[108] incidence of myocardial infarction, stroke and all important cardiovascular events, or cardiovascular mortality[95] (Appendix F, Evidence Table 3d, Table 5).

Cataract and age-related macular degeneration. In the ATBC trial, β-carotene supplementation had no effect on age-related cataract or age-related maculopathy[109,110] (Appendix F, Evidence Table 3d, Table 5).

Total mortality. β-carotene supplementation was associated with an 8 percent, 7 percent, and 5 percent increased risk of total mortality in the ATBC, WHS and SCP studies, respectively.[85,96,97] Only the increase in the ATBC trial reached statistical significance (p=0.02). In the post-trial follow up on total mortality (8 years of follow up) of the ATBC trial, the relative risk of total mortality in the groups receiving β-carotene compared to the corresponding placebo groups was 1.07 (95% CI 1.02-1.12)[103] (Appendix F, Evidence Table 3e, Table 5).

Summary

In summary, β-carotene was associated with increased risk of lung cancer incidence and mortality in persons who were heavy smokers or who were regularly exposed to asbestos. β-carotene supplementation did not reduce risk of other chronic disease outcomes, including cardiovascular disease, diabetes mellitus, cataract, and maculopathy. Taking into consideration the quantity, quality, and consistency of evidence, we concluded that the overall strength of evidence regarding the effects of β-carotene on the incidence of cancer and cardiovascular disease was "moderate" and on the prevalence of cataract or age-related maculopathy was "very low" (Table 6).

Vitamin A

Introduction

The following section summarizes the evidence from randomized controlled trials on the efficacy of vitamin A supplement use in the prevention of chronic disease.

Results of the literature search

Our literature search identified no data on the efficacy of vitamin A alone in the prevention of chronic disease. We identified 9 eligible articles that addressed the efficacy of pre-formed vitamin A, combined with zinc or β-carotene, in preventing chronic disease. Three articles were from the Linxian trial in China[64-66] in which retinyl palmitate and zinc was combined as one type of supplementation, and 5 articles were from the CARET in the United States[92-94,103,105] in which retinyl palmitate and β-carotene were combined as one type of supplementation.

Design of randomized controlled trials

The designs of the Linxian and CARET trials were described in a previous section of the Results chapter, Design of Randomized Controlled Trials, for Key Question 1 and Design of Randomized Controlled Trials for Key Question 3, β-carotene, respectively (Appendix F, Evidence Tables 3a-3c).

Results

In the Linxian trial, combined vitamin A and zinc had no impact on reducing deaths from stroke,[66] mortality,[64] or esophageal or gastric dysplasia or cancer.[111]

CARET used a combination of β-carotene and retinyl palmitate which increased the incidence of lung cancer (RR 1.28, 95% CI 1.04-1.57), mortality related to lung cancer (RR 1.46, 95% CI 1.07-2.00) and cardiovascular disease (RR 1.26, 95% CI 0.99-1.61).[93] The risk for cardiovascular disease was lower (RR 1.02) 6 years after supplementation was terminated.[94] Total mortality was higher in the group receiving retinyl palmitate and β-carotene at the end of the trial (RR 1.17, 95% CI 1.03-1.33) [93], but leveled off in a post-trial follow up for 6 years (RR 1.08, 95% CI 0.99-1.17)[94] (Appendix F, Evidence Tables 3d-3e).

Summary

Available evidence from two studies in selected populations (nutritionally inadequate or exposure to asbestos and/or cigarette smoke) suggests no benefit of combinations of vitamin A and zinc or vitamin A and β-carotene for cancer or cardiovascular disease prevention. Because no trial has been conducted to assess the efficacy of vitamin A alone in the prevention of the chronic diseases listed in the Key Question 1, we drew no conclusion for vitamin A by itself.

Vitamin E

Introduction

Vitamin E is the second most commonly used dietary supplement in the United States.[1] The following section reviews the evidence on the efficacy of vitamin E supplementation in the prevention of chronic disease.

Results of literature search

Our literature search identified 16 articles (including articles containing post-trial data) that provided evidence on the efficacy of vitamin E supplements in the prevention of chronic disease. These articles were generated from 4 randomized controlled trials, the ATBC trial, the WHS, the Primary Prevention Project (PPP), and the Vitamin E, Cataract, and Age-Related Maculopathy Trial (VECAT). The predominant source of evidence (from 12 articles, including articles containing post-trial data) on this topic stems from the ATBC trial.

Design of randomized controlled trials

The designs of the ATBC trial and the WHS were described in a previous section of the Results chapter, Design of Randomized Controlled Trials, on β-carotene (Appendix F, Evidence Tables 3f-3h).

The PPP was a randomized controlled, open-labeled, 2 by 2 factorial trial designed to investigate the efficacy of vitamin E (synthetic, 300 IU per day) and aspirin (100 mg per day) for cardiovascular disease prevention.[112] Participants were 4,495 men and women age 50 years or older with at least one of the major well-accepted risk factors for cardiovascular disease. Long-term vitamin E users were ineligible. At the end of the trial, the percent of participants lost to follow up was 13.6 percent in the vitamin E group. (Appendix F, Evidence Tables 3f-3h).

The VECAT was designed to evaluate whether daily vitamin E supplements reduced the risk of age-related cataracts in 1,193 Australians who were 55 to 80 years old upon entry into the study and who had early or no cataract. Trial participants were randomized to receive 500 IU per

day of natural vitamin E or placebo for 4 years. Approximately 27 percent of the trial participants had prior supplement use. The percent of participants lost to follow up was 25 percent, and among those who were retained in the trial, 12 percent ceased taking study supplements[113] (Appendix F, Evidence Tables 3f-3h).

Similarity and heterogeneity among trials

The participants in these trials had distinct characteristics, being female health professionals in the United States (WHS), male smokers in Finland (ATBC), or Italians who might have followed a Mediterranean diet (PPP). A total of 74,697 individuals were included in these trials with 87 percent being ATBC or WHS participants. Accordingly, approximately 27 percent of these trial participants were assigned to also take aspirin and 20 percent were assigned to also take β-carotene supplements. Vitamin E supplements used in these studies included synthetic form, natural source, and natural vitamin E at doses ranging from 50 IU per day in synthetic form to 600 IU per day of natural source (Appendix F, Evidence Tables 3f-3h).

Study quality

Inclusion/exclusion criteria were clearly defined in most trials. The quality of these trials was good with respect to randomization, double masking, ascertainment of trial endpoints, adherence, and use of an intention-to treat approach in statistical analyses (see Table 3, Assessment of Quality of Studies). There was a lack of descriptions as to whether concealment of allocation sequence was performed and whether there was an unintended crossover. The WHS and PPP trials collected data on lifestyle factors and medication use. None of the trials reported success of blinding and the extent of unintended crossover. Most trials provided no information on numbers and reasons for withdrawals and percent lost to follow up.

Results.

Cancer. In the ATBC trial, synthetic α-tocopherol of 50 IU per day had no benefit on the incidence of lung cancer and gastric neoplasm,[90,98] lung cancer mortality, or pancreatic cancer mortality,[97,99] but increased colorectal adenoma incidence (RR 1.66, 95% CI 1.19-2.32)[100]. Questions have been raised whether the finding on colorectal adenoma was due to increased rectal bleeding by α-tocopherol supplementation, leading to the increased diagnosis of polyps. In contrast to these findings, men who received α-tocopherol supplements had a non-significant protective effect on colorectal cancer development (RR 0.78, 95% CI 0.55-1.09)[102] and had a 32 percent and 41 percent reduction in the incidence of, and the mortality from prostate cancer respectively.[101] The reduction was evident for clinical prostate cancer but not for latent cancer. In the post-trial follow up, the protective effect of α-tocopherol against prostate cancer was attenuated (RR 0.88, 95% CI 0.76-1.03). The moderate protective effects of α-tocopherol on colorectal cancer during the trial was no longer evident in the 6-year post-trial follow up, and α-tocopherol had no late effects on other cancers.[103]

In the WHS study, vitamin E of 600 IU on alternate days did not affect the risk of developing total invasive cancer, breast cancer, lung cancer, and colon cancer, or the risk of cancer death[87] (Appendix F, Evidence Table 3i, Table 7).

Cardiovascular disease. In the ATBC trial, *all-rac*-α-tocopheryl acetate of 50 IU per day had a borderline effect in reducing the incidence of angina (RR 0.91 comparing alpha-tocopherol with or without beta-carotene to no alpha-tocopherol with or without beta-carotene; RR 0.97 comparing alpha-tocopherol alone to placebo), decreased the risk of cerebral infarction (RR 0.86,

95% CI 0.75-0.99), and increased the risk of subarachnoid hemorrhage (RR 1.50, 95% CI 0.97-2.32) and fatal subarachnoid hemorrhage (RR 1.81, 95% CI 0.49-1.32).[106] A similar increased risk in hemorrhagic stroke persisted during the post-trial follow up.[103]

In the PPP, [107] the evidence was inconclusive due to small numbers of events and premature stopping of the trial; there was a non-significant increased risk for main cardiovascular endpoints (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) (RR 1.07, 95% CI 0.74-1.56), but a lower risk for total cardiovascular events or diseases (RR 0.94, 95% CI 0.77-1.16)[112] (Appendix F, Evidence Table 3i, Table 7).

In the WHS, use of vitamin E, 600 IU every other day had no effects on fatal and non-fatal myocardial infarction and fatal and non-fatal stroke, but reduced total cardiovascular death (RR 0.76, 95% CI 0.59-0.98).[87,96] There was no effect of vitamin E supplementation on hemorrhagic stroke (RR 0.92, 95% CI 0.61-1.38)[87] (Appendix F, Evidence Table 3i, Table 7).

Serum lipid levels. Shekelle etal. conducted a systematic review of the effects of vitamin E on the prevention and treatment of cardiovascular disease.[114] The review, published in April 2004, was part of a larger evidence report on the effects of vitamin C, vitamin E, and coenzyme Q10 on cardiovascular outcomes.[115] The review included an examination of the effects of vitamin E on lipid levels. The search strategy was comprehensive and retrieved English and non-English studies from multiple electronic databases. Additional studies were obtained by hand-searching reference lists from key articles and by consulting experts in the field. Multiple synonyms for vitamin E and for clinical trials were used in the initial search, but only randomized trials in humans using clinical or important surrogate outcomes were included in the report. Two independent evaluators using a standardized form extracted study data, and quality was assessed using the Jadad scale. Both primary and secondary prevention trials were evaluated. Meta-analyses were performed whenever groups of studies were judged to be sufficiently similar (Appendix F, Evidence Table 3i, Table 7).

The Shekelle review included 84 eligible trials of the effect of vitamin E on cardiovascular outcomes. However, only four of the trials were primary prevention studies, and these were deemed to be too heterogeneous (with respect to the type of intervention) to permit meta-analysis to be performed. The individual results of these 4 studies (ATBC,[116] PPP,[117] SCP,[118] and Linxian[119]) were presented by the authors in narrative form. With respect to lipid lowering, the authors stated that "the 2 large primary prevention trials (ATBC and Linxian) reported clinically insignificant (but statistically significant) changes in (lipid) outcomes," and that "there is no evidence that vitamin E alone or in combination has a clinically or statistically significant favorable or unfavorable effect on lipids." In their meta-analyses of all primary and secondary prevention trials on the lipid effects of vitamin E compared to placebo, they found effect sizes that were not significant for total cholesterol (effect size -0.07, 95% CI -0.31 to 0.08), low-density cholesterol (effect size -0.07, 95% CI -0.24 to 0.10), or high-density lipoprotein (effect size 0.01, 95% CI -0.21 to 0.22).[116] A negative effect size would indicate a favorable effect of treatment (Appendix F, Evidence Table 3i, Table 7).

Cataract and age-related macular degeneration. The evidence concerning vitamin E supplements and cataract is compatible with no effect. In the VECAT trial,[113] the relative risk of cataract in the vitamin E group versus the placebo group was 1.0 for any cataract (95% CI 0.8-1.4). The relative risk for specific types of cataract were 0.9 for cortical cataract (95% CI 0.5-1.6), 1.1 for nuclear cataract (95% CI 0.8-1.5), and 0.5 for posterior subcapsular cataract (95% CI 0.2-1.1)[113] (Appendix F, Evidence Table 3i, Table 7).

In the ATBC trial, lens opacity was measured at the end of the trial in a random sample of 1,828 participants.[109] The results showed that participants randomized to the α-tocopherol group were not different from the non-α-tocopherol group with respect to the risk of having nuclear cataract (OR 0.8, 95% CI 0.4-1.4), cortical cataract (OR 0.9, 95% CI 0.6-1.4), or posterior subcapsular cataract (OR 0.9, 95% CI 0.4-1.8)[109](Appendix F, Evidence Table 3i, Table 7).

The same approach was used in the ATBC trial to assess the association between α-tocopherol and the end-of-trial prevalence of age-related maculopathy.[110] The prevalence of age-related maculopathy was higher among those assigned to receive α-tocopherol supplements than in the placebo group (32% versus 25%), showing no evidence of a beneficial affect of α-tocopherol[110](Appendix F, Evidence Table 3i, Table 7).

Total mortality. The relative risk for total mortality in the vitamin E supplement users compared to non-users was 1.04 (95% CI 0.93-1.16), 1.02 (95% CI 0.95-1.09), and 1.07 (95% 0.61-1.90) in the WHS, the ATBC, and the PPP, respectively. In the post-intervention follow up on mortality (8 years of follow up) of the ATBC trial, the relative risk of total mortality in α-tocopherol users compared to non-users was 1.01 (95% CI 0.96-1.05).[103] Investigators in the WHS reported that "the main causes of death, apart from cardiovascular and cancer deaths, were pulmonary diseases (32 vitamin E, 22 placebo) and violent deaths, excluding suicide (9 vs. 6). None of these causes of deaths was significantly related to vitamin E." [87] The relative risk of cardiovascular death and cancer death in the WHS was 0.76 (95% CI 0.59-9.98) and 1.12 (95% CI 0.95-1.32), respectively.[87] The VECAT documented 31 deaths (20 in vitamin E; 11 in placebo), and the authors reported "no consistent or unusual patterns were identified among the specific causes of death recorded"[113] (Appendix F, Evidence Table 3j, Table 7).

Summary

Vitamin E supplements have been studied for efficacy in the primary prevention of cancer, cardiovascular disease, cataract, and age-related macular degeneration. There was a lack of effects of vitamin E supplement use in the prevention of these diseases, except for a 32 percent reduction in prostate cancer incidence, a 41 percent reduction in the prostate cancer mortality, and a 22 percent reduction in colorectal cancer in the ATBC trial. The findings on hemorrhagic stroke were conflicting between the ATBC trial and WHS trial in that the former found a higher risk with use of low-dose α-tocopherol supplements but the latter found a lower risk with use of a high dose. Taking into consideration the quantity, quality, and consistency of evidence on the efficacy of vitamin E in preventing chronic disease, we concluded that the overall strength of evidence is "very low" for cancer, "low" for the relationship to cardiovascular disease, and "moderate" for cataract (Table 6).

Folic acid and B vitamins

Introduction

The co-prevalence of dementia and low circulating levels of micronutrients among the elderly has led to the research interest in vitamin supplementation as a means to prevent dementia. In various observational studies, low circulating levels of folate and vitamin B6 have been associated with poor cognitive function, dementia, and Alzheimer's disease[120-124] and hyperhomocysteinemia.[125,126] The essential role of folate and the B vitamins in homocysteine metabolism has been used to explain the possible role of these vitamins in dementia.

Results of literature search

Our search revealed two systematic reviews on single or paired vitamin supplementation with B vitamin(s) or folic acid for primary or secondary prevention of dementia and cognitive decline, and 4 articles from 1 trial that addressed vitamin B2 and niacin in the prevention of chronic disease. The systematic reviews were from the Cochrane Collaboration. The review on folic acid with or without vitamin B12 was comprised of 4 randomized controlled trials. The review of vitamin B6 was comprised of 2 randomized controlled trials. The trial on vitamin B2 and niacin was the Linxian trial. No studies were found to assess the efficacy of single or paired B vitamins or folic acid supplementation for prevention of other chronic diseases.

Design of Systematic Reviews

Malouf et al. systematically reviewed the literature to "assess the efficacy of vitamin B6 supplementation in reducing the risk of developing cognitive impairment by older healthy people, or improving cognitive functioning of people with cognitive decline and dementia,"[127] and to "examine the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy and demented people in preventing cognitive impairment or retarding its progress."[128] The search strategy, data collection and analysis methods were similar in both reviews. Trials were identified from a broad database by a predefined search strategy by the Dementia and Cognitive Improvement Group. Outcomes were measured as changes in continuous rating scales from baseline where available. When the same rating scales were used across trials, the weighted mean difference was presented for pooled trials. A standardized mean difference was reported for different rating scales. Weighted estimates for odds ratio were used for binary outcomes. When duration varied greatly and the range was considered too great to combine, a separate meta-analysis was conducted for smaller time periods. If there was evidence of heterogeneity of treatment effect between trials, either only homogeneous results were pooled or a random effect model was used. There was no pooled outcome measure presented due to heterogeneity of study participants and supplements.

Study quality

Design and quality of the meta-analyses on folic acid and vitamin B6 were similar. Strengths of these systematic reviews include: clarity of review question, description and completeness of search strategy, and reproducibility of review. Limitations were due primarily to heterogeneity among studies reviewed. The authors presented standardized outcomes of cognition when possible. No attempt was made to summarize outcome measures because of the great variation in trials included.

The review on vitamin B6 supplementation [127] reviewed 2 randomized controlled trials for primary prevention. [128,129] The authors attempted to minimize heterogeneity of study subjects by extracting data on older subjects. Follow up time varied from 5 to 12 weeks. Dosages of B6 supplementation varied from 20 to 75 mg per day. Among the different trials, there were wide disparities in dosages of folic acid (750 mcg to 15 mg) and vitamin B6 (20 to 75 mg).

The review on folic acid[130] reviewed 4 randomized controlled trials for primary and secondary prevention.[128, 131-133] The authors attempted to minimize heterogeneity of study subjects by extracting data on older subjects at the expense of decreasing sample size. Despite this, there was considerable heterogeneity in study population. One study for primary prevention involved only women.[128] The remaining 3 studies[131-133] were secondary prevention trials. Dosage of folic acid varied widely from 750 mcg to 15 mg per day. Two studies combined vitamin B12

with the folic acid supplementation and these results were combined together with those receiving folic acid alone.

Results.

Cognitive decline. Although the meta-analysis by Malouf found improvement in biochemical indicators of vitamin B6, no measurable improvement in cognition was found after short-term supplementation with vitamin B6. Although folic acid with vitamin B12 was effective in reducing serum homocysteine levels, the authors concluded that these limited studies did not support folic acid supplementation for prevention of cognitive decline.

Summary

There is limited evidence to suggest no benefit of vitamin B6, vitamin B12, or folic acid supplementation for primary prevention of cognitive decline. Taking into consideration the quantity, quality, and consistency of evidence on the efficacy of folic acid, vitamin B6 and vitamin B12 in preventing chronic disease, we concluded that the overall strength of evidence is "low" for folic acid with or without vitamin B12 and "moderate" for vitamin B6 (Table 6).

Vitamin B2 and niacin

Introduction

The following section summarizes the evidence on the efficacy of vitamin B2 and niacin supplement use in the prevention of chronic disease.

Results of the literature search

Our literature search identified 4 eligible articles from the Linxian General Population Trial that addressed the efficacy of vitamin B2 (3mg per day) and niacin (vitamin B3, 40 mg per day) in preventing cancer, cardiovascular disease or cataract. [64-66, 111] Data on other chronic diseases were lacking.

Design of randomized controlled trial

The design of the Linxian trial was described in a previous section of the Results chapter, Design of Randomized Controlled Trials, for Key Question 1 (Appendix F, Evidence Tables 3k-3o).

Results.

Cancer, cardiovascular disease and total mortality. In the Linxian trial, combined vitamin B2 and niacin had no impact on reducing deaths from stroke,[66] mortality,[64] or esophageal or gastric dysplasia or cancer.[111] (Appendix F, Evidence Tables 3k-3o)

Cataract. A lower prevalence of nuclear cataracts was observed in those who received riboflavin and niacin, and there was no difference between randomized groups in cortical cataracts.[65] However, a 2.64-fold increased prevalence in posterior subcapsular cataract was documented for the groups receiving riboflavin 3 mg and niacin 40 mg compared to the groups not receiving riboflavin and niacin[65] (Appendix F, Evidence Tables 3k-3o).

Summary

Data on the efficacy of vitamin B2 and niacin supplement use in the primary prevention of chronic disease are sparse and the only study was conducted in a nutritionally deprived Chinese population found no benefit of combined vitamin B2 and niacin for primary prevention of cancer, cardiovascular mortality, or cataracts.

Selenium

Introduction

Selenium functions as an antioxidant since it is essential to the antioxidant enzyme glutathione peroxidase.[129] Because selenium is involved in the biosynthesis of testosterone, another proposed mechanism involves its role in the endocrine and immune system. [130,131] Selenium has also been theorized to function on the molecular level by changing carcinogen metabolism, inhibiting protein synthesis or specific enzymes, and stimulating apoptosis.[132] The following section summarizes the evidence on the efficacy of selenium supplement use in chronic disease prevention.

Results of literature search

Our literature search identified 6 articles that provided evidence on the efficacy of selenium supplements in the prevention of cancer, cardiovascular disease. These publications were generated from 2 different trials, the Nutritional Prevention of Cancer (NPC) trial and another study. We included the NPC trial of patients with a history of non-melanoma skin cancer because the study reported on the risk of cancer other than non-melanoma skin cancer, and non-melanoma skin cancer is not a precursor of other cancers.

Design of randomized controlled trials

The NPC trial was a double-blind, placebo-controlled multi-center cancer prevention trial in 1,312 men and women to test the efficacy of selenium supplementation (200 mcg supplied as 500 mg high-selenium yeast tablets) in reducing chronic disease, specifically cancer.[133-135] Trial participants had a history of either 2 or more basal cell carcinomas (BCC) or one squamous cell carcinoma (SCC) of the skin within the prior year. Prior supplement users were eligible for enrollment. The primary outcome of interest was occurrence of a new non-melanotic skin cancer. Secondary endpoints included incidence of lung, colorectal, and prostate cancers, total mortality and cancer mortality. The total blinded treatment period was from September 1983 until January 1996. Interim analysis was published in 1996 on data from the full cohort of 1312 participants through December. 1993[133,134] Analyses at the end of the full, blinded treatment period in 1996 were published on total cancer outcomes, [136] prostate cancer, [137] and lung cancer.[135] Later analyses excluded 62 patients who had baseline blood tests more than 4 days after randomization.[135-137] Interim analysis for prostate cancer was performed on 974 male participants, accounting for a 2-year lag effect.[134] Re-analysis of prostate cancer data at the end of full, blinded treatment was done on 927 participants without a history of prostate cancer before randomization, using those individuals with a valid baseline blood draw less than 4 days after randomization. [137] By the end of the blinded study in 1996, 35.9 percent of participants were on supplementation, 16.6 percent were off supplementation, but continuing follow up, 22.1 percent were censored for dermatological endpoints but not other endpoints, and 24.8 percent had died. We did not include one study with melanotic skin cancer recurrences in the NPC trial

because it addressed secondary prevention. Full text of the articles on cardiovascular disease and colorectal cancer were published after the cutoff date of our review[138] Another study by Yu et al. was conducted in Qidong County, China and published in 1991.[139] (Appendix F, Evidence Tables 3k-3o).

Similarity and heterogeneity among trials

Participants in the NPC trial were recruited from dermatology clinics and had non-melanotic skin cancer without recent treatment for internal malignancy. Participants in the study by Yu etal. were selected to be at high risk for liver cancer because of a family history of cancer in addition to living in an area of China that has high rates of liver cancer. Both studies used 200 mcg per day of selenium as a yeast tablet.

Study quality

In the NPC Study, the study population, inclusion and exclusion criteria, flow of patients, outcome reporting and statistical analyses were well described. Well designed aspects of the study included: random assignment of patients, placebo control, confirmation of outcomes, efforts at blinding, assessment of adherence, appropriate handling of losses to follow up, reporting of statistical analyses, and intention-to-treat analysis. However, there was inadequate information reported regarding excluded patients, prior supplement use, prior and concurrent medication use, success of blinding, independent ascertainment of outcomes, unintended cross-over rates, description of supplements, and statistical power.[133] The study was initially designed to look at incidence of non-melanoma skin cancer, and other cancer endpoints were designated secondary outcomes 7 years after commencement of the trial.

The study by Yu et al. had inadequate data reporting on almost all aspects of the study with the exception of a fair description of supplements and assessment of adherence to supplements by biomarkers (Table 3).

Results.

Cancer. Initial interim analysis of the NPC trial through 1993 found that the selenium group had a significantly lower total cancer mortality (RR 0.5, 95% CI 0.31-0.8), total cancer incidence (RR 0.63, 95% CI 0.47-0.85), and significantly lower incidence of lung, colorectal, and prostate cancers (RR 0.56, 95% CI 0.31-1.01; RR 0.39, 95% CI 0.17-0.90; RR 0.35, 95% CI 0.18-0.65, respectively).[133] Cancer endpoints from the full trial period through 1996 were analyzed and had a mean follow up of 7.9 years. Selenium continued to reduce the risk of all cancers (HR 0.75, 95% CI 0.58-0.97) and prostate cancer (HR 0.51, 95% CI 0.29-0.87), lung cancer (HR 0.70, 95% CI 0.40-1.21) and colorectal cancer (HR 0.46, 95% CI 0.21-1.02), although the findings on lung cancer and colorectal cancer were not statistically significant.[135,137]

An interim reanalysis of 843 male patients with prostate specific antigen levels less than 4 ng/ml, taking into account a 2-year treatment lag, found that the selenium group had a significant reduction in prostate cancer (RR 0.37, p-value 0.002).[134] Subgroup analyses showed that the effect of selenium on prostate cancer was greatest in those with a baseline prostate specific antigen level less than 4 ng/ml (RR 0.35, 95% CI 0.13-0.87)[137] (Appendix F, Evidence Tables 3k-3o).

In the 2-year intervention trial with selenized yeast by Yu et al., the incidence of primary liver cancer was significantly less ($p<0.05$) in selenium supplemented subjects (10 of 1444;

0.69%) compared to control subjects (13 of 1030; 1.26%)[139] (Appendix F, Evidence Tables 3k-3o) (Appendix F, Evidence Tables 3k-3o).

Cardiovascular disease. Only the NPC study reported cardiovascular outcomes in the context of selenium supplementation, and there was no effect on cardiovascular disease (HR 1.03, 95% CI 0.78-1.37), stroke (HR 1.02, 95% CI 0.63-1.65), or cardiovascular mortality (HR 1.22, 95% CI 0.76-1.95) for primary prevention in those without prior cardiovascular disease.[133, 140] (Appendix F, Evidence Tables 3k-3o).

Total mortality. Total mortality in the NPC study was reduced by 21 percent in the group receiving selenium (HR 0.79, 95% CI 0.61-1.02) as compared to placebo[133] (Appendix F, Evidence Tables 3o).

Summary

Evidence on the role of selenium in cancer prevention is limited, but suggests some benefit in prevention of total and prostate cancer, with the greatest benefit in men with a normal baseline prostate specific antigen level. Selenium did not significantly reduce the risk of lung or colorectal cancer. The only well-designed randomized controlled study supporting selenium supplementation for cancer prevention was done in a population with non-melanotic skin cancer. Taking into consideration the quantity, quality, and consistency of evidence on the efficacy of selenium in preventing chronic disease, we concluded that the overall strength of evidence is "moderate" (Table 6).

Calcium and vitamin D

Introduction

Supplementation with calcium, vitamin D, or both has been recommended for primary prevention of osteoporosis. Physiologically, calcium supplementation corrects for suboptimal intake or decreased intestinal absorption of calcium. Left uncorrected, secondary hyperparathyroidism develops, leading to accelerated bone resorption and ultimately to increased risk for fractures. Supplemental vitamin D optimizes intestinal calcium absorption, and it also improves neuromuscular function and reduces the recurrences of fractures. [151]

Improvement in bone mineral density (BMD) is a marker for stronger bones and is predictive of fracture reduction.[150] However, fracture is the major clinical outcome of osteoporosis.

Due to the substantial amount of efficacy data on calcium/vitamin D and osteoporosis, we reviewed systematic review articles supplemented with data from recent randomized controlled trials. We also used data from randomized controlled trials meeting our inclusion criteria, that were not included in previous systematic reviews.

Results of literature search

Our search for evidence that supplemental calcium and/or vitamin D prevents osteoporosis/fractures/falls revealed 7 articles from 6 recent systematic reviews, authored by Shea et al.,[47,50] Mackerras and Lumley,[52] Papadimitropoulos et al.,[49] Avenell et al.,[143] and Bischoff-Ferrari et al.[144,145] Two articles on osteoporosis and colorectal cancer from the Women's Health Initiative study (WHI)[146] were released as we prepared this report. We also identified three small relevant randomized controlled trials [147-149] that were not included in previous systematic reviews. Using our search strategies, we identified no additional randomized

controlled trials for the efficacy of calcium with or without vitamin D supplement use in the primary prevention of other chronic diseases. In 2005, AHRQ awarded a contract to the University of Ottawa's EPC to conduct a systematic review of the efficacy of vitamin D on bone density and fracture risk, but that review was not available in time for inclusion in the evidence report.

All of this literature met our criteria for calcium and vitamin D formulations and doses. For calcium, the doses were less than 2.5 grams per day, the adult UL recommended by the Food and Nutrition Board (Appendix F, Evidence Tables 3p-3r). With regard to vitamin D, our interest was in over-the-counter supplements, but some systematic reviews included studies using formulations available only by prescription. Therefore, in summarizing these previous reviews, we extracted the relevant data reported for non-prescription vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) used in doses not exceeding the UL, 2000 IU per day (Appendix F, Evidence Tables 3p-3r).

Calcium

Design of systematic reviews. Three articles from 2 systematic reviews [47,50,52] examined the efficacy of calcium on BMD. Two of the reviews [47,50] by Shea etal. presented identical data, so only the more recent article [47] was used. Shea etal. analyzed randomized controlled trials published from 1978 to 1998 investigating skeletal effects of calcium supplementation in post-menopausal women. The randomized controlled trials addressed fractures in 5 trials (n = 638) and BMD in 15 trials (n=1826) of 1 to 4 years duration in women whose mean age ranged from 46 to 72 years. The Mackerras review [52] evaluated 8 randomized controlled trials from 1987 to 1995. However, Mackerras etal. had a different focus, concentrating on year-by-year BMD changes in a younger group of postmenopausal women (n = 1386, mean age 51 to 66 years) (Appendix F, Evidence Tables 3p and 3q).

Quality of reviews. The strengths of the Shea review were: attention to methodologic detail (e.g., contacting authors for details of randomization and blinding) and assessment of heterogeneity of BMD results across studies with various subgroup analyses (e.g., losses to follow up, time after menopause). A major limitation of the Shea review (and also that of Mackerras whose papers were all included in the Shea review) was that conclusions were compromised by problems inherent in the original studies. These problems included small sample size, large losses to follow up, and significant heterogeneity of study populations and interventions (e.g., the variable use of vitamin D in addition to calcium in treated and control subjects) (Appendix F, Evidence Tables 3p and 3q).

Strengths of the Mackerras review were: strict attention to precision and quality control issues involving bone density measurements that are often overlooked (e.g., excluded a study that changed densitometers mid-study); rigorous analysis of BMD data (e.g., did not pool measurements from different anatomical sites and measured BMD change year by year rather than averaging total change over the treatment period); and subgroup analyses to evaluate effects of calcium on bone density independent of other potential effectors, especially vitamin D and exercise. An important weakness of the Mackerras review, in addition to those mentioned above, was lack of discrimination against poorly randomized trials. Mackerras etal. did not contact investigators for missing information.

Design of randomized controlled trials. The WHI published 2 articles comparing the effect of calcium and vitamin D with placebo for primary prevention of fractures [146] and colorectal cancer

[152] in healthy postmenopausal women. A subgroup of 2431 women had BMD measured at annual visits 3, 6, and 9.

Storm et al.[149] compared the effect of calcium supplementation versus dietary calcium intake or placebo on seasonal (i.e. winter) bone loss in healthy, older postmenopausal women (n = 60, age greater than 65 years).

Meier et al.[147] compared the effect of calcium and vitamin D versus no treatment on seasonal bone loss in healthy, German, community dwellers (Appendix F, Evidence Tables 3s and 3t).

Similarity and heterogeneity among randomized controlled trials. The WHI studies [146,152] selected participants from multiple United States cities. WHI studies allowed personal calcium and vitamin D supplementation up to 1000 mg and 600 IU daily respectively and thus had a baseline average daily intake of 1150 mg calcium and 365 IU vitamin D as assessed by a food frequency questionnaire. Meier [147] did not allow prior or personal use of calcium or vitamin D supplements, but did not assess baseline calcium or vitamin D intake at baseline. Storm limited calcium intake to less than 800 mg per day as measured by food frequency questionnaire and thus had an average baseline calcium intake of 684 mg per day (Appendix F, Evidence Tables 3s and 3t).

Quality of randomized controlled trials. Strengths of the WHI study included: double blinded, placebo-controlled study, large sample size, rigorous quality control, reporting of baseline characteristics, clearly documented protocol, appropriate analytic methods, few losses to follow-up, long follow-up, and central adjudication of outcomes. Weaknesses of the study included: possible inadequate ascertainment of all outcomes, lack of adherence to treatment regimen, high baseline intake of calcium and vitamin D (though diet and supplement use), and inadequate power, all of which may bias this study to the null.

Strengths of the Storm study[149] were the administration of calcium alone without vitamin D, double blinding with placebo and treatment group, description of baseline calcium intake, description and number of withdrawals, quality control and outcome ascertainment and measurement of serum 25-hydroxyvitamin D levels during the study period. Weaknesses included small sample size, poor description of adherence assessment, and clarity and appropriateness of statistical analyses.

Strengths of the Meier study[147] included randomization with description of baseline equivalence of groups. Weaknesses of this study include: lack of placebo-control and double blinding, unclear description of inclusion and exclusion criteria, no description of adherence, high rate of withdrawals, short supplementation time, and heterogeneity of a relatively small sample size of participants.

Results

Calcium and bone density. Both Shea et al. and Mackerras et al. reported a small positive effect of calcium in preventing bone loss. Shea et al., who averaged BMD changes across the entire treatment period, concluded that BMD at four different sites was consistently 1.5 to 2.0 percent higher after two years of treatment. In a more rigorous analysis of BMD data, Mackerras et al. found that calcium's effects occurred mainly in the first year. They concluded that BMD losses actually occurred in both treated and control groups, but that losses were relatively greater in controls (0.5-2.8% from baseline at 10 different sites) than in treated groups (with corresponding losses of only 0.1-1.1%).

The WHI[146] found significant cumulative dose-responsive difference in total hip BMD between patients treated with 1000 mg calcium and 400 IU vitamin D and placebo-treated patients, but no significant difference in spine BMD.

Storm et al. found that supplemental calcium alone (1000 mg per day) prevented seasonal bone loss of the greater trochanter (associated with a 25% decrease in serum 25-hydroxyvitamin D levels) and significantly increased BMD of the femoral neck by 3 percent from baseline. In contrast, seasonal bone loss occurred in placebo-treated women who had a 3 percent loss of BMD in the greater trochanter and 0.3 percent loss in the femoral neck after 2 years. Dietary calcium treated subjects (average 1000 mg per day) had a 1.5 percent loss in greater trochanter BMD and 1.8 percent loss in the femoral neck BMD. (Appendix F, Evidence Table 3r).

Meier et al. found that 500 mg calcium and 500 IU vitamin D supplementation significantly increased lumbar (+0.8%, p=.04) and femoral BMD (+0.1%, p=.05) compared to the previous year without any supplementation, which was significantly different (p=.03 for lumbar spine, and p=.05 for femoral bone) from the control group, which had a decrease in lumbar and femoral BMD[147] (Appendix F, Evidence Table 3u).

Calcium and fractures. Shea et al. found in calcium-treated individuals, a trend toward reduction of vertebral fractures (RR 0.79, 95% CI 0.55-1.13). There was no significant effect of calcium on non-vertebral fractures. Fracture results were consistent across studies but the strength of the conclusion was limited by the small study populations and short follow up periods (Appendix F, Evidence Table 3r).

Intention-to-treat analysis of the WHI study [146] found that calcium plus vitamin D supplementation did not significantly decrease the incidence of hip fracture (HR 0.88, 95% CI 0.72-1.08), clinical spine fracture (HR 0.90, 95% CI 0.74-1.10) or total fractures (HR 0.96, 95% CI 0.91-1.02) (Appendix F, Evidence Table 3u).

Calcium and colorectal cancer. A secondary outcome of the WHI trial was colorectal cancer. [152] Intention to treat analysis found that calcium plus vitamin D supplementation did not significantly decrease the incidence of invasive colon cancer (HR 1.08, 95% CI 0.86-1.34).

Summary. The studies showed a consistent small effect of calcium on prevention of BMD loss (approximately 2%) over a period of 2 or more years in postmenopausal women. The effects occurred mainly in the first year. Calcium supplementation prevented the seasonal bone loss associated with wintertime drops in vitamin D levels. Based on very limited data, Shea also raised the possibility that calcium may reduce vertebral, but not non-vertebral, fractures. (Appendix F, Evidence Tables 3r and 3u).

Vitamin D

Four articles from 3 systematic reviews, [49, 143-145] and one article from the WHI [146] addressed the effect of vitamin D on fractures. Vitamin D effects on BMD were also assessed in one of these reviews, by Papadimitropoulos et al.,[49] as well as in the WHI study and 2 small randomized controlled trials.[147,148]

Design of Systematic reviews. The most comprehensive of the systematic reviews, the Avenell study, [143] investigated the effects of vitamin D with or without calcium on fractures. Avenell et al. analyzed 38 randomized controlled trials; 12 of these (from 1983-2005) are pertinent to our review because they involved treatment with vitamin D_3, 400-800 IU per day, in about 35,000 men and women, age 65 or more. Included among the 12 trials is the large Porthouse primary prevention trial (n=3454 women)[150]which employed a treatment regimen of vitamin D3 (800 IU/day) and calcium (1000 mg/day). The other 26 trials were not considered in this review because they used active hydroxylated metabolites of vitamin D (Appendix F, Evidence Tables 3p and 3q).

Of the two systematic reviews by Bischoff-Ferrari et al., the first [145] explored anti-fracture efficacy of vitamin D with or without calcium in older persons (8 trials, n = 9820, mean age 75 to 85 years), whereas the second [144] tested the effects of vitamin D_3 on fall prevention in a similar but smaller population (3 trials, n = 613).

The Papadimitropoulos review, limited to older postmenopausal women (mean age 72 to 84 years), evaluated 25 randomized controlled trials, 10 of which we included in our review because they employed vitamin D_3 in doses of 300-2000 IU/day. Of the 10 trials, 6 measured BMD changes (n = 956), and 4 evaluated fracture prevention (n = 5780) (Appendix F, Evidence Tables 3p and 3q).

Quality of Reviews. The strengths of the Avenell et al. review included its large size and comprehensive nature that allowed independent assessment of the anti-fracture effects of vitamin D and calcium, administered separately and in combination. Also important were assessments of methodological quality for each reviewed trial (revealing a range of quality from poor to satisfactory). A weakness of the Avenell et al. study was lack of information on dropouts from both treatment and control arms of some studies, possibly causing inaccurate estimates of outcome events by the intention to treat analysis. Similar to Avenell et al., a strength of the Papadimitropoulos review was the assessment of methodologic quality of each eligible study. In addition, *a priori* hypotheses concerning study design, population, intervention, and methodologic quality were developed in an attempt to identify reasons for differences in results across studies. Nevertheless, both the Avenell and Papadimitropoulos reviews suffered from marked heterogeneity across the included studies.

A strength of the Bischoff-Ferrari fracture prevention review [145] was the consistency of treatment across studies with regard to vitamin D_3 doses, but a problem was that calcium was also used with some patients, possibly obscuring the effects of vitamin D alone. Other problems were the small number of trials analyzed and the absence of specific large relevant studies.[150,151] Similar issues of scope and variability in treatment regimens apply to Bischoff-Ferrari's review on fall prevention (Appendix F, Evidence Tables 3p and 3q). [144]

Design of randomized controlled trials. The WHI study assessed the efficacy of vitamin D_3 (400 IU/day) with calcium (1000 mg/day) for primary prevention of fractures in healthy postmenopausal women (n = 36,282, mean age 63 years).[146] BMD was followed at annual visits 3, 6, and 9 in a subgroup (n = 2431) (Appendix F, evidence tables 3s-3u).

Meier etal. (519) compared the effect of supplemental vitamin D_3 (500 IU/day) plus calcium (500 mg/day) with no treatment for prevention of wintertime BMD losses in health German men and women (n=55, age range 34-75 years).

Hunter etal. [148] compared the effect of vitamin D (800 IU cholecalciferol/day) with placebo in a twin-control on change in BMD in healthy postmenopausal women living in the United Kingdom over 2 years (Appendix F, Evidence Tables 3s and 3t).

Similarity and heterogeneity among randomized controlled trials. Most studies included primarily postmenopausal women. Only Meier et al.[147] included men in addition to postmenopausal women. There was wide variation in baseline calcium and vitamin D intake and exposure. The WHI studies [152,146] selected participants from multiple United States cities. Two studies were conducted in areas of northern latitude, Germany,[147] and the United Kingdom, with presumably less sunlight exposure. WHI studies allowed personal calcium and vitamin D supplementation up to 1000 mg and 600 IU daily respectively and thus had a baseline average daily intake of 1150 mg calcium and 365 IU vitamin D as assessed by a food frequency questionnaire. Hunter [148] did not allow vitamin D or calcium supplementation, but participants

had daily baseline calcium and vitamin D intakes of 1050 mg and 135 IU respectively. Meier et al. [147] did not allow prior or personal use of calcium or vitamin D supplements, but did not assess baseline calcium or vitamin D intake at baseline. Treatment intervention regimens also varied among the different studies. Three studies used both calcium and vitamin D.[146,147,152] One study used only vitamin D.[148] Vitamin D formulation was cholecalciferol[146,147,152] with dosage ranging from 400 to 500 IU daily (Appendix F, Evidence Tables 3s and 3t).

Quality of randomized controlled trials. Strengths of the WHI study included: double blinded, placebo-controlled study, large sample size, rigorous quality control, reporting of baseline characteristics, clearly documented protocol, appropriate analytic methods, few losses to follow-up, long follow-up, and central adjudication of outcomes. Weaknesses of the study included: possible inadequate ascertainment of all outcomes, lack of adherence to treatment regimen, high baseline intake of calcium and vitamin D (though diet and supplement use), and inadequate power, all of which may bias this study to the null.

Strengths of the Meier study [147] include randomization with description of baseline equivalence of groups. Weaknesses of this study include: lack of placebo-control and double blinding, unclear description of inclusion and exclusion criteria, no description of adherence, high rate of withdrawals, short supplementation time, and heterogeneity of a relatively small sample size of participants.

Hunter et al. [148] described inclusion/exclusion criteria, flow of patients, and baseline equivalence of patients well. Other strengths of the study included double blinding, placebo-control, and assessment of adherence. Small size of the study, nearly 20 percent withdrawal rate, and high baseline intake of calcium and vitamin D may have limited the power of the study.

Results.

Bone mineral density. The Papadimitropoulos review also analyzed BMD effects of vitamin D. Treatment with vitamin D_3 between 300 and 2000 IU/day caused only marginal positive effects of the vitamin D and calcium intervention (increases by about 1% in the femoral neck in year 5 and in the lumbar spine in year 1).

The WHI[146,] found a mean difference in total hip BMD of 0.59 percent ($p<.001$) at 3 years, 0.86 percent ($p<.001$) at 6 years, and 1.06 percent ($p=.01$) at 9 years between those treated with calcium and vitamin D and placebo group. There was no significant difference in BMD in the spine.

Hunter et al.[148] did not find any significant difference in spine or hip BMD between those treated with vitamin D alone and control.

Meier et al.[147] found calcium and vitamin D supplementation significantly increased lumbar BMD (+0.8%, $p=.04$) and femoral BMD (+0.1%, $p=.05$) compared to the previous year without any supplementation, which was significantly different ($p=0.03$ for lumbar spine, and $p=0.05$ for femoral bone) from the control group that had a decrease in lumbar and femoral BMD (Appendix F, Evidence Tables 3r and 3u)

Fractures. The review by Avenell et al. included data from primary prevention trials as well as secondary prevention trials. They reported that vitamin D alone did not prevent hip, vertebral, or any non-vertebral fractures, and that vitamin D (700-800 IU per day) plus calcium (1000 mg/day) reduced hip fractures (RR 0.81, 95% CI 0.68-0.96) and non-vertebral fractures (RR 0.87, 95% CI 0.78-0.97), but the combination was no more effective than calcium alone. There was no effect on vertebral fractures. Subgroup analysis indicated that the effects on hip and non-vetabral fracture were primarily reported from studies of the incidence of fracture (3 trials, n=4242; RR 0.75, 95% CI 0.62-0.91 for hip fracture; RR 0.83, 95% CI 0.72-0.95 for non-

vertabral fracture), but not recurrence of fracture (4 trials, n=6134; RR 1.02, 95% CI 0.71-1.47 for hip fracture; RR 0.93, 95% CI 0.79-1.10 for non-vertebral fracture). Another subgroup analysis showed that the effects on hip fracture were primarily reported from studies in institutionalized groups (2 trials, n=3853, RR 0.75, 95% CI 0.62-0.92), but not in community-dwelling groups (5 trials, n=6523, RR 1.01, 95% CI 0.70-1.44), whereas the effects on non-vertabral fracture were similar between the two types of populations (RR 0.85 and 0.89, respectively). Baseline mean serum 25-OH vitamin D levels (measured in 9 of the studies) were generally quite low (≤ 15 ng/mL), but levels after vitamin D supplementation were not available.

In the Papadimitropoulos review, fracture results were similar to those of Avenell et al. Comparable treatment regimens of vitamin D_3 and calcium were associated with a non-significant trend in reduction of non-vertebral fractures (RR 0.78, 95% CI 0.55 – 1.09). (Appendix F, Evidence Table 3r).

In contrast, both of the reviews by Bischoff-Ferrari et al. showed definitive positive effects of vitamin D_3, with or without calcium, on fracture reduction and prevention of falls. Analysis of all the fracture results revealed heterogeneity that was resolved by pooling studies into separate high-dose (700-800 IU/day) and low dose (≤ 400 IU/day) subgroups. Studies using the high-dose regimen showed reductions in the pooled relative risk of hip fracture (RR 0.74, 95% CI 0.61-0.88) and of non-vertebral fracture of (RR 0.83, 95% CI 0.70-0.98). In a similar analysis of the effect of vitamin D on falls, supplementation with 800 IU/day with or without calcium had a pooled odds ratio for prevention of falls of 0.78 (95% CI 0.64-0.92) (Appendix F, Evidence Table 3r).

Incidence of fractures was the primary outcome of interest in the WHI study.[146,] Intention-to-treat analysis found that calcium plus vitamin D supplementation did not significantly decrease the incidence of hip fracture (HR 0.88, 95% CI 0.72-1.08), clinical spine fracture (HR 0.90, 95% CI 0.74-1.10) and total fractures (HR 0.96, 95% CI 0.91-1.02) in the total trial participants. A subgroup analysis of women who took at least 80 percent of study medication showed a significant risk reduction in hip fracture (HR 0.71, 95% CI 0.52-0.97) (Appendix F, Evidence Table 3u).

Colorectal Cancer. A secondary outcome of the WHI trial was colorectal cancer.[152] Intention to treat analysis found that calcium plus vitamin D supplementation did not significantly decrease the incidence of invasive colorectal cancer (HR 1.08, 95% CI 0.86-1.34) (Appendix F, Evidence Table 3u).

Summary. The majority of published literature on calcium and vitamin D are studies in postmenopausal women. Review of this evidence supports improvement in BMD with calcium with or without vitamin D supplementation for postmenopausal women. The evidence also indicates that calcium supplementation was associated with a non-significant trend toward decreasing the risk of vertebral fractures. The greatest benefit of calcium supplementation was found to occur in the first year of use. There is a paucity of data on the effect of vitamin D alone on BMD. Vitamin D combined with calcium prevented hip fracture and non-vertebral fracture with the greatest benefit seen in populations with a low baseline intake of calcium and/or vitamin D. A high dose of vitamin D (700-800 IU per day) with or without calcium prevented hip fracture, non-vertebral fracture and falls. Taking into consideration the quantity, quality, and consistency of evidence on the efficacy of vitamin D and calcium, we concluded that the overall strength of evidence is “low" for calcium to prevent loss in BMD, vitamin D to prevent loss in BMD, and for vitamin D to prevent fractures, "very low" for calcium to prevent fractures, and

"high" for combined calcium and vitamin D to prevent BMD loss, hip fracture or non-vertebral fracture (Table 6).

Key Question 4

What is Known about the Safety of Use of the Following Single Nutrients in the General Population of Adults and Children, Based Primarily on Data From Randomized Controlled Trials and Observational Studies?

Calcium and vitamin D

In a recent Cochrane review,[48] it was concluded that studies are too different (exposure time, doses, etc) to draw general conclusions regarding the safety of calcium supplements. A case report of nephropathy with calcified lesions in a patient consuming 1g/day of calcium lactate appears to be the result of the combined use of high dose ascorbic acid (6,000mg/day) plus laxatives that led to chronic hypokalemia.[79]

The calcium-vitamin D arm of the WHI study [146] administered 1g of calcium carbonate and 400 IU of vitamin D daily to 18,000 postmenopausal women for 7 years. The study reported an increased risk for kidney stones in the active group (HR 1.17). No other significant differences among the study groups were observed, including gastrointestinal symptoms.

Long-term consumption of 1g or more per day of calcium may increase risk of kidney stones. It is not clear whether this finding can be generalized to premenopausal women or to men.

Vitamin A

Randomized controlled trials

A number of studies compared retinol or β-carotene supplementation with placebo. The CARET trial in smokers [93] administered 25,000 IU per day of vitamin A and 30 mg per day of beta-carotene for 5 years, and reported no adverse effects other than yellowing of the skin in 0.3 percent of people in the active group. In this study,[153] the active group also exhibited a modest but significant rise in serum triglycerides. This increase remained stable after the first year of follow up, i.e., it was non-progressive (Appendix F, Evidence Tables 4a-4d).

Another study in healthy adults aged 18-54 years[77] compared the effects of 15,000 IU per day of vitamin A (4500 RE) with a group receiving only 75 IU per day, for 5 years. The only relevant finding was an increase in serum triglycerides in the high-dose group, from 1.0 at baseline to 1.30 at year 3 and 1.18 at year 5. There was no effect on liver enzymes, and no increase above defined maximal plasma retinol levels (3.49 μmol/L) (Appendix F, Evidence Tables 4a-4d).

Observational studies

The possibility that high intakes of retinol increase the risk of hip fractures, particularly in postmenopausal women, has been raised by one observational study that tracked 35 77-year-old women for 18 years. [154] This study reported an increased risk of hip fractures in persons at the higher quartile of total retinol intake. However, there was no significant difference in fracture risk between users and non-users of multivitamin or vitamin A supplements. These provided around 25 percent of the total daily retinol intake, or around 400-500μg RE/day. There was no

association between hip fractures and β-carotene intake, either total, from foods, or from supplements.

Another, 9-year observational study in 34,000 postmenopausal women found no significant correlation between food or supplemental retinol intake and hip or all-type fractures.[155]

Cross-sectional studies

A cross-sectional study in 178 Swedish women[156] reported a significant negative correlation between dietary retinol intake and BMD. The authors attributed this finding to the very high retinol intake in Nordic countries, associated with the common use of cod liver oil and the fortification of milk with vitamin A. The potential contribution of vitamin supplements was not reported in this study. Another more recent cross-sectional assessment of 11,000 women enrolled in the WHI cohort [157] found no correlation between diet-only or total retinol intake and BMD. Blood retinol levels, measured in a subsample, were not correlated with BMD either. Similarly, an analysis of data from the NHANES III survey found no correlation between serum retinyl ester concentrations and BMD.[158]

In terms of the possible effects of total daily vitamin intake, a conservative interpretation of the limited human data may be warranted, because of the biological plausibility of a negative effect of excess vitamin A on bone. However, the data specifically linking vitamin A supplements or multivitamins containing retinol to fracture risk are very limited and insufficient to draw a definitive conclusion at this time.

Vitamin E

The VECAT study administered 500 IU of vitamin E per day to 1200 volunteers (50-88 years of age) for 4 years. [113] No difference in adverse events or mortality was identified between active and placebo groups.

Another study administered vitamin E to healthy adults, but is not discussed here because of its low sample size (n=42 total, divided in 4 arms), short follow up (6 weeks), and lack of outcome data relevant to this report.

In the WHS,[87] participants received 600 IU of vitamin E every other day. No excess adverse effects were identified in the active group, except for marginally significant increased epistaxis. Authors attributed this to a chance finding, since there was no other evidence of an adverse effect on bleeding (coagulation time, hemorrhage, hemorrhagic stroke, etc). The PPP study[112] administered 300 mg/d for 3.6 years, to people more than 65 yrs of age. Only bleeding and mortality were monitored, and no significant differences in these outcomes were found between active and control groups (Appendix F, Evidence Tables 4e-4g).

β-carotene

The beta-carotene arm of the WHI study [96] administered 50 mg/day of beta-carotene to about 20,000 women for 2 years. The only adverse effect associated with treatment was yellowing of the skin.

Another randomized controlled trial [84] followed about 400 adults for 4 years, administering 30 mg/day of beta-carotene or placebo. This study did not report specific events associated with the beta-carotene arm, but the number of withdrawals associated with self-reported adverse effects of the supplement was 65 in the active group and 64 in the placebo group.

The PHS administered 50 mg of beta-carotene on alternate days to about 11,000 participants for almost 12 years. The only significant adverse effects reported were yellowing of the skin (1700 in active vs. 1500 in placebo) and minor gastrointestinal symptoms, such as belching (275 in active vs. 124 in placebo) (Appendix F, Evidence Tables 4a-4d).

Selenium

One randomized controlled trial administered 200 µg/day of selenium for 4.5 years to 1300 patients with a history of skin cancer. [133] More participants complained of gastrointestinal symptoms in the active group than in the placebo group (21 vs. 14). There were no differences in plasma selenium levels between those reporting symptoms and those who did not (Appendix F, Evidence Tables 4h-4j).

Iron

The possible adverse effect of iron supplementation in healthy children is an issue receiving intense scrutiny at this time. An early report from a small randomized trial in 40 iron-sufficient, non-anemic children showed a significant reduction in weight gain over 4 months in supplemented (3mg/kg/day) children compared to placebo [159]. More recent trials have not fully clarified this issue, because they targeted deficient populations and/or included other micronutrients in the intervention formulation (Appendix F, Evidence Tables 4h-4j).

Chapter 4. Discussion

The biological effects of vitamins and minerals have sparked enormous scientific enthusiasm in examining their potential as agents for preventing a variety of chronic diseases and conditions. Over the past four decades, there have been more than 355,000 peer-reviewed articles addressing one or more of the nutrients that often are included in multivitamin/mineral supplements. The evidence accumulated to date primarily concerns vitamin/mineral supplement use in relation to the prevention of cancer, cardiovascular disease, and bone health, and less frequently, eye disease and cognitive function. In this context, the nutrients that have been studied the most include multivitamins, β-carotene, vitamin E, folic acid/vitamin B6/vitamin B12, calcium, vitamin D, and to a lesser extent, selenium.

In 2003, the United States Preventive Services Task Force released a report concluding that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease. The Task Force also concluded that β-carotene supplementation provides no benefit in the prevention of cancer or cardiovascular disease in middle-aged and older adults.[160] In addition to providing an update on the available evidence, this evidence report goes beyond the scope of the United States Preventive Services Task Force review to have included systematic reviews and original studies on the efficacy of multivitamin/mineral supplement use in the prevention of chronic diseases and conditions, in addition to cancer and cardiovascular disease, in the general adult population, and on the safety of multivitamin/mineral supplements, vitamin A, vitamin D with or without calcium, vitamin E, folic acid, β-carotene, selenium, and iron supplementation in the general population of adults and children.

Summary of the Key Findings

Results from this systematic review indicate a relative paucity of data that specifically address the efficacy of multivitamin/mineral supplement use in the prevention of chronic disease in the general population of the United States. The data were on the efficacy of designed combinations of vitamins and minerals; none of the trials used the one-a-day multivitamins (of approximately 100% of the RDAs) prevailing on the market. The Linxian trial suggests that supplementation with combined β-carotene, vitamin E and selenium supplements at doses 1 to 2 times the RDA for 5 years had 13 percent to 21 percent reductions in gastric cancer incidence, gastric cancer mortality, and total cancer mortality in a nutritionally deprived Chinese population. The reduction in cancer mortality was stronger in women than in men, and in persons of age 55 or younger. There were no significant effects on total cancer incidence and cerebrovascular mortality. The SU.VI.MAX study in a French population documented a 31 percent reduction in overall cancer risk by use of 5 antioxidants (vitamin C, vitamin E, β-carotene, selenium, and zinc) for 8 years in men but not in women, and a 12 percent reduction in prostate cancer risk, particularly a 48 percent risk reduction in those with normal prostate specific antigen levels at baseline. There was no significant effect of the combined antioxidants on ischemic cardiovascular disease incidence. In this trial, men had lower serum levels of vitamin C and β-carotene than women at baseline. Multivitamin/mineral supplement use for 3 to 6 years had no significant benefits in preventing cataract in 3 trials in the United States (with one trial also in United Kindom) and the Linxian trial. High-dose zinc combined with antioxidants had beneficial effects on age-related macular degeneration only in those with intermediate age-

related macular degeneration in one or both eyes, or those with advanced age-related macular degeneration in one eye.

Overall, total mortality data pointed to either no increased risk or lower risk in the groups with multivitamin/mineral supplement use. Total mortality was 9 percent lower among those who received β-carotene, selenium, and vitamin E in the Linxian trial; there was no sex- or age-difference in the relative risks. In the AREDS study, total mortality was 6 percent higher in the group receiving antioxidants compared to the group receiving no antioxidants, but the increase was not statistically significant. Among the participants at high risk for age-related macular degeneration, total mortality was 13 percent to 20 percent lower in the groups receiving zinc alone or zinc combined with antioxidants.[64,75] In the SU.VI.MAX study, a sex-difference was documented for the relative risk of total mortality among those receiving antioxidants and zinc compared to those receiving placebo. In the REACT, total mortality rate was not calculated. Nine deaths occurred in the antioxidant group, whereas 3 deaths occurred in the placebo group. The deaths in the antioxidant group were caused by esophagitis, sudden death, aneurysm, pulmonary fibrosis, cancer, and coronary thrombosis.

Daily supplementation with β-carotene of 20 mg, 30 mg or 50 mg was not protective against malignancies, cardiovascular disease outcomes, diabetes mellitus, cataract or age-related maculopathy. Supplementation with β-carotene with or without vitamin A increased the incidence of lung cancer in persons with asbestos exposure or in cigarette smokers, and was associated with increased mortality in some trials. To date, there has been no randomized controlled trial that assessed the efficacy of vitamin A alone in preventing chronic disease. Studies in selected populations (nutritionally inadequate, asbestos exposure, or smokers) showed no benefit of combinations of vitamin A and zinc or vitamin A and β-carotene for the prevention of stroke mortality, esophageal or gastric cancer incidence, or cardiovascular or all-cause mortality.

Vitamin E supplements (synthetic α-tocopherol 50 mg or 300 IU per day, or natural source, 600 IU per day) have been studied for primary prevention of cancer, cardiovascular disease, cataract, and age-related eye disease. The evidence predominantly comes from the ATBC and WHS studies.[68,87,90,96,98-100,107] There was a lack of effects of vitamin E in the prevention of these diseases, except for a 32 percent reduction in prostate cancer incidence, a 41 percent reduction in the prostate cancer mortality, and a 22 percent reduction in colorectal cancer in heavy smokers in the ATBC, and decreased cardiovascular deaths (primarily sudden death) in the WHS participants, particularly in those aged 65 years or older. The findings on hemorrhagic stroke were conflicting between the ATBC trial and the WHS; the former found a higher risk with use of low-dose α-tocopherol supplements but the latter found a lower risk with use at a high dose.

Two previous systematic reviews reported that supplementation with folic acid at daily doses of 0.75 mg or 30 mg, alone or in combination with vitamin B12 and/or vitamin B6 for 5-12 weeks, had no significant effects on cognitive function in 5 small randomized controlled trials. Combined vitamin B2 and niacin supplement use for 5 years had no significant effects on cerebrovascular mortality, total mortality, total cancer incidence, and esophageal or gastric dysplasia/cancer incidence and esophageal or gastric cancer mortality in a poorly nourished population in China.

In a study in persons with a history of non-melanoma skin cancer, supplementation with selenium of 200 mcg per day had no effect on cardiovascular outcomes, but had protective effects on total mortality and incidence of lung, colorectal, and prostate cancers. Another study

in China found a significantly reduced risk for liver cancer in those who used selenium supplements of 200 mcg/day for two years.

Due to the substantial amount of efficacy data on calcium/vitamin D and osteoporosis, we reviewed systematic review articles supplemented with data from recent randomized controlled trials and data from randomized controlled trials meeting our inclusion criteria that were not included in previous systematic reviews. The previous reviews reported that supplementation with calcium has short-term (particularly within one year) benefit on retaining bone mineral density in postmenopausal women, and a possible effect in preventing vertebral fractures. The reviews also indicated that combined vitamin D_3 (700-800 IU/day) and calcium (1000 mg/day) may reduce the risk of hip and other non-vertebral fractures in populations with low levels of vitamin D and/or calcium. Recent published data from the WHI trial were consistent with these systematic reviews in showing a 1.06 percent higher hip bone density ($p<.02$) and a 12 percent non-significant lower risk for hip fracture in postmenopausal women after receiving calcium carbonate (500 mg twice a day) and vitamin D_3 (200 IU twice a day) for an average of 7 years as compared to women receiving a placebo. In this trial, participants were allowed to have self-selected use of multivitamin supplement as well as calcium and vitamin D supplements up to 1000 mg and 600 IU per day, respectively, and thus had a baseline average daily intake of 1150 mg calcium and 365 IU vitamin D. Hence, the WHI participants had higher intake of calcium than the general population (761 mg per day). The WHI trial found no benefit of calcium and vitamin D supplementation in preventing colorectal cancer incidence.

For evidence on the safety of multivitamin/mineral supplements when used for the purpose of preventing chronic disease, we identified 10 studies using multivitamin/mineral preparations and 24 studies using single nutrients for primary prevention of chronic disease. Doses were usually 2 to 10 times the RDA. Overall, we found no consistent pattern of increased adverse effects in the active group compared with the placebo group, with the exception of changes in skin color, which was common in studies in which beta-carotene was part of the multivitamin preparation.

Supplementation with β-carotene with or without vitamin A also increased the incidence of lung cancer in persons with asbestos exposure or in heavy smokers, and was associated with increased mortality. Vitamin A supplementation may moderately increase serum triglyceride levels. Calcium supplementation increased the risk of kidney stones. Vitamin E supplementation was associated with an increased incidence of epistaxis but was not associated with an increased risk of more serious bleeding events, such as hemorrhagic stroke. Iron supplementation was found to reduce weight gain in iron-sufficient, non-anemic children in a small randomized controlled trial. But more recent trials have not fully clarified this issue, because they targeted deficient populations and/or included other micronutrients in the intervention formulation.

Efficacy of Multivitamin/mineral Supplements

Between the Linxian trial and the SU.VI.MAX trial, the types of vitamin/mineral supplements overlapped and the doses were similar. The efficacy was somewhat different, but had similar implications. [64,68-70,111,161,162] While the multivitamin/mineral supplements used in the Linxian trial reduced cancer mortality by 21 percent in women and by 7 percent in men, the efficacy of the multivitamin/mineral supplementation in the SU.VI.MAX in reducing cancer incidence was only evident in men. This sex-dependent efficacy may be accounted for by the different nutritional status of the study populations, i.e., generally poor nutritional status in the

Linxian population and the suboptimal antioxidant status in men compared with women in the SU.VI.MAX.[69] These findings also corroborated observational studies that suggest benefits of fruits and vegetables on cancer prevention. However, they did not suggest that supplementation with multivitamins and minerals can replace a balanced, healthful diet to achieve an optimal health state because these studies were not designed to address that question. In view of the inadequate nutritional intake in the Linxian population and the "French paradox," the generalizability of the findings from the SU.VI.MAX and Linxian trials to the United States population is uncertain.

For cataract prevention, AREDS was the largest trial with findings internally consistent in showing no benefits of multivitamin/mineral supplement use. While the REACT found a deceleration in cataract progression in the United States study site, similar benefits were not seen in the United Kingdom study site. For the prevention of age-related macular degeneration, the AREDS study found benefits of high-dose (10 times RDA) zinc alone or in combination with antioxidants in persons with intermediate age-related macular degeneration in one or both eyes, or persons with advanced age-related macular degeneration in one eye. The MONMD study was conducted in persons with advanced dry age-related macular degeneration. The study suffered from missing data and unclear data analysis and presentation, but the authors concluded that the antioxidant supplements used in the study stabilized but did not improve dry age-related macular degeneration. It appears that benefits of multivitamin/mineral supplements in the prevention/management of age-related macular degeneration were limited to persons with moderate or advanced age-related macular degeneration. However, such inference was based on findings from two trials (n=3,580) with one that was very small (n=71).

With multivitamin/mineral supplements in wide use by the general public in the United States, particularly middle-aged or older individuals, it would be difficult now to recruit trial participants for the conduct of large-scale randomized placebo-controlled trials to determine the efficacy of multivitamin supplementation in chronic disease prevention. In the AREDS, 55 percent of study participants had used some vitamins/minerals before enrollment, and consequently, the study investigators provided a free brand name multivitamin to 66 percent of the study participants. Because many nutrients share common mechanisms of action, self-selected supplement use may attenuate the net efficacy, if any, of the nutritional supplements under investigation. This conjecture is supported by the findings that 40 percent of the WHS participants had multivitamin/mineral supplement use in addition to study supplements, and when limited to non-multivitamin supplement users, the relative risk of major cardiovascular disease was 0.88 (95% CI 0.75-1.03), in contrast to a relative risk of 1.02 (95% CI 0.84-1.25) among multivitamin supplement users.[87] We have found that very few studies reported participants' self-selected supplement use, and most studies allowed use of supplements that were not under investigation. This limitation was rarely addressed in the literature.

Efficacy of β-carotene

Much research interest has been devoted to elucidating how β-carotene may increase lung cancer risk in high-risk individuals. "Antioxidants" have been assumed to exert in vivo anti-oxidative effects, based on in vitro observations. In fact, the oxidative propensity of a purported "antioxidant" depends at least on the concentrations, the redox potential of the molecule, and the biological environment the molecule is in (e.g., the oxygen tension and the existence of other oxidants/antioxidants). For example, carotenoids may inhibit or enhance apoptosis depending on

their concentration, concerted action of other oxidants/antioxidants, cell type, and redox status.[163] At low oxygen tension, β-carotene may act as an antioxidant, while at high oxygen tension, it may behave as a pro-oxidant,[164] although a pro-oxidant effect was not corroborated by an in vitro experiment on human bronchial epithelial cells.[165] While β-carotene has a pivotal role in preventing vitamin A deficiency, the general lack of benefits from β-carotene supplementation and its potential harms in increasing lung cancer risk among high-risk individuals argue against supplementation with β-carotene alone for chronic disease prevention in the general population.

Efficacy of Vitamin E

In addition to β-carotene, vitamin E is the most extensively studied single nutrient as a chemopreventive agent. Several systematic review articles on vitamin E were identified in our literature search.[114,166-169] However, in the majority of the previous reviews, primary prevention trials were not separated from secondary prevention trials,[166,114,168] and when aggregate efficacy was calculated, the efficacy of a single nutrient in one intervention arm was not separated from the efficacy of multiple nutrients in one intervention arm.[166,114,168] A systematic review can give misleading results for the efficacy of a single nutrient by including data from trials of multiple nutrients in an intervention arm (which is a multivitamin/mineral intervention). This argument is based on the rationale that several nutrients share common mechanisms of action, that nutrient-nutrient interaction may exist, and that the efficacy of an individual nutrient cannot be determined in a trial that includes multiple nutrients in an intervention arm. This argument is also substantiated by a systematic review in which the aggregate effect of vitamin E alone on cardiovascular death, fatal myocardial infarction, non-fatal myocardial infarction was consistently in the protective direction (RR 0.96, 0.97, and 0.72, respectively), but the RR was 1.03, 1.02, and 0.99 respectively when efficacy was calculated for vitamin E in combination with other nutrient(s).[114]

The general lack of benefits of vitamin E in the primary and secondary prevention of cancer, cardiovascular disease, cataract, and age-related macular degeneration was unexpected in view of the substantial evidence from experiments, animal studies and epidemiologic studies that showed great promise of vitamin E. Natural vitamin E has eight forms, α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, δ-tocotrienols. Supplements of RRR-α-tocopherol, that is not naturally occurring, but derived from methylating γ-tocopherol in vegetable oil, are often commercially labeled as "natural source" vitamin E (as used in the WHS[87]).[96] It has been shown that high intake of α-tocopherol may enhance the metabolism of other forms of vitamin E.[170-171] Because γ-tocopherol is the predominant (70%) vitamin E in the typical American diet,[172] and because γ-tocopherol and its metabolite may have biological effects,[173,174] it has been hypothesized that reductions in circulating γ-tocopherol levels by α-tocopherol supplementation may compromise the efficacy of α-tocopherol, if any.[175] In the present review, we found that many trials that used vitamin E did not report the chemical forms. Presumably, all trials used some esters of α-tocopherol because α-tocopherol was the center of research attention in the past, and γ-tocopherol or mixed tocopherols were only available on the market in recent years.

Based on data from the PPP and WHS, neither synthetic α-tocopherol of 300 IU per day for a short term, 3.6 years, nor natural source α-tocopherol of 600 IU every other day for a long-term, 10 years, had beneficial effects in the primary prevention of cardiovascular outcomes.[87,112] One intriguing finding from the WHS was the significantly lower risk of cardiovascular death (primarily sudden death), which might have been due to chance alone.[87]

Prompted by the findings from the ATBC trial and the NCP trial on the reduced risk for prostate cancer,[101,133] the National Cancer Institute has launched the Selenium and Vitamin E Cancer Prevention Trial (SELECT) to test for the efficacy of daily use of α-tocopherol supplements in the primary prevention of prostate cancer in 32,400 men. The SELECT trial uses synthetic α-tocopherol of a high dose, 400 IU, and will be closed out in 2013.[176]

Vitamin/mineral Supplement Use and Total Mortality

The implications of the impact of vitamin/mineral supplement use on total mortality are uncertain. Total mortality is relevant to the context of chronic disease prevention because it may provide a clue to potential harms and can be considered as a reference outcome in risk/benefit analysis. However, because two of the causality criteria cannot be applied to death outcome (i.e., response to re-challenge and response to discontinuation of use), the risk for death should be considered based on plausible biological mechanisms and the evidence on the effects of the nutrients on specific disorders. With this rationale along with the consideration on the great heterogeneity in the study design (i.e., factorial design vs. parallel-arm design), doses of supplements, duration of supplement use, and characteristics of study participants, we did not attempt to calculate an aggregate estimate for total mortality for the trials that reported such data. Instead, we examined the causes of death that might have accounted for the difference in total mortality between randomized groups.

The 9 percent reduced risk of total mortality by multivitamins/minerals in the Linxian trial was likely to be driven by the reduction in stomach cancer mortality. Similarly, reduced total mortality in men in the SU.VI.MAX may reflect the 31 percent reduction in cancer incidence.

The higher total mortality by β-carotene supplementation during the conduct of ATBC trial was primarily due to lung cancer and cardiovascular disease, whereas the higher total mortality in the first 4 years of post-trial follow up was primarily due to a wide spectrum of cardiovascular diseases.[103] How β-carotene increased the risk of cardiovascular mortality remains unclear.

A contentious issue regarding vitamin E supplementation is its impact on total mortality. The issue was set off by a recent meta-analysis from which an excess of 39 deaths per 10,000 persons was reported (95% CI 3 to 74 per 10,000) for trials using vitamin E at doses greater than or equal to 400 IU per day.[168] In contrast, mortality was reduced (risk difference was –16 per 10,000 (–40 to 10 per 10,000) for trials using lower doses (less than 400 IU per day).[168] This meta-analysis had the shortcoming in combining 9 primary prevention trials and 10 secondary prevention trials, and combining data from 9 trials using vitamin E alone and data from 10 trials using vitamin E combined with other nutrients, including β-carotene which has been linked with an increased risk for total mortality. Furthermore, most trials that used high doses were secondary prevention trials in persons with various types of diseases and medication use.

In the present review on vitamin E supplement use for primary prevention, the ATBC and the WHS participants comprised 87 percent of the study populations. In the ATBC trial, a 2 percent increased risk of total mortality was observed at the end of the supplementation period, but a 4 percent risk "reduction" was observed in the next 3 years, followed by a 5 percent increase for the next 3 years and 0 percent for the next 2 years.[103] The overall relative risk of total mortality during the 8 years of post-trial follow up was 1.01 (95% CI 0.96 to 1.05) and there was no difference in the relative risk of mortality throughout the post-trial follow up period.[103] These findings suggest no late effects of α-tocopherol supplementation on risk of death in heavy smokers. In the WHS,[87] the authors reported that "the main causes of death, apart from

cardiovascular and cancer deaths, were pulmonary diseases (32 vitamin E, 22 placebo) and violent deaths, excluding suicide (9 vs. 6). None of these causes of deaths was significantly related to vitamin E." The relative risk of cardiovascular death and cancer death in the WHS was 0.76 (95% CI 0.59-9.98) and 1.12 (95% CI 0.95-1.32), respectively.[87] The VECAT documented 31 deaths (20 in vitamin E; 11 in placebo), and the authors reported that "no consistent or unusual patterns were identified among the specific causes of death recorded."[113] In view of these data along with consideration of biological plausibility, we find no convincing evidence to suggest vitamin E supplement use increases risk of death per se.

Timing and Duration of Supplement Use

Timing and duration of supplement use is an important determinant of the efficacy. However, these issues have rarely been addressed in the literature and little is known about the optimal time to start and stop supplementation. For the reasons of feasibility and resource constraints, most randomized controlled trials have had a follow up period of approximately 5 years, and some followed for only 2 years, while a chronic disease may take 10 to 20 years to develop.

In the ATBC and CARET studies, lung cancer risk was increased by β-carotene alone or by combined β-carotene and retinol over 5 to 10 years of supplementation among heavy smokers and persons regularly exposed to asbestos, suggesting that the supplementation regimens might have accelerated the progression of carcinogenesis in these high-risk groups.

The CARET study reported a late effect of β-carotene supplementation on lung cancer.[94] The ATBC trial observed a late effect on colorectal cancer, but not lung cancer.[103] These post-trial follow up data may provide some clues to how likely the link between β-carotene supplementation and increased lung cancer incidence was causal, and how the effects may vary with carcinogenesis processes, but the data may also be simply due to chance alone or be subject to confounding by trial participants' changes in supplement use after the closeout of the trial.

An intriguing finding from the WHS study was that a significantly lower risk of major cardiovascular events was limited to women aged 65 or older who received vitamin E supplements for 10 years (RR 0.74).[87] This finding is not congruent with the oxidative hypothesis stating that oxidative damage occurs early in the atherosclerosis process,[177] nor with the data that showed that early atherosclerotic lesions occurred in adolescents.[178,179] In the Linxian trial with 5 years of follow up, benefits of α-tocopherol, selenium and β-carotene on cancer mortality, cardiovascular mortality and total mortality were more evident in those aged less than 55 years.[67] The SU.VI.MAX trial found a protective effect of antioxidants on prostate cancer incidence among men who had normal prostate specific antigen levels, but not in men who had elevated prostate specific antigen levels after 8 years of follow up.[70] The benefit on prostate cancer by β-carotene supplement use in the ATBC trial was limited to clinical prostate cancer but not for latent cancer.[101] If cancer development takes more than 10 years to develop, these data would seem to have provided paradoxical information on whether antioxidant supplements should be used earlier or later in the life span, let alone whether different chemopreventive agents may act differently along the carcinogenesis process. Additional data from subgroup analyses from trial enrollment to diagnosis with adjustment for potential confounding variables such as age in other completed or on-going trials are needed before a clear picture can be seen.

Doses of Vitamin/mineral Supplements

The RDA is the average daily dietary intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) apparently healthy individuals in a particular age and gender group. There is a wide range of doses of vitamins and minerals formulated into over-the-counter supplements. The "one-a-day" type of multivitamins/mineral supplements may contain nutrients of 100% to 300% of the RDAs for adults. The doses of B vitamins in other multivitamin preparations are high; usually 1667% of the RDAs, and up to 6000% of the RDAs. For vitamin E, commonly used doses in individual vitamin E or multivitamin supplements are 100, 200, 400, and 800 IU which, if of natural form, correspond to 333%, 667%, 1332% and 2640% of the RDA for vitamin E. For vitamin C, commonly used doses in individual vitamin C supplements or multivitamin supplements are 250 mg, 500 mg, and 1000 mg, which correspond to approximately 417%, 833%, and 1667% of the RDA for vitamin C.

In this review, only two trials of multivitamin/minerals supplements reported data on cancer and cardiovascular outcomes and the benefits on these outcomes were implicated in those who had inadequate nutrient intake. The active supplements (combined vitamin E, selenium, and β-carotene; combined vitamin E, selenium, β-carotene, vitamin C and zinc) in these two trials were of doses around 100%-200% of the RDAs. Hence, the efficacy of lower or higher doses of the nutrients was not known. With respect to prevention of age-related macular degeneration, the AREDS study used a high dose of vitamin E (400 IU) and zinc (2 times the UL), and the benefit on preventing the progression to advanced age-related macular degeneration appeared to have come primarily from the groups receiving zinc. In this study, of nearly 100 comparisons, a few adverse effects occurred more often in participants receiving zinc as compared to participants receiving no zinc, including more difficulties in swallowing the pill (17.8% vs. 15.3%), more hospitalizations due to genitourinary problems (7.5% vs. 4.9%), more "adverse circulatory experiences" (0.9% vs. 0.3%) and more anemic individuals (13.2% vs. 10.2%).

In the WHI study, participants were allowed to have self-selected use of multivitamin supplements, as well as calcium and vitamin D supplements up to 1000 mg and 600 IU per day, respectively. Hence, the WHI participants had a baseline average daily intake of 1150 mg calcium and 365 IU vitamin D. If women randomized to the calcium supplementation group also used their own calcium supplements and multivitamin supplements that contained calcium, a daily total intake could have approached the UL, 2500 mg, and led to a higher risk for adverse effects such as kidney stone formation.

Safety Consideration

As noted previously, the potential adverse effects of multivitamin or single-nutrient supplements have not been systematically studied in well-controlled trials. Because of the uncertainties regarding design (exposure, doses, etc.) and the ethical constraints, such studies may never be carried out. Our assessment of the safety of supplements, therefore, must rely on the safety monitoring during randomized controlled trials and on case reports and other observational data.

Since the ULs were defined based on limited data or extrapolations, and generally were based on one single indicator of adverse effects, it is not surprising that several trials reported no adverse effects after consumption of doses above the UL. These studies may have used indicators other than those used to define the UL for that nutrient, or may have had only slight

increases in an adverse effect that was not significantly different from the placebo group. A few adverse effects, because they appear with certain consistency in different trials, may be interpreted as common responses in the general population. For example, yellowing of the skin with sustained consumption of β-carotene at daily doses of 8 mg or higher has been described in most studies using this nutrient. Similarly, increases in serum triglycerides with vitamin A supplementation have been reported in several studies. Minor bleeding, particularly epistaxis, also appears to be a relatively common effect of vitamin E supplementation. But as noted above, there is no evidence that this vitamin results in an increased risk of more serious bleeding events, such as hemorrhagic stroke.

A general conclusion, with the caveats mentioned regarding the limited data available, is that consumption of multivitamin supplements for prolonged periods (1 to 8 years) appears to be safe. We found no reports of major, life-threatening adverse effects, and no evidence of increased mortality in groups consuming multivitamin supplements. A similar general conclusion can be reached for single-nutrient supplements. However, the late effects of β-carotene on cardiovascular death in heavy smokers deserve further investigation for the underlying mechanisms. In addition, some studies confirmed the adverse effects used to define the UL, as for example, gastrointestinal symptoms and/or diarrhea with vitamin C. While the UL for this nutrient was set at 2 g per day, some studies have reported these symptoms with doses of 750 mg per day. It is recognized that the ULs represent a probability of an adverse event in the general population, and that that probability (and therefore the UL threshold) may vary across subgroups and in different circumstances.

Limitations

An enormous volume of literature exists on the effects of multivitamin/mineral supplements when seeking to include the literature on all of the single nutrients that are often included in multivitamin supplements. To find the most relevant literature on our questions, we had to design a search strategy that sacrificed some degree of sensitivity in order to have reasonable specificity. Thus, it is possible that the search strategy missed some studies that have potentially relevant data. We tried to minimize this problem by performing hand searching of the references in key articles and reviews, and by asking our peer reviewers to identify any important studies that were missing in the draft report. Clinical experts may question the efficiency of our systematic approach to searching the massive volume of literature on multivitamin/mineral supplements, but we were concerned about the risk of bias in selecting articles for inclusion in the review if we had relied only on experts for identifying eligible studies.

In addition, for our review of evidence on the efficacy of multivitamin/mineral supplements in preventing chronic disease, we focused on randomized controlled trials as the strongest source of evidence. We also focused on primary prevention studies because they are the ones most relevant to use of multivitamins in the general population of healthy adults. Although we focused on randomized controlled trials only for efficacy data, we included observational studies in our consideration of the safety of multivitamins/mineral supplements.

Many of the studies had important methodologic limitations. One particularly important limitation is that study groups often were permitted to use vitamin/mineral supplements other than the assigned study interventions. Such leeway would have attenuated the observed efficacy of study supplements. In addition, most studies did not provide information on trial participants'

characteristics, such as medication use, that may have modified the effects of the nutrients of interest.

There is marked heterogeneity of the literature on our key questions, with differences in study design (e.g., some of the trials used a factorial design), targeted study population (with different cultural/lifestyle and genetic backgrounds), chemical forms and doses of supplements, and specific outcome measures. This degree of heterogeneity makes it difficult to synthesize results across studies, and generally makes it inappropriate to perform quantitative synthesis (i.e., meta-analysis). The differences in study populations are particularly problematic because few studies have examined the efficacy of multivitamin/mineral supplements in the general United States population, making it difficult to determine whether the results of studies in other countries such as China and France can be applied to the United States population.

There has been inconsistent reporting on the potential adverse effects of the nutrients of interest. A significant proportion of data in the literature concerning adverse events came from case reports that are subject to serious methodological limitations. As a result, the overall strength of the evidence on adverse effects is weak. In addition, the implications of data from case reports are uncertain. In a previous systematic review of case reports of adverse effects of drugs, it was found that 83 percent of suspected adverse reactions were not further evaluated in confirmatory studies, and adverse effect alerts were not systematically incorporated into published drug reference information.[140]

Conclusions

Limited evidence accumulated to date suggests potential benefits of multivitamin/mineral supplements in the primary prevention of cancer in individuals with poor nutritional status or suboptimal antioxidant intake. However, the heterogeneity in the study populations upon which this evidence is based limits generalization to the United States population. The evidence also indicates that multivitamin/mineral supplement use does not have significant effects in the primary prevention of cardiovascular disease and cataract, but may confer benefits to slow the progression of age-related macular degeneration among persons at high risk for developing advanced stages of the disease.

We also conclude that regular supplementation with a single nutrient or a mixture of nutrients for years has no significant benefits in the primary prevention of cancer, cardiovascular disease, cataract, age-related macular degeneration or cognitive decline. A few exceptions, that were reported in a single or a few trials, included a decreased incidence of prostate cancer with use of synthetic α-tocopherol (50 mg per day) in smokers, a decreased progression of age-related macular degeneration with high doses of zinc alone or zinc in combination with antioxidants in persons at high risk for developing advanced stages of the disease, and a decreased incidence of cancer with use of selenium (200 mcg per day). Supplementation with calcium has short-term (particularly within one year) benefit on retaining bone mineral density in postmenopausal women, and a possible effect in preventing vertebral fractures. Combined vitamin D_3 (700-800 IU/day) and calcium (1000 mg/day) may reduce the risk of hip and other non-vertebral fractures in individuals with low levels of intake. Supplementation with β-carotene increased lung cancer risk in persons with asbestos exposure or cigarette smoking.

The overall quality and quantity of the literature on the safety of multivitamin/mineral supplements is limited. Available data suggest multivitamin/mineral supplement use for 1 to 8 years is safe. Among the adverse effects reported in randomized controlled trials, a prominent

one is yellowing of the skin among β-carotene supplementation. Vitamin A supplementation may moderately increase serum triglyceride levels. Calcium supplementation may increase the risk of kidney stones. Vitamin E supplementation was associated with an increased incidence of epistaxis but was not associated with an increased risk of more serious bleeding events.

Future Research

In vitro studies and animal models have helped us to understand the function of nutrients under a controlled environment. However, these types of studies often have over-simplified the sophistication of the human body. There is a gap in our knowledge of how specific nutrients work in vivo to prevent disease. Future research should be directed toward filling the gap by developing valid in vivo biomarkers and applying them in the settings of randomized controlled trials to examine how nutrients influence the body's physiological function and pathological processes, and how nutrients work in concert to do so. Identifying an optimal dose in dose-response studies is critical to guide the design of future large-scale randomized controlled trials when the conduct of the trials is considered worthwhile.

Nutritional research has adopted a reductionist approach that emphasizes the role of individual nutrients in physiologic function or disease process. In view of the complex pathological processes of chronic diseases, the idea of using a single nutrient or a few nutrients to modify disease risk carries considerable optimism. The design and conduct of several large-scale randomized controlled trials on antioxidants was derived from epidemiological data that showed a lower risk of chronic disease (predominantly cancer and cardiovascular disease) in those who had higher circulating levels or dietary intake of some micronutrients. Because of residual confounding and measurement errors in dietary assessment, dietary data from observational studies can be better examined by patterns of food consumption with a multivariate approach, rather than by ranking of specific nutrient intake with a univariate approach.

We have found that many studies did not report study participants' self-selected supplement use before and during the trial participation, and allowed self-selected supplement use during the trial. Similarly, there was a lack of information on other variables that might have modified the effects of study supplements. Collective study findings also may not apply to every individual. Additional research should be done, particularly in existing randomized controlled trials, to examine how efficacy may vary by age, time since trial enrollment to diagnosis, self-selected supplement use, dietary patterns, disease history, medication use, and/or genetic polymorphisms.

With many food products being fortified with several nutrients, Americans' dietary intake of certain nutrients may well be above the RDAs. Hence, it is important to study the level of intake among consumers and assess how nutrient fortification may influence the public's health. An adverse event reporting system needs to be in place to facilitate this type of research.

For policy making, research should be conducted to estimate the cost-effectiveness and the risk/benefit profile of multivitamin/mineral supplement use or more generally, dietary supplement use, in the general population. Such research should also consider subpopulations for which these parameters may differ.

Implications

The results of this systematic review have important implications for clinical practice and public health policy. When people ask about the need for multivitamin/mineral supplements, clinical practitioners should be aware that while multivitamin/mineral supplements are unlikely to have serious adverse effects, it remains unclear whether multivitamin/mineral supplementation is efficacious in preventing cancer, cardiovascular disease, or other major chronic diseases and conditions in the general United States adult population. Clinical practitioners may need to take into consideration other factors, such as nutritional status, when making recommendations about the need for multivitamin/mineral supplements. For public health policy makers, our conclusion is that evidence is insufficient to universally recommend or discourage routine use of multivitamin/mineral supplements by adults in the general United States population for primary prevention of chronic disease.

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SUMMARY TABLES

Table 1. Number of articles by key questions and disease categories

	KQ 1 (N = 11)	KQ 2 (N = 10)	KQ 3 (N= 44)							KQ 4 (N = 24)		
			β-caro-tene (N = 20)	Vitamin A (N = 7)	Vitamin E (N = 12)	Vitamin B2 and niacin (N = 3)	Selenium (N = 6)	Vitamin D/ calcium (systematic reviews) (N= 6)	Vitamin D/ calcium (RCTs) (N=5)	β-caro-tene (N= 13)	Vitamin E (N = 7)	Other nutrients (N = 6)
Cancer	2		14	2	8	1	5		1			
Cardio-vascular disease	2		10	2	4	1	2					
Cataract	4		1	1	2	1						
Age-related macular degen-eration	2				1							
Bone mineral densisty								3	2			
Fracture prevention								5	1			
Total mortality	4		3	2	4	1	1			5	3	1
Hospital-ization		2									1	
General illness		1								4	4	2
Yellowing of skin		5								4		
Anemia		1								1	1	
Genito-urinary		1										
Circulation		1								2	1	
Gastro-intestinal		3								1	4	1
Cardio-vascular		2								2	2	1
Renal		1										2
Psychiatric										1		

Numbers within the table may exceed total numbers in each category; nutrients may have more than one effect.
KQ = key question; Other nutrients include: Vitamin B2, selenium, zinc, and niacin

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
Linxian General Population Trial [64 66] Fractional factorial trial	Linxian, China 1986-91	29,584	age 44-60 55% women nutritionally deprived low intake of fresh fruits, meat, and other animal products low circulating levels of micro-nutrients, but overt clinical deficiencies were not common	Groups of placebo, AB, AC, AD, BC, BD, CD, ABCD where A: Retinol palmitate 10,000 IU + Zinc oxide 45 mg, B: Riboflavin 5.2 mg + Niacin 40 mg, C: Ascorbic acid 180 mg + Molybdenum Yeast complex 30 µg, D: β-carotene 15 mg + Selenium yeast 50 µg + α-tocopherol 60 mg	≈1-2 x RDAs	5.25 years	Not reported (Prior supplement users were ineligible for trial enrollment)	SIGNIFICANT: (1) *In the groups receiving β-carotene, vitamin E and selenium:* gastric cancer incidence 0.84 (0.71-1.00), cancer mortality 0.87 (0.75-1.00), stomach cancer mortality 0.79 (0.64-0.99), total mortality 0.91 (0.84-0.99) (2) *in the groups receiving retinol and zinc:* non-cardia stomach cancer mortality 0.59 (0.37-0.93) (3) *in the groups receiving retinol, zinc, β-carotene, vitamin E and selenium:* Stroke death 0.71 (0.50-1.00) NON-SIGNIFICANT: (1) *No effects of A, B, or C on:* Total mortality, stroke death, esophageal cancer mortality, esophageal/ gastric cardia mortality, gastric cancer mortality, cancer mortality, total cancer incidence, gastric cancer incidence, esophageal cancer incidence, esophageal/ gastric cardia cancer incidence (2) *No effect of D on:* Stroke death, esophageal cancer mortality, esophageal/ gastric cardia mortality, total cancer incidence, esophageal cancer incidence, esophageal/ gastric cardia cancer incidence (3) *no effects of AB, AC, AD, BC, BD, CD, or ABCD on:* Stroke deaths (except for AD group), total mortality

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
Linxian General Population Trial – end-of-trial endo-scopy survey[68]	Linxian, China 1991	391	Mean age: 53 45% women younger, more men, more smokers, more alcohol use compared to the total trial participants	Groups of placebo, AB, AC, AD, BC, BD, CD, ABCD where A: Retinol palmitate 10000 IU + Zinc oxide 45 mg, B: Riboflavin 5.2 mg + Niacin 40 mg, C: Ascorbic acid 180 mg + Molybdenum Yeast complex 30 µg, D: β-carotene 15 mg + Selenium yeast 50 µg + α-tocopherol 60 mg	≈1-2 x RDAs	Endo-scopy done at the end of the trial	Not reported	SIGNIFICANT; None NON-SIGNIFICANT: *No effects of A, B, C, or D on:* Dysplasia and cancer in the esophagus and stomach cancer in the esophagus and stomach COMMENT: Overall prevalence of dysplasia and cancer was extraordinarily high, 15%. Small sample size.

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
Linxian General Population Trial – end-of trial cataract study[65]	Linxian, China 1985-91	5,390	age 45-74 55% women	Groups of placebo, AB, AC, AD, BC, BD, CD, ABCD where A: Retinol palmitate 10000 IU + Zinc oxide 45 mg, B: Riboflavin 5.2 mg + Niacin 40 mg, C: Ascorbic acid 180 mg + Molybdenum Yeast complex 30 µg, D: β-carotene 15 mg + Selenium yeast 50 µg + α-tocopherol 60 mg	≈1-2 x RDAs	Eye exams done at the end of the trial	Not reported (Prior supplement users were ineligible for trial enrollment)	SIGNIFICANT: (1) *in the groups receiving riboflavin and niacin*: prevalence of nuclear cataract in those aged 65-74, OR (95% CI) = 0.45 (0.31-0.46) (2) *in the groups receiving riboflavin and niacin:* prevalence of posterior subcapsular cataract in those aged 45-74, OR (95% CI) = 2.64 (1.31-5.35) NON-SIGNIFICANT: (1) *no effects of A, C, or D on the* prevalence of nuclear cataract , cortical cataract, and posterior subcapsular cataract (2) *no effects of B on the* prevalence of nuclear cataract In those aged 55-64

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
SU.VI.MAX [69,70] Parallel-arm design	France 1994-2002	12741	62% women Mean(SD) age: women: 46.6 (6.6); men: 51.3 (4.7)	Vit C 120mg+ vit E 30mg+ β-carotene 6mg+ selenium 100µg+ zinc 20mg vs. Placebo	≈ 1-2 x RDAs (vitamin E: chemical forms not specified)	7.5 years	Not reported (Regular users of any of the vitamins and minerals provided in the study were ineligible for trial enrollment.)	SIGNIFICANT: Men: total cancer incidence 0.69 (0.53-0.91) total mortality 0.63 (0.42-0.93) prostate cancer in men with PSA<3 µg/L 0.52 (0.29-0.92) NON-SIGNIFICANT: Men & women: Ischemic cardio-vascular disease Women: cancer incidence, total mortality Men: Prostate cancer for those with PSA ≥ 3 µg/L or the subgroups by age, smoking, BMI, and serum levels of β-carotene, vitamin C, α-tocopherol, selenium, and zinc no effect on circulating PSA and IGF levels COMMENT: Well-designed Men had lower serum levels of β-carotene and vitamin C at baseline. Cardiovascular events in women were only 22.6% of the events in men. Information on prior or concomitant supplement use was not reported.
		5141 (men)	Mean (SD) age: 51.3 (4.6)			8 years		

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
REACT[72] Parallel-arm design	US UK 1990-1995	297	Mean (SD) age: UK: 67.55 (8.47) US: 64.2 (8.49)	β-carotene 18mg + vit C 750mg + *all-rac* α-tocopherol acetate 600 mg, 3 divided doses per day vs. Placebo	Vit C: 10x RDA for women ≈8x RDA for men *all-rac* α-toco-pherol acetate: 40x RDA	3 years	Not reported (Regular users of any vitamin supplement were ineligible for trial enrollment.)	SIGNIFICANT: Anterior % pixel opaque (primary endpoint): Mean (95% CI) Placebo: baseline 5.0 (1.4), last 8.3 (2.2), Mean change from baseline: 3.3 (1.4); Supplement: baseline 5.7 (1.6), last 7.3(2.0), Mean change from baseline: 1.7 (1.0); Difference from placebo: -1.6 (p=0.048) NON-SIGNIFICANT: Retro data posterior % pixel opaque (secondary endpoint): Retro data posterior % pixels opaque, retro data anterior pupil diameter, retro data posterior pupil diameter, nuclear color, nuclear cataract, posterior subcapsular cataract, cortical cataract COMMENT: After 3 years, the positive effects were greater in the U.S. group (% pixel opaque = 0.389 vs. 2.517 in the vitamin vs. placebo group, p=0.0001), but not the UK group

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
AREDS – cataract[73] Parallel-arm design	U.S. (11- center trial) 1992-2001	4596	Median age: 56	β-carotene 15 mg + vit C 500 mg + vit E 400 IU vs. Placebo	Vit C: 6.6x RDA Vit E: chemical form not specified Zinc: 10x RDA	6.3 years	55% of trial participants who had prior vitamin/ mineral supplement use were enrolled and supplied with Centrum. Additionally, 13% of trial participants chose to take Centrum.	SIGNIFICANT: None NON-SIGNIFICANT: Total lens event, nuclear event, cortical event, posterior sub-capsular event, cataract surgery, severe lens event, loss of visual acuity, total mortality COMMENT: The study had the strengths in documenting key aspects of the study conduct, including details on withdrawal, compliance and dropout. The major limitations are the option of multivitamin use (66% of the study participants) and self-selected use of non-study supplements (20% of participants) that contain at least one of the study nutrients. Data on how the self-selected supplement use distributed across randomized groups and AMD categories were not reported.

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
AREDS – age-related macular degeneration[75] 2 by 2 factorial design		3509	Median age: 69	Groups of placebo, A, B, C where A: β-carotene 15 mg + vit C 500 mg + vit E 400 IU B: zinc 80 mg as zinc oxide + copper 2mg as cupric oxide C: β-carotene 15 mg + vit C 500 mg + vit E 400 IU + zinc 80 mg as zinc oxide + copper 2mg as cupric oxide				SIGNIFICANT: (1) *zinc vs. no zinc:* Progression to advanced AMD (among participants in AMD categories 3&4), OR (99% CI) = 0.79 (0.62-0.99) Neovascular AMD OR (99% CI) = 0.76 (0.58-0.98) (2) *zinc vs. placebo* Progression to advanced AMD (among participants in AMD categories 3&4), OR (99% CI) = 0.71 (0.52-0.99) (3) *Antioxidants + zinc vs. placebo:* Progression to advanced AMD (among participants in AMD categories 3&4; 2&3&4), OR (99% CI) = 0.66 (0.47-0.91); 0.72 (0.52-0.98) Loss of visual acuity score of ≥15 letters from baseline(among participants in AMD categories 3&4), OR (99% CI) = 0.73 (0.54-0.99) Risk of neovascular AMD(among participants in AMD categories 3&4), OR (99% CI) = 0.62 (0.43-0.90) NON-SIGNIFICANT: (1) *No effects of A or B on:* Progression to advanced AMD (among participants in AMD categories 2&3&4) Loss of visual acuity score of ≥15 letters from baseline(among participants in AMD categories 3&4) (2) *No effects of A, B, or C on:* Loss of visual acuity score of >=15 letters from baseline (among participants in AMD categories 2&3&4) Central geographic atrophy(among those in AMD categories 3,4) (3) *No effects of A on:* Progression to advanced AMD (among participants in AMD categories 3&4) Neovascular AMD

Table 2. Summary of randomized controlled trials on multivitamin/mineral supplements and chronic disease prevention (continued)

Study name/ Study design	Study Site/ year	Sample Size	Character-istics of Study Population	Study design Randomized groups	Doses (RDA)	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings, RR (95% CI) Comment
MONMD [71, 74] Parallel-arm design	U.S. 1992	71	Veterans	β-carotene 20,000IU + vit E 200IU + vit C 750mg + citrus bioflavonoid complex 125mg+ quercitin 50 mg + rutin 50 mg+ biberry extract 5 mg+ zinc picolinate 12.5 mg+ selenium50mcg+ taurine 100mg+ N-acetyl cysteine 100 mg+ l-glutathione 5mg + vit B2 25mg+ Chromium 100 mcg vs. Placebo	Vitamin E: 6.6x RDA Vit C: 10x RDA for women 8.3x RDA for men Zinc: 0.83xRDA Selenium: 0.71xRDA Vit B2: ≈18xRDA	18 months	Not reported (Persons who had vitamin use in the year prior to enrollment were ineligible.)	SIGNIFICANT: Distance acuity declined in the placebo group, but stable in the multivitamin group (p=0.03). The multivitamin group had better M print acuity and fewer number of scotoma in left eyes in the multivitamin group (p=0.07), which occurs after the 12th month. NON-SIGNIFICANT: No significant difference between randomized groups in refraction, metamorphopsia and LOCS II readings on nuclear color, nuclear opalescence, and posterior subcapsular opacities. Unanticipated cortical cataractogenic effects for right eyes in the multivitamin group. COMMENT: Instruments used to measure cataract transparence were not the same over the study period and the examiners were not well instructed.

SU.VI.MAX = SUppléments en VItamines et Minéraux AntioXydants; REACT = Roche European American Cataract Trial; AREDS = Age-Related Eye Disease Study; ARMD = Age-Related Macular Degeneration; MONMD = Multicenter ophthalmic and nutritional age-related macular degeneration study

Table 3. Assessment of the quality of randomized controlled trials on the efficacy of multivitamin/mineral supplements and single nutrients in the prevention of chronic diseases and conditions.

Author, year	Represent-ativeness[a]		Bias and Confounding[b]		Adherence and follow-up[c]		Statistical Analysis[d]		Conflict of Interest[e]	
Multivitamin Studies, Cancer Prevention										
Blot, 1993[64]	Medium		Medium		Low		Low		Low	
Wang, 1994[68]	Medium		Medium		Medium		Medium		Low	
Meyer, 2005[70]	High		Medium		Low		High		Low	
Hercberg, 2004[69]	High		Medium		Medium		High		High	
		Medium		Medium		Medium		Medium		Low
Multivitamin Studies, Cardiovascular disease prevention										
Mark, 1998[66]	Low		Low		Low		Medium		Low	
Hercberg, 2004[69]	High		Medium		Medium		High		High	
		Medium		Medium		Low		High		Medium
Multivitamin Studies, Eye Disease Prevention										
Sperduto, 1993[65]	Medium		Medium		High		Medium		Low	
Chylack, 2002[72]	High		High		High		High		Low	
AREDS, 2001a[73]	High		High		Medium		High		High	
AREDS, 2001b[75]	High		High		High		High		High	
Richer, 1996[74]	Medium		Low		Medium		Low		Low	
		High		Medium		Medium		Medium		Low
Vitamin A/ Beta-carotene Studies, Cancer Prevention										
ATBC, 1994[97]	High		Medium		Medium		High		Low	
Albanes, 1996[98]	Medium		Medium		Low		High		Low	
Rautalahti, 1999[99]	High		Medium		Medium		High		Low	
Varis, 1998[90]	High		Medium		Medium		High		Low	
Omenn, 1996[105]	Medium		Medium		Low		High		Medium	
Omenn, 1996[93]	Medium		Medium		Medium		High		Low	
Green, 1999[84]	Medium		Medium		Low		High		Medium	
Greenberg, 1996[85]	Medium		Medium		Medium		High		High	
Cook, 2000[104]	Medium		Medium		Medium		Medium		Medium	
Frieling, 2000[86]	Medium		Medium		Low		Medium		Medium	
Hennekens, 1996[95]	Medium		Medium		Low		Medium		Low	

Table 3. Assessment of the quality of randomized controlled trials on the efficacy of multivitamin/mineral supplements and single nutrients in the prevention of chronic diseases and conditions. (continued)

Author, year	Represent-ativeness[a]		Bias and Confounding[b]		Adherence and follow-up[c]		Statistical Analysis[d]		Conflict of Interest[e]	
Vitamin A/ Beta-carotene Studies, Cancer Prevention (continued)										
Lee, 1999[96]	High		Medium		Medium		High		Medium	
Blot, 1993[64]	High		Medium		Medium		Medium		Low	
		Medium		Medium		Medium		Medium		Low
Vitamin A/ Beta-carotene Studies, Cardiovascular Disease Prevention										
Rapola, 1996[106]	High		Medium		Medium		High		Low	
Leppalla, 2000[107]	High		Medium		Medium		High		Low	
Omenn, 1996[105]	Medium		Medium		Low		High		Medium	
Goodman, 2004[94]	Medium		Medium		Medium		Medium		Medium	
Greenberg, 1996[85]	Medium		Medium		Medium		High		High	
Liu, 1999[108]	Medium		Medium		Low		High		Medium	
Hennekens, 1996[95]	Medium		Medium		Low		Medium		Low	
Lee, 1999[96]	High		Medium		Medium		High		Medium	
Mark, 1998[66]	Low		Low		Low		Medium		Low	
		63		60		57		76		46
Vitamin A/ Beta-carotene Studies, Eye Disease Prevention										
Teikari, 1997[109]	High		Medium		Medium		Medium		Low	
Sperduto, 1993[65]	Medium		Medium		High		Medium		Low	
		High		Medium		Medium		Medium		Low
Vitamin E Studies, Cancer Prevention										
Varis, 1998[90]	High		Medium		Medium		High		Low	
Albanes, 1996[98]	Low		Medium		Low		High		Low	
Albanes, 2000[102]	High		Medium		Medium		High		Low	
ATBC, 1994[97]	High		Medium		Medium		High		Low	
Rautalahti, 1999[99]	High		Medium		Medium		High		Low	
Heinonen, 1998[101]	High		Medium		Medium		High		Medium	
Lee, 2005[87]	High		Medium		Medium		High		High	
		Medium		Medium		Medium		Medium		Low

Table 3. Assessment of the quality of randomized controlled trials on the efficacy of multivitamin/mineral supplements and single nutrients in the prevention of chronic diseases and conditions. (continued).

Author, year	Represent-ativeness[a]		Bias and Confounding[b]		Adherence and follow-up[c]		Statistical Analysis[d]		Conflict of Interest[e]	
Vitamin E Studies, Cardiovascular Disease Prevention										
Rapola, 1996[106]	High		Medium		Medium		High		Low	
Leppalla, 2000[107]										
Lee, 2005[87]	High		Medium		Medium		High		High	
Lee, 1999[96]	High		Medium		Medium		High		Medium	
DeGaetano, 2001[112]	Medium		Medium		Medium		High		High	
Sacco, 2003[181]	Medium		Medium		Low		High		High	
		Medium		Low		Medium		High		Medium
Vitamin E Studies, Eye Disease Prevention										
McNeil, 2004[113]	High		Medium		Medium		High		Medium	
Teikari, 1997[109]	High		Medium		Medium		Medium		Low	
		High		Medium		Medium		Medium		Low
Other Nutrients, Cancer Prevention										
Clark, 1996[133]	Medium		Medium		Medium		High		Medium	
Clark, 1998[134]	Medium		Medium		Low		Medium		Low	
Reid, 2002[135]	Medium		Low		Low		Medium		Medium	
Duffield-Lillico, 2002[136]	Medium		Low		Low		Medium		Low	
Duffield-Lillico, 2002[137]	Medium		Low		Low		Medium		Low	
Blot, 1993[64]	High		Medium		Medium		Medium		Low	
Yu, 1991[139]	Low		Low		Low		Low		Low	
		Medium		Low		Low		Medium		Low
Other Nutrients, Cardiovascular Disease Prevention										
Clark, 1996[133]	Medium		Medium		Medium		High		Medium	
Mark, 1998[66]	Low		High		Low		Medium		Low	
Other Nutrients, Eye Disease Prevention										
Sperduto, 1993[65]	Medium		Medium		High		Medium		Low	
		Medium		Medium		High		Medium		Low

For each study, we assigned a rating of high, medium or low quality for each domain of study quality based on whether the score for that domain was designated High (80-100%), Medium (50-79%), or Low (0-49%) quality.

Table 3. Assessment of the quality of randomized controlled trials on the efficacy of multivitamin/mineral supplements and single nutrients in the prevention of chronic diseases and conditions. (continued).

[a] Representativeness: Score was based on a total maximum score of 8 points. This included the authors' description of setting (2 points), details on inclusion and exclusion criteria (2 points), information on excluded or non-participating individuals (2 points), and description of key participant characteristics (2 points).
[b] Bias and Confounding: Score was based on a total maximum score of 28 points. This included the authors' description of patient assignment (2 points), details on concealment (2 points), description of differences in patient characteristics between groups (2 points), reporting on prior supplement use (2 points), description of the differences between groups in the prior use of supplements (2 points), description of medication use during the study (2 points), details on blinding (2 points) and the success of blinding (2 points), confirmation of medical diagnoses by medical chart (2 points), independent interpretation of clinical outcomes (2 points), overall blinding (2 points), randomization of arms (2 points), detail of description of study supplements (2 points), and overall assessment of the adherence to study supplements (2 points).
[c] Adherence and Follow-up: Score was based on a total maximum score of 12 points. This included the authors' description of flow of participants through each stage (2 points); patient adherence to study supplement use (2 points); description or identification of unintended cross-over between randomized groups (2 points); reporting (2 points) and description of withdrawals from the study (2 points), identifying if the study stopped earlier than planned (2 points).
[d] Statistical Analysis: Score was based on a total maximum score of 12 points. This included the authors' description of statistical tests (2 points), how unintended cross-over (2 points) and loss-to-follow-up (2 points) was handled, reporting of primary endpoints (2 points), adjustment for confounders (2 points), reporting of statistical power (2 points).
[e] Conflict of Interest: Score was based on a total maximum score of 2 points. This included the authors' description identifying the sources of funding (2 points).

Table 4. Grading of the quality of evidence of the efficacy of multivitamins/minerals in the prevention of chronic disease

	Key Question 1 Efficacy of Multivitamins/minerals			
	Cancer	**CVD**	**Cataract**	**AMD**
Quantity of Evidence: **Number of studies**	2 (Linxian, SU.VI.MAX)	2 (Linxian, SU.VI.MAX)	4 (REACT, Linxian, AREDS, MONMD)	2 (AREDS, MONMD)
Total number of patients studied	42325 (12741+29584)	42325 (12741+29584)	10354 (297+4596+ 5390+71)	3580 (3509+71)
Quality and Consistency of Evidence: **Were study designs randomized trials (high quality), non-randomized controlled trials (medium quality), or observational studies (low quality)?**	4 (RCTs)	4 (RCTs)	4 (RCTs)	4 (RCTs)
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-1	-1	0	0
Did the studies have important inconsistency? (-1)	0	0	0	0
Was there some (-1) or major (-2) uncertainty about the directness or extent to which the people, interventions and outcomes are similar to those of interest?	-2	-2	-1	-1
Were data imprecise or sparse? (-1)	-1	-1	-1	-1
Did the studies have high probability of reporting bias? (-1)	0	0	0	0
Did the studies show strong evidence of association between intervention and recruitment outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	+1	+1	0	0
Overall grade of evidence (high, medium, low, very low)	Very low	Very low	Low	Low

CVD = Cardiovascular disease; AMD = Age-related macular degeneration.

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease

Study name/ Design	Study site/ Year	Sample size	Study population (Age, sex, special characteristics)	Active supplements	Supplementation period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
PHS[86,95,104,108] 2 by 2 factorial trial of β-carotene and aspirin	USA/ 1982-1995	22071 [95,104]	Age range: 40-84 100% men US male physicians	β-carotene 50 mg on alternate day	12.9 years [104] (mean) 12 years[95] (mean)	Vitamin A supplement users were ineligible for trial enrollment. 23% used multivitamin supplements at baseline. 6.4% of the placebo group reported taking β-carotene or vitamin A supplements during the trial. 22% of the β-carotene group stopped taking the study supplements before the end of the trial.	STATISTICALLY SIGNIFICANT: Bladder cancer (RR 1.5, 95% CI 1.0-2.2) Thyroid cancer (RR 9.5, 95% CI 2.2-40.7) STATISTICALLY NON-SGINIFICANT: prostate cancer, colon cancer, rectal cancer, lung cancer, lymphoma, leukemia, melanoma, brain cancer, stomach cancer, pancreatic cancer, all cancer mortality, all cancer incidence, myocardial infarction, CVD death, all major CVD events
		21884 [86]			12 years (mean)		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma
		21468 [108]			12 years (mean)		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Type 2 Diabetes mellitus

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name/ Design	Study site/ Year	Sample size	Study population (Age, sex, special characteristics)	Active supplements	Supplemen-tation period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
WHS [87] 2 by 2 by 2 factorial trial of β-carotene, vitamin E and aspirin All data are from 2 post-trial follow-up studies	USA Supple-mentation 1993-1996 Follow-up 1993-1996	39876	Mean age: 54.6 100% women Female health care professionals	β-carotene 50 mg on alternate day	2.1 years β-carotene supplemen-tation was terminated earlier than planned. 40% used multivitamin supplements outside the trial	Users of individual supplements of vitamin A, vitamin E, or β-carotene more than once per week were ineligible for trial enrollment. At the end of termination of the β-carotene component, 87% of the active group reported taking at least two thirds of the study capsules, and 9.9% of the placebo group reported taking β-carotene or vitamin A supplements outside the trial.	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: All cancers other than non-melanoma skin cancer, death from cancer, CVD incidence, total mortality, CVD mortality, myocardial infarction, stroke, all major CVD events
NSCP [84] 2 by 2 factorial trial of sun screen and β-carotene	Australia 1992-1996	809	Mean age: 48.8 56.3% women	β-carotene 30 mg per day	4.5 years	No reported	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Basal-cell carcinoma, squamous-cell carcinoma

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name/ Design	Study site/ Year	Sample size	Study population (Age, sex, special characteristics)	Active supplements	Supplementation period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC [90,97,98,101-103,106,107,109,99,100,110] 2 by 2 factorial trial of α-tocopherol and β-carotene	Finland 1984-1993	29133 [99]	Mean age: 57.7 Age range: 50-69 100% men Smokers (5 or more cigarettes per day)	β-carotene 20 mg per day	6.1 years	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Pancreatic cancer incidence, pancreatic cancer mortality
		1344 [90]	Mean age: 58.8 100% men Low serum pepsinogen; Smokers (5 or more cigarettes per day)		5.1 years (median) Serum pepsinogen measured in 1989-91 and 1992-93		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Gastric dysplasia, carcinoma, carcinoid
		1828 [109]	Mean age: 64.5-65.1 years 100% men Smokers (5 or more cigarettes per day)		6.6-6.7 years Ophthalmology exam performed in Nov 1992-March 1993		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Nuclear cataract, cortical cataract, posterior subcapsular cataract, cataract severit
		941 [110]	Age 65 or older 100% men Smokers (5 or more cigarettes per day)		Ophthalmology exam performed in Dec 1992-March 1993		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Age-related maculopathy

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	29133 [98]	Age range: 50-69, 100% men; Smokers (5 or more cigarettes per day) Stratified by baseline data	β-carotene 20 mg per day	6.1 years	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: Lung cancer (RR 1.16, 95% CI 1.02-1.33) for the total group, (RR 1.39, 95% CI 1.03-1.88) in those aged 65-69; (RR 1.25, 95% CI 1.07-1.46) in those smoker 20+ cigarettes/day; (RR 1.23, 95% CI 1.04-1.47) in those who always inhale cigarette smoke; (RR 1.17, 95% CI 1.03-1.34) in those exposed to asbestos; (RR 1.40, 95% CI 1.10-1.78) in those with dietary intake <8.1 mg/d; (RR 1.35, 95% CI 1.01-1.81) in those drank ethanol >11 g/d; RR (1.33, 95% CI 1.01-1.73) in those with baseline serum α-tocopherol 11.6-13.1 mg/L STATISTICALLY NON-SIGNIFICANT: Lung cancer in the counterparts of the subgroups described in the left column. Lung cancer in the subgroups defined by baseline dietary β-carotene, vitamin C, or retinol, and by serum β-carotene or retinol.

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supple-mentation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	22269 [106]	Median age: 56.9, 100% men Smokers (5 or more cigarettes per day) With no history of angina	β-carotene 20 mg per day	4.7 years (median)	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Incidence of angina pectoris
		29133 [97]	Mean age: 57.2 100% men Smokers (5 or more cigarettes per day)		6.1 years (median)		STATISTICALLY SIGNIFICANT: Lung cancer incidence (RR 1.18, 95% CI 1.03-1.36); lung cancer mortality (RR 1.08, 95% CI 1.01-1.16)
		28519 [107]	Mean age: 57.7 100% men Smokers (5 or more cigarettes per day) With no history of stroke		6 years (median)		STATISTICALLY SIGNIFICANT: Intracerebral hemorrhage (RR 1.62, 95% CI 1.10-2.36) STATISTICALLY NON-SIGNIFICANT: Incidence of all strokes, sub-arachnoid hemorrhage, and cerebral infarction. Mortality of subarachoid hemorrhagic stroke, intracerebral hemorrhagic stroke, cerebral infarction, all strokes

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplemen-tation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	29133[102]	Mean age: 57.1 100% men Smokers (5 or more cigarettes per day)	β-carotene 20 mg per day	6 years (mean)	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Colorectal cancer
		29133[101]					STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Prostate cancer incidence, prostate cancer mortality
		15618 [100]	Mean age: 57.0 100% men Smokers (5 or more cigarettes per day)		6.3 years (mean)		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Colorectal adenoma
		Post-trial follow up 29133[103]	Age range: 50-69, 100% men Smokers (5 or more cigarettes per day)	No study supplement use during post-trial follow up	6 years for cancer incidence and cause-specific mortality 8 years for total mortality		STATISTICALLY SIGNIFICANT: Colorectal cancer 3 to 6 years after trial (RR 1.88, 95% CI 1.28-2.76) Total mortality (RR 1.07, 95% CI 1.02-1.12) STATISTICALLY NON-SIGNIFICANT: Lung cancer, prostate cancer, total mortality, urothelial cancer, stomach cancer, kidney cancer, pancreatic cancer, other cancers, coronary heart disease mortality, hemorrhagic stroke mortality, non-hemorrhagic stroke mortality

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name/ Design	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
SCP[85] Parallel-arm design	United States 1983-1993	1720	Mean age: 63.2 31% women	β-carotene 50 mg /day	Median supplementation: 4.3 yrs Follow up: 8.2 years	No exclusion was made on supplement use	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: All deaths, cardiovascular deaths, cancer deaths
CARET[93,105,183] Parallel-arm design	Seattle, WA; Portland, OR; San Francisco, CA; Baltimore, MD; New Haven CT; Irvine, CA. Pilot study 1983-1988 Main study 1985-1996	18314[105]	Mean age: 58 34.3% women smokers or asbestos workers	Retinyl palmitate 25000 IU + beta-carotene 30 mg Retinol in pilot phase (1985-1988) then retinyl palmitate (1988-1996)	4 years (mean)	Participants agreed to have Vitamin A intake<5500 IU/day, and to not use beta-carotene supplements	STATISTICALLY SIGNIFICANT: Lung cancer (RR 1.36, 95% CI 1.07-1.73), Lung cancer mortality (RR 1.59, 95% CI 1.13-2.23) from weighted analysis STATISTICALLY NON-SIGNIFICANT: Leukemia (p=0.06), mesothelioma, breast cancer, colorectal cancer, head/neck cancer, lymphoma, prostate cancer, bladder cancer
		18314[93]					STATISTICALLY SIGNIFICANT: Lung Cancer (RR 1.29, 95% CI 1.04-1.57), Total mortality (RR 1.17, 95% CI 1.03-1.33), Lung cancer death (RR 1.46, 95% CI 1.07-2.00) STATISTICALLY NON-SIGNIFICANT: Mesothelioma, cardiovascular death, prostate cancer

Table 5. Summary of randomized controlled trials on beta-carotene and chronic disease (continued)

Study name/ Design	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
CARET (cont'd)		17140 [184] year 1996-2001	Mean age: 62, 35% women	None	Post-trial follow up (6 years)	Participants were asked to stopped taking the study supplements in 1996	STATISTICALLY SIGNIFICANT: Lung cancer mortality (RR 1.20, 95% CI 1.01-1.43) Lung cancer, all cause mortality, cardiovascular mortality, Lung cancer (RR 1.12, 95% CI 0.97-1.31) total mortality (RR 1.08, 95% CI 0.99-1.17)

PHS (Physicians Health Study); WHS (Women's Health Study); NS (Not Specified); ATBC (Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial); CARET (Beta Carotene and Retinol Efficacy Trial).

Table 6. Grading of the quality of evidence of the efficacy of single nutrients in the prevention of chronic disease

	Key Question 3 Efficacy of single nutrients and related pairs								
	Vitamin E (alone)				Selenium	Beta-carotene			
	CVD	Cancer	Cataract	Total mortality	Cancer	Cancer	CVD	Cataract	Total mortality
Quality and Consistency of Evidence: **Were study designs randomized trials (high quality), non-randomized controlled trials (medium quality), or observational studies (low quality)?**	High	High	High	High	High	High		High	
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-1	-1	0	-1	0	0		-1	
Did the studies have important inconsistency? (-1)	0	-1	0	0	0	-1		0	
Was there some (-1) or major (-2) uncertainty about the directness or extent to which the people, interventions and outcomes are similar to those of interest?	-1	-1	0	-1	-2	0		-2	
Were data imprecise or sparse? (-1)	0	0	-1	0	-1	0		-1	
Did the studies have high probability of reporting bias? (-1)	0	0	0	0	0	0		0	
Did the studies show strong evidence of association between intervention and recruitment outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))	0	0	0	0	2	0		0	
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0		0	
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	0	0		0	
Overall grade of evidence (high, medium, low, very low)	Low	Very low	Moderate	Low	Low	Moderate		Very low	

Table 6. Grading of the quality of evidence of the efficacy of single nutrients in the prevention of chronic disease (continued)

	Key Question 3 Efficacy of single nutrients and related pairs					
	Calcium		Vitamin D		Vitamin D + calcium	
	BMD	Fracture	BMD	Fracture	BMD	Fracture
Quality and Consistency of Evidence: **Were study designs randomized trials (high quality), non-randomized controlled trials (medium quality), or observational studies (low quality)?**	4	4	4	4	4	4
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-2	-1	-1	-1	0	0
Did the studies have important inconsistency? (-1)	-1	-1	-1	-1	0	0
Was there some (-1) or major (-2) uncertainty about the directness or extent to which the people, interventions and outcomes are similar to those of interest?	0	0	0	0	0	0
Were data imprecise or sparse? (-1)	0	-1	0	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	0	0	0	0
Did the studies show strong evidence of association between intervention and recruitment outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))	+1	0	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	1	0
Overall grade of evidence (high, medium, low, very low)	Low	Very Low	Low	Low	High	High

CVD = Cardiovascular disease; BMD = bone mineral density

Table 7. Summary of randomized controlled trials on vitamin E and chronic disease

Study name/ Design	Study site/ Year	Sample size	Study population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
WHS [87] 2 by 2 by 2 factorial trial of β-carotene, vitamin E and aspirin	USA 1992-2004	39876	Mean age (SD): 54.6 (7.0), 100% women	*α*-tocopherol (natural source, 600 IU on alternate day)	10.1 years	Users of individual supplements of vitamin A, vitamin E, or β-carotene more than once per week were ineligible for trial enrollment 40% used multivitamin supplements outside the trial	STATISTICALLY SIGNIFICANT: Cardiovascular death (RR 0.76, 95% CI 0.59-0.98) STATISTICALLY NON-SIGNIFICANT: Major cardiovascular event, incidence of myocardial infarction, incidence of stroke, ischemic stroke incidence, hemorrhagic stroke incidence, total cancer, breast cancer, lung cancer, colon cancer, cancer mortality, total mortality
ATBC [90,97,98,101-103,106,107,109,99,100,110] 2 by 2 factorial trial of α-tocopherol and β-carotene	Finland 1984-1993	29133 [99]	Mean age: 57.7 Age range: 50-69 100% men Smokers (5 or more cigarettes per day)	*α*-tocopheryl acetate 50 mg per day	6.1 years	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Pancreatic cancer incidence, pancreatic cancer mortality
		1344 [90]	Mean age: 58.8 100% men Low serum pepsinogen; Smokers (5 or more cigarettes per day)		5.1 years (median) Serum pepsinogen measured in 1989-91 and 1992-93		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Gastric dysplasia, carcinoma, carcinoid

Table 7. Summary of randomized controlled trials on vitamin E and chronic disease (continued)

Study name/ Design	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	1828 [109]	Mean age: 64.5-65.1 years 100% men Smokers (5 or more cigarettes per day)	*α*-tocopheryl acetate 50 mg per day	6.6-6.7 years Ophthalmology exam performed in Nov 1992-March 1993	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Nuclear cataract, cortical cataract, posterior subcapsular cataract, cataract severity
		941 [110]	Age 65 or older 100% men Smokers (5 or more cigarettes per day)		Ophthalmology exam performed in Dec 1992-March 1993		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Age-related maculopathy
		29133 [98]	Age range: 50-69, 100% men; Smokers (5 or more cigarettes per day) Stratified by baseline data		6.1 years		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Lung cancer Overall and in the subgroups defined by age, cigarettes smoking, years of cigarette smoking, cigarette smoke inhalation, asbestos exposure, dietary intake of vitamin E, β-carotene, vitamin C, retinol, alcohol as ethanol, and serum levels of α-tocopherol, β-carotene, and retinol

Table 7. Summary of randomized controlled trials on vitamin E and chronic disease (continued)

Study name	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	22269 [106]	Median age: 56.9, 100% men Smokers (5 or more cigarettes per day) With no history of angina	α-tocopheryl acetate 50 mg per day	4.7 years (median)	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: Angina (RR 0.91, 95% CI 0.83-0.99 for α-tocopherol to no α-tocopherol) STATISTICALLY NON-SIGNIFICANT: Angina (RR 0.97 and 0.96 in the α-tocopherol group and α-tocopherol+β-carotene group, respectively, compared to placebo)
		29133 [97]	Mean age: 57.2 100% men Smokers (5 or more cigarettes per day)		6.1 years (median)		STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Lung cancer, lung cancer mortality, total mortality
		28519 [107]	Mean age: 57.7 100% men Smokers (5 or more cigarettes per day) With no history of stroke		6 years (median)		STATISTICALLY SIGNIFICANT: Fatal subarachnoid hemorrhagic stroke (RR 2.81, 95% CI 1.37-5.79) Cerebral infarction (RR 0.86, 95% CI 0.75-0.99) STATISTICALLY NON-SIGNIFICANT: Incidence of all strokes, sub-arachnoid hemorrhage (RR 1.50, 95% CI 0.97-2.32), intracerebral hemorrhagic stroke, mortality of intracerebral hemorrhagic stroke, cerebral infarction, all strokes

Table 7. Summary of randomized controlled trials on vitamin E and chronic disease (continued)

Study name	Study Site/ year	Sample Size	Study Population (Age, sex, special characteristics)	Active Supplements	Supplementation Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
ATBC (continued)	Finland 1984-1993	29133[102]	Mean age: 57.1 100% men Smokers (5 or more cigarettes per day)	α-tocopheryl acetate 50 mg per day	6 years (mean)	Users of vitamin A, vitamin E, or β-carotene in excess of predefined doses (20,000IU, 20 mg, or 6 mg, respectively) were ineligible	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Colorectal cancer (RR 0.78, 95% CI 0.55-1.09)
		29133[101]					STATISTICALLY SIGNIFICANT: Prostate cancer incidence (RR 0.68, 95% CI 0.53-0.88) Prostate cancer mortality (RR 0.59, 95% CI 0.35-0.99) STATISTICALLY NON-SIGNIFICANT: None
		15538 [100]	Mean age: 57.0 100% men Smokers (5 or more cigarettes per day) No colorectal cancer diagnosis (15 cases had a history of polyps)		6.3 years (mean)		STATISTICALLY SIGNIFICANT: Colorectal adenoma (RR 1.66, 95% CI 1.19-2.32) STATISTICALLY NON-SIGNIFICANT: None
		Post-trial follow up 29133[103]	Age range: 50-69 100% men Smokers (5 or more cigarettes per day)	No study supplement use during post-trial follow up	6 years for cancer incidence and cause-specific mortality 8 years for total mortality		STATISTICALLY SIGNIFICANT: Hemorrhagic stroke mortality (RR 1.40, 95% CI 1.00-1.96) STATISTICALLY NON-SIGNIFICANT: Lung cancer, prostate cancer, colorectalc cancer, total mortality, urothelial cancer, stomach, kidney cancer, pancreatic cancer, other cancers, coronary heart disease mortality, non-hemorrhagic stroke mortality, total mortality

Table 7. Summary of randomized controlled trials on vitamin E and chronic disease. (continued)

Study name/ Design	Study Site/ year	Sample Size	Study Population (Age, sex, special character-istics)	Active Supplements	Supplementa-tion Period	Self-selected supplement use	Statistically significant and statistically non-significant findings (list of diseases)
PPP[112,181] 2 by 2 factorial trial of *all-rac α*-tocopheryl acetate and aspirin Premature termination of the trial	Italy, 1994-1998	1031[182]	Mean age (SD): 64.2 (7.6) 42% women Stratified by type 2 diabetes among those with at least one risk factor of cardiovascular disease at baseline	*all-rac α* - tocopherol 300 IU per day	3.4 years (median)	Prior long-term use of vitamin E was an exclusion criterion	STATISTICALLY SIGNIFICANT: Peripheral artery disease (RR 0.37, 95% CI 0.14-0.96) in persons with no type 2 diabetes at baseline STATISTICALLY NON-SIGNIFICANT: Combined CV deaths, nonfatal MI and stroke, total CV events , CV deaths, non CV deaths, all MI, all stroke , angina pectoris, transient ischemic attack, revascularization procedure, all deaths in persons with or without diabetes; Peripheral artery disease in persons with diabetes
		4495[112]	Mean age (SD): 64.4 (7.6) 57% women With at least one risk factor for cardiovascular disease; 23% disbetics	*all-rac α* - tocopherol 300 IU per day	3.7 years (median)	Prior long-term use of vitamin E was an exclusion criterion	STATISTICALLY SIGNIFICANT: Peripheral artery disease (RR =0.54, CI = 0.30-0.99) STATISTICALLY NON-SIGNIFICANT: Main combined endpoint, total CV events or diseases, CV Deaths, non-CV deaths, all MI, non-fatal MI, all stroke, non-fatal stroke, transient ischemic attack, peripheral artery disease, revascularization procedures, angina pectoris, all deaths
VECAT [113]	Melbourne, Australia, 1995-2000	1193	Mean age: 65.7 56% women	*RRR-α*-tocopherol 500 IU per day	4 years planned	24%	STATISTICALLY SIGNIFICANT: None STATISTICALLY NON-SIGNIFICANT: Cortical cataract, nuclear cataract, posterior subcapsular cataract, any cataract

WHS (Women's Health Study); VECAT (Vitamin E, Cataract and Age-Related Maculopathy Trial); ATBC (Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial); CARET (Beta Carotene and Retinol Efficacy Trial); PPP (Primary Prevention Project); SD (Standard Dilatation).

FIGURES

Figure 1. Conceptual framework for the prevention of chronic diseases and conditions with vitamin/mineral supplements (circled numbers represent the key questions addressed in this systematic review)

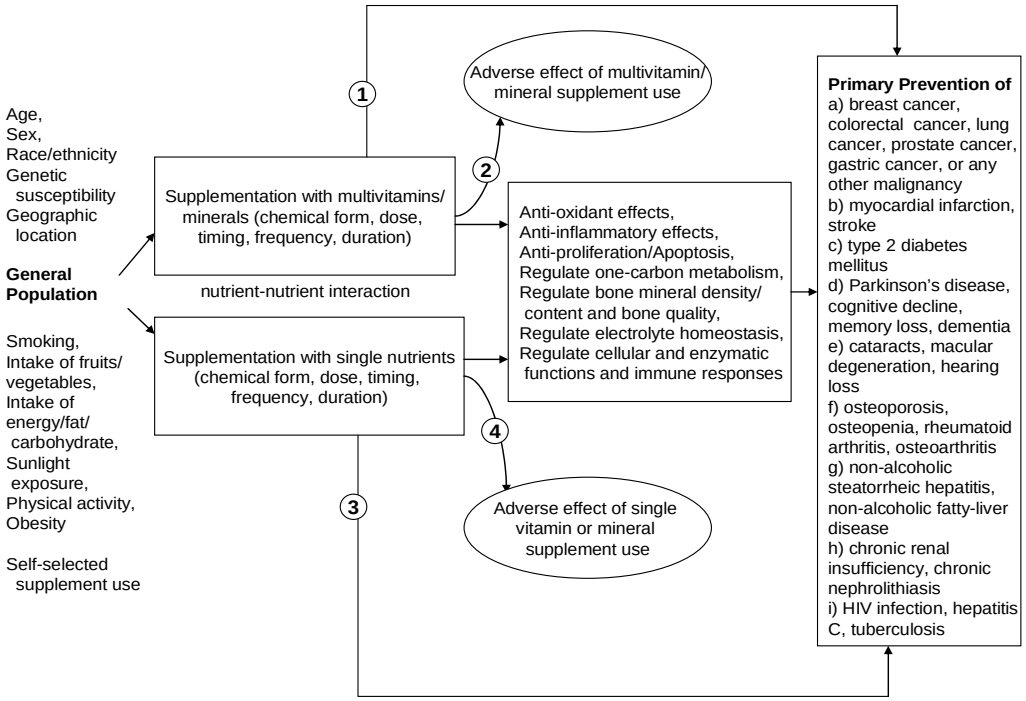
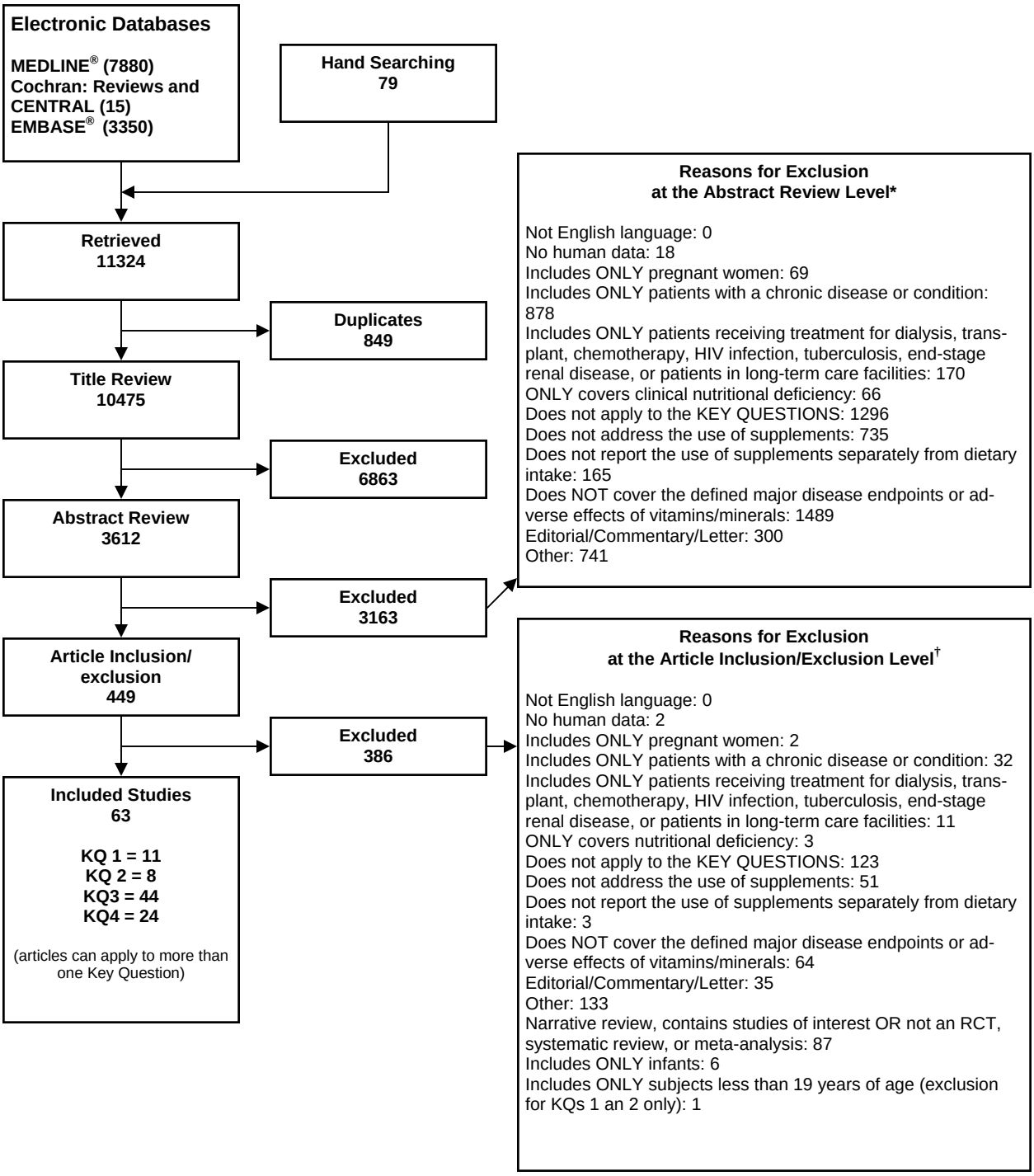


Figure 2. Summary of literature search and review process (number of articles)

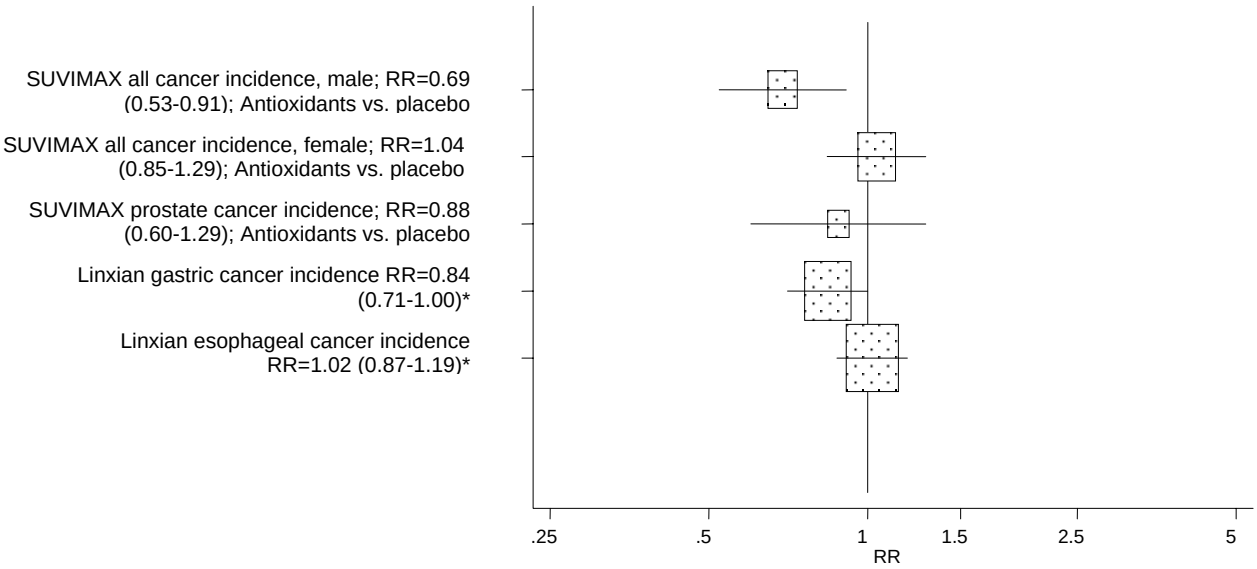


KQ = Key Question; RCT = randomized controlled trial.

* Total is greater than 3062, reviewers were allowed to choose more than one reason for exclusion at this level.

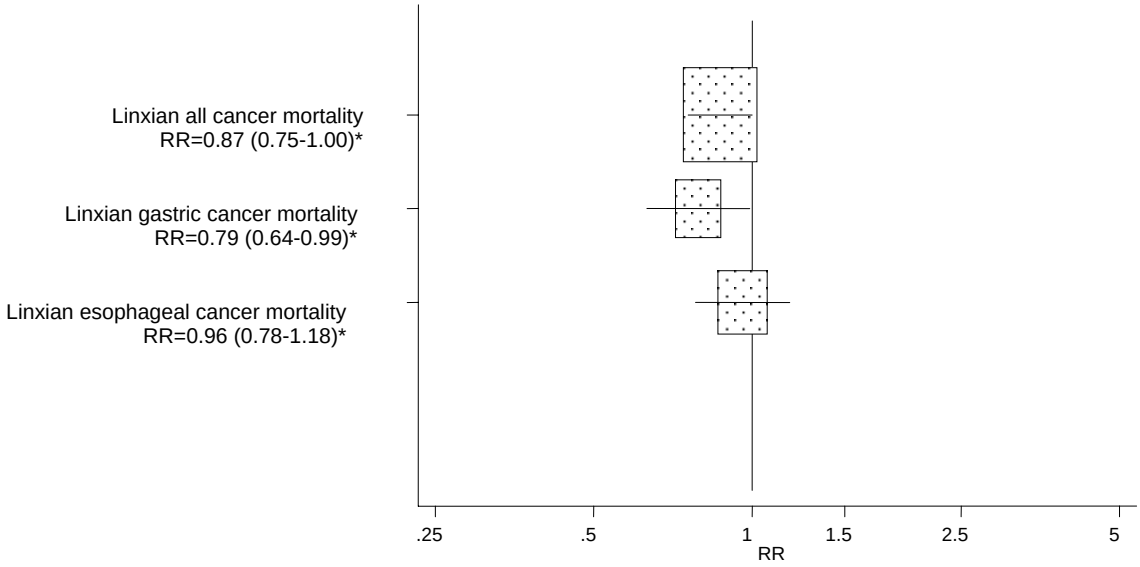
† Total is greater than 296, reviewers were allowed to choose more than one reason for exclusion at this level.

Figure 3. Relative risk (RR) of total cancer, gastric cancer and esophageal cancer incidence in relation to multivitamin/mineral supplement use



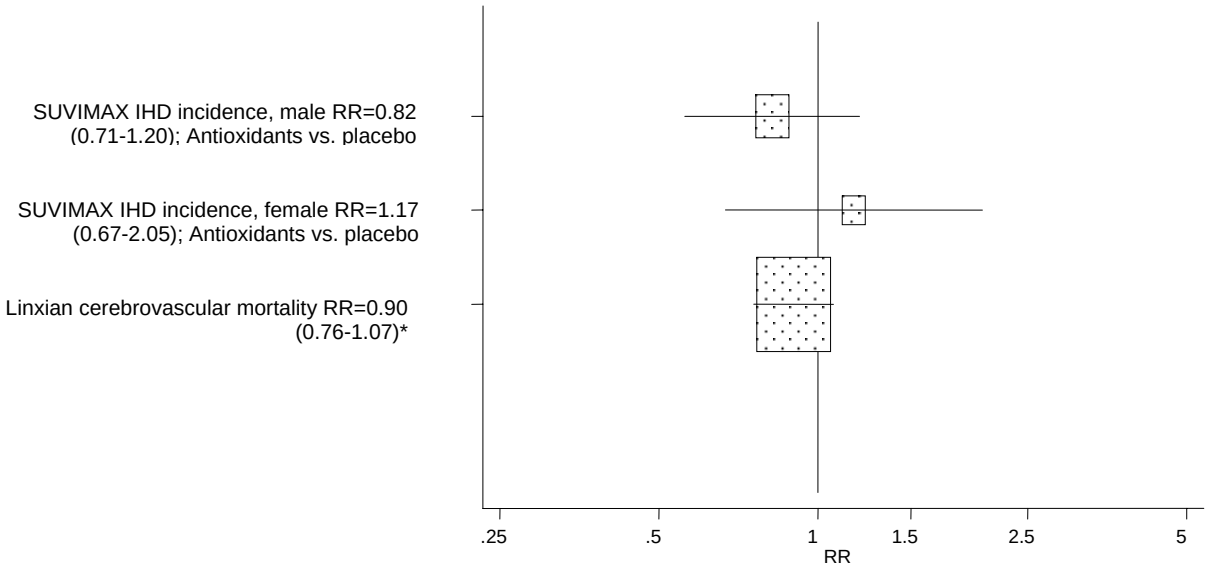
*For beta carotene, vitamin E and selenium users vs. non-users

Figure 4. Relative risk (RR) of total cancer, gastric cancer and esophageal cancer mortality in relation to multivitamin/mineral supplement use



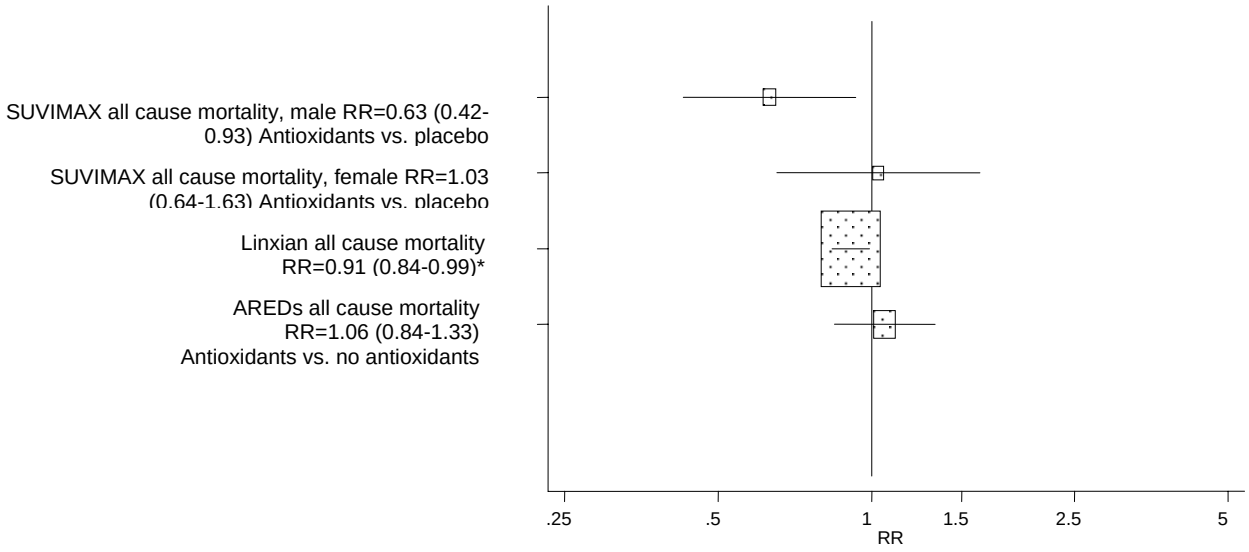
*For beta carotene, vitamin E and selenium users vs. non-users

Figure 5. Relative risk (RR) of cardiovascular disease incidence in relation to multivitamin/mineral supplement use



*For beta carotene, vitamin E and selenium users vs. non-users

Figure 6. Relative risk (RR) of all cause mortality in relation to multivitamin/ mineral supplement use



*For beta carotene, vitamin E and selenium users vs. non-users

APPENDIXES

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All Journals Hand Searched
January 2005 through February 2006

Annals of Epidemiology
Annals of Internal Medicine
Annals of the New York Academy of Science
Archives of Ophthalmology
Cancer Causes and Control
Cancer Research
Cancer Research
Controlled Clinical Trials
International Journal for Vitamin and Nutrition Research
Journal of Bone and Mineral Metabolism
Journal of the American Medical Association
Journal of the National Cancer Institute
Lancet
Osteoporosis International
The Journal of Nutrition

MEDLINE Strategy

((((“Calcium, dietary”[mh] OR “dietary Calcium”[tiab] OR “Calcium supplement*”[tiab] OR “folic acid”[tiab] OR “folic acid”[mh] OR folate[tiab] OR “folate supplement*”[tiab] OR “Vitamin B 6”[tiab] OR “Vitamin B6”[tiab] OR Pyridoxine[tiab] OR “Vitamin B 6”[mh] OR “Vitamin B 12”[tiab] OR “Vitamin B12”[tiab] OR “Vitamin B 12”[mh] OR “Vitamin D”[tiab] OR Cholecalciferol[tiab] OR “Vitamin D”[mh] OR “Vitamin E”[tiab] OR Tocopherol[tiab] OR “Vitamin E”[mh] OR “Vitamin C”[tiab] OR “Ascorbic acid”[tiab] OR ascorbate[tiab] OR “Ascorbic acid”[mh] OR “Vitamin A”[tiab] OR “Vitamin A”[mh] OR “beta carotene”[tiab] OR “beta carotene”[mh] OR (iron[tiab] AND (“dietary supplement*”[tiab] OR supplement*[tiab])) OR “iron, dietary”[mh] OR (zinc[tiab] AND (“dietary supplement*”[tiab] OR supplement*[tiab])) OR (Magnesium[tiab] AND (“dietary supplement*”[tiab] OR supplement*[tiab])) OR “Vitamin B 1”[tiab] OR “Vitamin B1”[tiab] OR Thiamin[tiab] OR Thiamine[tiab] OR Thiamine[mh] OR “Vitamin B 2”[tiab] OR “Vitamin 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Cochrane Library (Reviews and CENTRAL) Strategy

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EMBASE Strategy

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('nicotinic acid'/exp/mj OR 'nicotinic acid') OR ('multivitamin'/exp/mj OR 'multivitamin') OR ('vitamin'/exp/mj OR 'vitamin') OR vitmins OR ('mineral'/exp/mj OR 'mineral') OR minerals OR multiminerals AND [english]/lim AND [humans]/lim) OR ((('iron'/exp/mj OR 'iron') OR ('zinc'/exp/mj OR 'zinc') OR ('magnesium'/exp/mj OR 'magnesium')) AND (supplement OR ('dietary supplement'/exp/mj OR 'dietary supplement')) AND [english]/lim AND [humans]/lim)) AND ((neoplasm or 'hearing loss' or 'colorectal polyps' or 'colon polyps' or adenoma or polyp or 'myocardial infarction' or 'heart arrest' or 'myocardial ischemia' or 'heart attack' or stroke or 'cerebrovacular accident' or 't ype 2 diabetes' or 'diabetes mellitus' or 'adult onset diabetes' or dementia or cataract or cataracts or 'macular degeneration' or deafness or osteoporosis or osteoarthritis or osteopenia or fracture or 'rheumatoid arthritis' or 'rheumatiod arthritis' or steatohepatits or nash or nafld or 'renal insufficiency' or 'chronic kidney failure' or nephrolithiasis or nephropathy or 'hiv infection' or aids or 'acquired immunodeficiency syndrome' or 'hepatitis c' or tuberculosis or 'chronic obstructive pulmonary disease' or emphysema or 'chronic bronchitis')or AND ((cardiovascular OR 'endocrin system' OR ('nervous system'/exp/mj OR 'nervous system') OR ('eye'/exp/mj OR 'eye') OR musculoskeletal OR ('digestive system'/exp/mj OR 'digestive system') OR ('kidney'/exp/mj OR 'kidney') OR communicable OR infectious OR ('lung'/exp/mj OR 'lung') OR ('coronary artery'/exp/mj OR 'coronary artery') OR ('ischemic heart'/exp/mj OR 'ischemic heart') OR cerebrovascular OR alzheimer's or parkinson's OR 'degenerative joint' OR 'metabolic bone' OR ('fatty liver'/exp/mj OR 'fatty liver')) AND ('disease'/exp/mj OR 'disease')) OR ((('lung'/exp/mj OR 'lung') OR ('breast'/exp/mj OR 'breast') OR ('colon'/exp/mj OR 'colon') OR colorectal OR ('prostate'/exp/mj OR 'prostate') OR gastric OR ('stomach'/exp/mj OR 'stomach') OR abdominal) AND (('cancer'/exp/mj OR 'cancer') OR ('neoplasm'/exp/mj OR 'neoplasm'))) AND [english]/lim AND [humans]/lim)) AND ('randomized controlled trial':it OR 'controlled clinical trial':it AND [english]/lim AND [humans]/lim)) OR (((((('calcium'/exp/mj OR 'calcium') OR ('folic acid'/exp/mj OR 'folic acid') OR ('folate'/exp/mj OR 'folate') OR ('vitamin b6'/exp/mj OR 'vitamin b6') OR ('vitamin b 6'/exp/mj OR 'vitamin b 6') OR ('pyridoxine'/exp/mj OR 'pyridoxine') OR ('vitamin b12'/exp/mj OR 'vitamin b12') OR ('vitamin b 12'/exp/mj OR 'vitamin b 12') OR ('vitamin d'/exp/mj OR 'vitamin d') OR ('cholecalciferol'/exp/mj OR 'cholecalciferol') OR ('vitamin e'/exp/mj OR 'vitamin e') OR ('tocopherol'/exp/mj OR 'tocopherol') OR ('vitamin c'/exp/mj OR 'vitamin c') OR acorbate OR ('ascorbic acid'/exp/mj OR 'ascorbic acid') OR ('vitamin a'/exp/mj OR 'vitamin a') OR ('beta carotene'/exp/mj OR 'beta carotene') OR ('vitamin b1'/exp/mj OR 'vitamin b1') OR ('vitamin b 1'/exp/mj OR 'vitamin b 1') OR ('thiamin'/exp/mj OR 'thiamin') OR ('thiamine'/exp/mj OR 'thiamine') OR ('vitamin b2'/exp/mj OR 'vitamin b2') OR ('vitamin b 2'/exp/mj OR 'vitamin b 2') OR ('riboflavin'/exp/mj OR 'riboflavin') OR ('niacin'/exp/mj OR 'niacin') OR ('nicotinic acid'/exp/mj OR 'nicotinic acid') OR ('multivitamin'/exp/mj OR 'multivitamin') OR ('vitamin'/exp/mj OR 'vitamin') OR vitmins OR ('mineral'/exp/mj OR 'mineral') OR minerals OR multiminerals) OR (('iron'/exp/mj OR 'iron') OR ('zinc'/exp/mj OR 'zinc') OR ('magnesium'/exp/mj OR 'magnesium') OR ('selenium'/exp/mj OR 'selenium')) AND (supplement OR ('dietary supplement'/exp/mj OR 'dietary supplement'))) AND [english]/lim AND [humans]/lim) AND (('safety'/exp/mj OR 'safety') OR 'adverse event' OR ('pharmacology'/exp/mj OR 'pharmacology') OR 'adverse effects' OR ('adverse effect'/exp/mj OR 'adverse effect') OR ('side effect'/exp/mj OR 'side effect') OR 'product surveillance' OR ('adverse reaction'/exp/mj OR 'adverse reaction') OR ('drug toxicity'/exp/mj OR 'drug toxicity') AND [english]/lim AND [humans]/lim)))	3350

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Albanes D. Beta-carotene and lung cancer: a case study. Am J Clin Nutr 99;69(6):1345S-1350S. **Narrative review**

Allender PS, Cutler JA, Follmann D et al. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. Ann Intern Med 96;124(9):825-31. **Does not cover the defined disease endpoints**

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Bridge EV. Chemoprophylaxis: a major adjunct in the prevention of tuberculosis. Mich Med 67;66(24):1553-5. **Does not apply to the key questions, does not address the use of supplements, does not cover the defined disease endpoints**

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Browne R, Boag F. What is your patient taking? Dietary supplements in an HIV-positive patient. Int J STD Aids 2005;16(9):639-641. **Includes ONLY patients with a particular chronic disease**

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Anonymous. Calcium supplements. Med Lett Drugs Ther 96;38(989):108-109. **Narrative review**

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Camarasa JG, Serra-Baldrich E, Lluch M. Contact allergy to vitamin B6. Contact Dermatitis 90;23(2):115.

Canner PL, Berge KG, Wenger N K et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 86;8(6):1245-55. **Includes ONLY patients with a particular chronic disease**

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Cats A, Kleibeuker JH, Van der et al. Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. J Natl Cancer Inst 95;87(8):598-603. **Includes ONLY patients with a particular chronic disease, Does not cover the defined disease endpoints**

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Moon JC. A brief history of vitamin D toxicity. J Appl Nutr 97;49(1-2):18-31. **Narrative review**

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Onel S. Dietary supplements: A definition that is black, white, and gray. Am J Law Med 2005;31(2-3):341-348. **Editorial**

Opara EC. Oxidative stress, micronutrients, diabetes mellitus and its complications. J R Soc Promot Health 2002;122(1):28-34. **Narrative review**

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Puig L, Moreno A, Llistosella E et al. Granulation tissue proliferation during isotretinoin treatment. Int J Dermatol 86;25(3):191-3. **Does not apply to the key questions, Does not address the use of supplements**

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Sutton NA. The safety of calcium fortification. Med Health RI 2000;83(11):364-366. **Narrative review**

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Teegarden D, Legowski P, Gunther CW et al. Dietary calcium intake protects women consuming oral contraceptives from spine and hip bone loss. J Clin Endocrinol Metab 2005;90(9):5127-33. **Does not address the use of supplements**

The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. Ann Epidemiol 94;4(1):1-10. **Other**

Touvier M, Boutron-Ruault MC, Volatier JL et al. Efficacy and safety of regular vitamin and mineral supplement use in France: Results from the ECCA study. Int. J Vitam Nutr Res. 2005;75(3):201-209. **Does not apply to the key questions**

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Ward BJ. Retinol (Vitamin A) supplements in the elderly. Drugs Aging 96;9(1):48-59. **Narrative review**

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Wijewardene K. Does vitamin E prevent retinopathy of prematurity in low birth weight babies? Ceylon Med J 90;35(2):37-9. **Does not apply to the key questions, Includes only infiants**

Willett WC, MacMahon B. Diet and cancer--an overview. N Engl J Med 84;310(10):633-8. **Narrative review**

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Wright HO. Vitamin A supplementation. J Appl Nutr 95;47(1-2):32-33. **Editorial**

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Yusuf S, Dagenais G, Pogue J et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342(3):154-60. **Does not apply to the key questions**

Zhang YH, Kramer TR, Taylor PR et al. Possible immunologic involvement of antioxidants in cancer prevention. Am J Clin Nutr 95;62(6 Suppl):1477S-1482S. **Does not apply to the key questions, Does not cover the defined disease endpoints**

Zhao XQ, Morse JS, Dowdy AA et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). Am J Cardiol 2004;93(3):307-12. **Includes ONLY patients with a particular chronic disease, Does not apply to the key questions, Does not address th use of supplements, Does not cover the defined disease endpoints**

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Previewing at Level 1

Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R.. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 353 6, 566-75-2005;
Ref ID: 1
Abstract: BACKGROUND: We evaluated whether patients with osteoporosis treated with long-term alendronate have a response to parathyroid hormone treatment and whether short, three-month cycles of parathyroid hormone therapy could be as effective as daily administration. METHODS: We randomly assigned 126 women with osteoporosis who had been taking alendronate for at least 1 year to continued alendronate plus parathyroid hormone (1-34) subcutaneously daily, continued alendronate plus parathyroid hormone (1-34) subcutaneously daily for three 3-month cycles alternating with 3-month periods without parathyroid hormone, or alendronate alone for 15 months. RESULTS: In both parathyroid hormone groups, bone formation indexes rose swiftly. Among the women who were receiving cyclic parathyroid hormone, bone formation declined during cycles without parathyroid hormone and increased again during cycles with parathyroid hormone. Bone resorption increased in both parathyroid hormone groups but increased progressively more in the daily-treatment group than in the cyclic-therapy group. Spinal bone mineral density rose 6.1 percent in the daily-treatment group and 5.4 percent in the cyclic-therapy group (P<0.001 for each parathyroid hormone group as compared with the alendronate group and no significant difference between parathyroid hormone groups). One woman in the daily-treatment group, two in the cyclic-therapy group, and four in the alendronate group had new or worsening vertebral deformities. CONCLUSIONS: This study suggests that a regimen of three-month cycles of parathyroid hormone alternating with three-month cycles without parathyroid hormone causes the early phase of action of parathyroid hormone (characterized by pure stimulation of bone formation) to be dissociated from the later phase (activation of bone remodeling). The early phase may be more important to the increase in spinal bone mineral density. In patients with persistent osteoporosis after prior alendronate treatment, both daily treatment and cyclic treatment with parathyroid hormone increase spinal bone mineral density.

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1. **Does this article POTENTIALLY apply to any of our Key Questions?**

- ( ) POTENTIALLY Eligible
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Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Keywords:
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Abstract:
BACKGROUND: We evaluated whether patients with osteoporosis treated with long-term alendronate have a response to parathyroid hormone treatment and whether short, three-month cycles of parathyroid hormone therapy could be as effective as daily administration. METHODS: We randomly assigned 126 women with osteoporosis who had been taking alendronate for at least 1 year to continued alendronate plus parathyroid hormone (1-34) subcutaneously daily, continued alendronate plus parathyroid hormone (1-34) subcutaneously daily for three 3-month cycles alternating with 3-month periods without parathyroid hormone, or alendronate alone for 15 months. RESULTS: In both parathyroid hormone groups, bone formation indexes rose swiftly. Among the women who were receiving cyclic parathyroid hormone, bone formation declined during cycles without parathyroid hormone and increased again during cycles with parathyroid hormone. Bone resorption increased in both parathyroid hormone groups but increased progressively more in the daily-treatment group than in the cyclic-therapy group. Spinal bone mineral density rose 6.1 percent in the daily-treatment group and 5.4 percent in the cyclic-therapy group (P<0.001 for each parathyroid hormone group as compared with the alendronate group and no significant difference between parathyroid hormone groups). One woman in the daily-treatment group, two in the cyclic-therapy group, and four in the alendronate group had new or worsening vertebral deformities. CONCLUSIONS: This study suggests that a regimen of three-month cycles of parathyroid hormone alternating with three-month cycles without parathyroid hormone causes the early phase of action of parathyroid hormone (characterized by pure stimulation of bone formation) to be dissociated from the later phase (activation of bone remodeling). The early phase may be more important to the increase in spinal bone mineral density. In patients with persistent osteoporosis after prior alendronate treatment, both daily treatment and cyclic treatment with parathyroid hormone increase spinal bone mineral density.

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1. Should this article be INCLUDED? (Choose one)

- ○ No abstract (pull article)
- ○ No (exclude)
- ○ No (Pull article for future reference)--included in this category: narrative reviews, and articles containing base-line data but no outcomes of interest.
- ○ Yes (include)
- ○ Yes (Pull article for reference)

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2. Reason for exclusion (check all that apply)

- ☐ Not English Language
- ☐ No human data
- ☐ Includes ONLY pregnant women
- ☐ Includes ONLY patients with a particular chronic disease (cancer, CVD, HIV)
- ☐ Includes ONLY patients receiving the following treatments or treatments for: dialysis, transplant, chemotherapy, HIV infection, tuberculosis, end-stage renal disease, patients in long-term care facilities.
- ☐ ONLY covers clinical nutritional deficiency
- ☐ Does not apply to the KEY QUESTIONS
- ☐ Does not address use of supplements
- ☐ Does not report use of supplements separately from dietary intake
- ☐ Does NOT cover the defined major disease endpoints or adverse effects of vitamins/minerals
- ☐ Editorial/commentary/letter
- ☐ Other

3. Is this article a randomized-controlled trial, systematic review, or a meta-analysis?

- ○ Yes (article MAY be eligible for any of the key questions)
- ○ No (article is NOT ELIGIBLE for key questions 1 and 2, but may be eligible for key questions 3 and 4)

Not applicable/can't tell

Clear Selection

4. This article potentially applies to the following key question(s) (choose all that apply).

Key Question 1: What is the efficacy determined in randomized controlled trials of supplementation with the single nutrients or functionally related nutrient pairs listed below, each at a dose less than the upper limit determined by the Food and Nutrition Board, in the general adult population for the primary or secondary prevention* of the following chronic diseases/conditions. (i.e., for those without clinically diagnosed disease, who could have risk factors or asymptomatic disease)?

Key Question 2: What is the efficacy determined in randomized controlled trials of multivitamin/mineral supplement use (defined as 3 or more vitamins and/or minerals without herbs, hormones, or drugs), each at a dose less than the upper limit determined by the Food and Nutrition Board, in the general adult population for the primary or secondary prevention of the diseases/conditions listed below?

Key Question 3: What is known about the safety of use of multivitamin/mineral supplements (as defined in question 2), in the general population of adults and children, based primarily on data from randomized controlled trials and well-designed observational studies? We may also consider case-reports and post-marketing surveillance data.

Key Question 4: What is known about the safety of use of the following single nutritional supplements, selenium, iron, â-carotene, and vitamin A, in the general population of adults and children, based primarily on data from randomized controlled trials and well-designed observational studies? We may also consider case-reports and post-market surveillance data. (We will focus primarily on selenium, iron, beta carotene, and vitamin A. Vitamin E, calcium (with or without Vitamin D), vitamin D, and folate may also be considered.)

Does not apply to any of the KEY QUESTIONS

5. Select the nutrients included in this study. Answer ONLY if this article applies to KQ1 and/or KQ2 (check all that apply)

Calcium

Folic acid

Vitamin B6

Vitamin B12

Vitamin D

Vitamin E

Vitamin C

Vitamin A

Iron

Zinc

Magnesium

Vitamin B1

Vitamin B2

Niacin

beta-carotene

Selenuim

☐ Multivitamin

6. Select the disease/conditions included in this study. Answer ONLY if this article applies to KQ1 or KQ2 (choose all that apply).

☐ Oncologic: breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric, (colorectal polyps will be included in this category)

☐ Cardiovascular: myocardial infarction, stroke

☐ Endocrine: type II diabetes

☐ Neurologic: Parkinson's disease, dementia

☐ Age-related sensory loss: cataracts, macular degeneration, hearing loss

☐ Musculoskeletal: osteoporosis, rheumatoid arthritis, osteoarthritis, osteopenia

☐ Gastroenterologic: non-alcoholic steatorrheic hepatitis, non-alcoholic fatty-liver disease

☐ Renal: chronic renal insufficiency, chronic nephrolithiasis

☐ Infectious: HIV infection, hepatitis C, tuberculosis

☐ Pulmonary: chronic obstructive pulmonary disease

DEFINITIONS

"Primary prevention denotes an action taken to prevent the development of a disease in a person who is well and does not have the disease in question."
"Secondary prevention denotes the identification of people who have already developed a disease, at an early stage in the disease's natural history, through screening and early intervention."

Submit Data

Form took 0.4375 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 3

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

1. After reviewing the ENTIRE article, should it be INCLUDED in the review (choose one)

- ○ Yes
- ○ No

Clear Selection

2. Reason for exclusion (choose all that apply).

- ☐ Not English language
- ☐ No human data
- ☐ Includes ONLY pregnant women
- ☐ Includes ONLY patients with a particular chronic disease (cancer, CVD, HIV)
- ☐ Includes ONLY patients receiving the following treatments or treatments for: dialysis, transplant, chemotherapy, HIV infection, tuberculosis, end-stage renal disease, patients in long-term care facilities)
- ☐ ONLY covers nutritional deficiency
- ☐ Does not apply to the KEY QUESTIONS
- ☐ Does not address use of supplements
- ☐ Does not report supplement use separately from dietary intake
- ☐ Does NOT cover the defined major endpoints or advers effects of vitamins/minerals
- ☐ Editorial/commentary/letter
- ☐ Other
- ☐ Narrative review--contains studies of interest OR Not an RCT, Systematic Review, or Meta-analysis [NOTE: Narrative Review articles ARE NOT applicable to Key Questions 1 or 2 but MAY BE APPLICABLE to Key Questions 3 and/or 4]
- ☐ Includes ONLY infants (children less than 1 year old)
- ☐ Includes only subjects less than 19 years of age [article is NOT eligible fo rKey Questions 1 or 2, but MAY be eleigible for Key Qestins 3 and/or 4]

3. Choose article type: (Choose one)

- ○ Randomized controlled trial
- ○ Systematic review/meta-analysis
- ○ Non-randomized trial (with comparison group)
- ○ Narrative review
- ○ Cross-sectional study
- ○ Cohort study (with concurrent or historical historic group)
- ○ Case-control study
- ○ Nested case-control study
- ○ Case series (2 or more case reports
- ○ Other post-market surveillance not otherwise specified

Other

Clear Selection

Inclusion criteria

4. Specific EXCLUSION criteria for Key questions 1 and 2:

QUESTION SCHEDULED FOR DELETION, DO NOT ANSWER

Includes only subjects LESS than 18 years of age (article NOT eligible for Key questions 1 OR 2)

Is NOT a Randomized Controlled Trial, Sytematic Review, or Meta-analysis (article NOT eligible for Key questions 1 OR 2)

5. Select ONLY the Key Questions that this article applies to.

Key Question 1: What is the efficacy determined in randomized controlled trials of supplementation with the single nutrients or functionally related nutrient pairs listed below, each at a dose less than the upper limit determined by the Food and Nutrition Board, in the general adult population for the primary or secondary prevention of the chronic diseases/conditions listed below. (i.e., for those without clinically diagnosed disease, who could have risk factors or asymptomatic disease)?

Key Question 2: What is the efficacy determined in randomized controlled trials of multivitamin/mineral supplement use (defined as 3 or more vitamins and/or minerals without herbs, hormones, or drugs), each at a dose less than the upper limit determined by the Food and Nutrition Board, in the general adult population for the primary or secondary prevention of the diseases/conditions listed below?

Key Question 3: What is known about the safety of use of multivitamin/mineral supplements (as defined in question 2), in the general population of adults and children, based primarily on data from randomized controlled trials and well-designed observational studies? We may also consider case-reports and post-marketing surveillance data.

Key Question 4: What is known about the safety of use of the following single nutritional supplements, selenium, iron, beta carotene, and vitamin A, in the general population of adults and children, based primarily on data from randomized controlled trials and well-designed observational studies? We may also consider case-reports and post-market surveillance data. (We will focus primarily on selenium, iron, beta carotene, and vitamin A. Vitamin E, calcium (with or without Vitamin D), vitamin D, and folate may also be considered.)

Does not apply to the KEY QUESTIONS

Nutrients:

Calcium, Folic acid (folate), Vitamin B6, Vitamin B12, Vitamin D, Vitamin E Vitamin C, Vitamin A, Iron, Zinc, Magnesium, Vitamin B1 (thiamine), Vitamin B2 (riboflavin), Niacin.

Diseases/conditions:

Oncologic: breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric (includes colorectal polyps)
Cardiovascular: myocardial infarction, stroke
Endocrine: type II diabetes
Neurologic: Parkinson's disease, dementia
Age-related sensory loss: cataracts, macular degeneration, hearing loss
Musculoskeletal: osteoporosis, rheumatoid arthritis, osteoarthritis, osteopenia
Gastroenterologic: non-alcoholic steatohepatitis, non-alcoholic fatty-liver disease
Renal: chronic renal insufficiency, chronic nephrolithiasis
Infectious: HIV infection, hepatitis C, tuberculosis
Pulmonary: chronic obstructive pulmonary disease

DEFINITIONS

"Primary prevention denotes an action taken to prevent the development of a disease in a person who is well and does not have the disease in question."
"Secondary prevention denotes the identification of people who have already developed a disease, at an early stage in the disease's natural history, through screening and early intervention."

Submit Data

Form took 0.5195313 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 4

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

GENERAL STUDY CHARACTERISTICS

This form is applicable to ALL Key Questions

1.

Study name and abbreviation (if applicable).

Enlarge Shrink

2. Study Design (choose one)

Please Select

3. Choose one type of RCT ONLY if you selected "Randomized Controlled Trial" in question 2:

Please Select

4. "Other" RCT

Enlarge Shrink

5. Choose one type of Observational Study ONLY if you selected "Observational Study" in question 2:

Please Select

6. "Other" Observational Study

Enlarge Shrink

7. Choose one type of Case Series ONLY if you selected "Case series" in question 2:

Please Select

8. "Other" Case Series

Enlarge Shrink

9. Define "other" study design

Enlarge Shrink

10. Study period:

Start year

End year

Not reported (explain)

11. Follow-up period:

Start year

End year

Not reported (i.e., follow-up not reported)

Not applicable

	Years	Months	Weeks	Not applicalbe	Not reported
12. Total follow-up time:					
13. Median follow-up duration:					
14. Mean follow-up duration:					

Eligibility criteria of **STUDY PARTICIPANTS**--note: these are not study outcomes (only answer those that apply, be as explicite and comprehensive as possible).

	Inclusion	Exclusion	
15. Age			Clear
16. Male			Clear
17. Female			Clear
18. Cancer (specify type)			Clear
19. Myocardial infarction			Clear
20. Stroke			Clear
21. Type II diabetes			Clear
22. Parkinson's disease			Clear
23. Dementia			Clear
24. Cataracts			Clear
25. Macular degeneration			Clear
26. Hearing loss			Clear
27. Osteoporosis or ostepenia (specify)			Clear
28. Arthritis (osteo or rheumatiod) (specify)			Clear
29. Non-alcoholic steatohepatitis			Clear
30. Non-alcoholic fatty liver disease			Clear
31. Chronic renal insufficiency			Clear
32. Chronic nephrolithiasis			Clear

33. HIV infection Clear

34. Hepatitis C Clear

35. Tuberculosis Clear

36. Chronic obstructive pulmonary disease Clear

37. Other disease (specify) Clear

38. Other disease (specify) Clear

39. Other disease (specify) Clear

40. Other disease (specify) Clear

41. Other disease (specify) Clear

42. Other disease (specify) Clear

43. Prior use of supplements (specify supplement) Clear

44. Prior use of supplements (specify supplement) Clear

45. Prior use of supplements (specify supplement) Clear

46. Prior use of supplements (specify supplement) Clear

47. Prior use of supplements (specify supplement) Clear

48. Prior use of supplements (specify supplement) Clear

49. OTHER inclusion/exclusion criteria (specify) Clear

50. OTHER inclusion/exclusion criteria (specify) Clear

51. OTHER inclusion/exclusion criteria (specify) Clear

52. OTHER inclusion/exclusion criteria (specify) Clear

Study participants.

53. Total sample size at enrolment (*N*)

Enlarge Shrink

54. Country, State, County, City, or other Geographic Area as reported.

Enlarge Shrink

55. Recruitment setting

- Clinical
- Community
- Other

Clear Selection

Patient Characteristics (these are OPTIONAL questions, please be as detailed as possible when filling out the following tables).

	Range	Mean	Standard Deviation
56. Age (in years)			

	n	%
57. Male		
58. Female		

Race:

	n	%
59. White		
60. Black/ African American		
61. Native Hawaiian/other Pacific Islander		
62. Native American/Alaska Native		
63. Hispanic/Latino		
64. Asian		

Other Race, not specified in above table (please specify below).

	Specify	n	%
65. Other 1			
66. Other 2			
67. Other 3			

Smoking status:

	n	%
68. Never smoked		
69. Former smoker		
70. Current smoker		
71. Other smoker		

Alcohol use status:

	n	%	
72. Never used/drank alcohol			
73. Former alcohol user/drinker			
74. Current alcohol user/drinker			
75. Other alcohol user/drinker			

Other patient characteristics:

	Range	Mean	Median	Standard Deviation
76. BMI <25				
77. BMI 25-29				
78. BMI ≥ 30				

	Define	Range	Mean	Median	Standard Deviation
79. Other study characterisitcs					
80. Other study characterisitcs					
81. Other study characterisitcs					
82. Other study characterisitcs					
83. Other study characterisitcs					
84. Other study characterisitcs					
85. Other study characterisitcs					
86. Other study characterisitcs					
87. Other study characterisitcs					
88. Other study characterisitcs					

Supplements used prior to this study.

	n	%
89. Calcium		
90. Folic acid		
91. B 6		
92. B 12		
93. Vitamin D		
94. Vitamin E		
95. Vitamin C		
96. Vitamin A		
97. beta-carotene		
98. Iron		
99. Zinc		
100. Magnesium		
101. B 1		
102. B 2		
103. Niacin		

	Specify	n	%
104. Selenium			
105. Other 1			
106. Other 2			
107. Other 3			
108. Other 4			

109. NOTES on General Study Characteristics

please add any information that you believe will contribute to the outcome of the systematic review

Enlarge Shrink

110. Does this study include data on adverse events?

- Yes, study covers BOTH efficacy and adverse events--Fill out BOTH OUTCOMES forms (Levels 13 and 14)
- Yes, study covers ONLY adverse events--Fill out ONLY the OUTCOMES FORM for key questions 3 and 4 (Level 14)
- No, study covers ONLY efficacy --Fill out ONLY the OUTCOMES FORM for key questions 1 and 2 (Level 13)

Clear Selection

Submit Data

Form took 2.1875 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 5

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

1. Arm 1 (define)

Enlarge Shrink

Control arms (answer these questions ONLY if no nutrient interveniton was provided):

	Exposure--WEEKS	Exposure--MONTHS	Exposure--YEARS
2. Placebo			
3. No dietary supplements or No standard care			
4. Standard care			
5. Nutritional/dietary education			

Intervention arms (answer these questions ONLY if a nutrient interveniton was provided):

	Calcium	Folic acid	Vitamin B6	Vitamin B12	Vitamin D	Vitamin E	Vitamin C	Vitamin A	Iron	Zinc	Magnesium	Vitamin B1	Vitamin B2	Niacin	Selenuim
6. Select ALL of the nutrients (those that apply to this study's key questions) represented in this arm	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Identify ALL of the nutrients (those not listed in this study's key questions) represented in this arm.

7. Other
☑ 1 co-Qa

8. Other
☐ 2

9. Other
☐ 3

10. Other
☐ 4

11. Other
☐ 5

12. Other
☐ 6

13. Other
☐ 7

14. Other
☐ 8

INSTRUCTIONS FOR COMPLETING INTERVENTION ARM GENERAL DATA:
1. Include information on all forms and combinations of nutrients and other therapies in each arm of this study (example: if a study has 3 arms; placebo, calcium, and calcium/HRT, we need the information on calcium for BOTH intervention arms).
2. If more than one chemical form of the same nutrient is used in an arm, fill out the specific nutrient information for ONE of the chemical forms and use "other" at the end of this form for the remaining chemical forms. If you do not have enough "other" options, contact Renee immediately and more will be added.

CALCIUM

15. Chemical form

Please Select

16. Chemical form "other"

Specify

17. Total Dose

Specify amount

18. Units

Please Select

19. Unit, "other"

Specify

20. Frequency of use

Please Select

21. Frequency of use, "other"

Specify

22. Timing of use

Please Select

23. Timing of use, "other"

Specify

24. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

FOLIC ACID (folate)

25. Chemical form

Please Select

26. Chemical form "other"

Specify

27. Total Dose

Specify amount

28. Units

Please Select

29. Unit, "other"

Specify

30. Frequency of use

Please Select

31. Frequency of use, "other"

Specify

32. Timing of use

Please Select

33. Timing of use, "other"

Specify

34. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN B6 (pyridoxine)

35. Chemical form

Please Select

36. Chemical form "other"

Specify

37. Total dose

Specify amount

38. Units

Please Select

39. Unit, "other"

Specify

40. Frequency of use

Please Select

41. Frequency of use, "other"

Specify

42. Timing of use

Please Select

43. Timing of use, "other"

Specify

44. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN B12 (cyanocobalamin)

45. Chemical form

Please Select

46. Chemical form "other"

Specify

47. Total dose

Specify amount

48. Units

Please Select

49. Units, "other"

Specify

50. Frequency of use

Please Select

51. Frequency of use, "other"

Specify

52. Timing of use

Please Select

53. Timing of use, "other"

Specify

54. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN D

55. Chemical form

Please Select

56. Chemical form "other"

Specify

57. Total dose

Specify amount

58. Units

Please Select

59. Unit, "other"

Specify

60. Frequency of use

Please Select

61. Frequency of use, "other"

Specify

62. Timing of use

Please Select

63. Timing of use, "other"

Specify

64. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN E

65. Chemical form
Please Select
66. Chemical form "other"
Specify
67. Total dose
Specify amount
68. Units
Please Select
69. Unit, "other"
Specify
70. Frequency of use
Please Select
71. Frequency of use, "other"
Specify
72. Timing of use
Please Select
73. Timing of use, "other"
Specify
74. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified

VITAMIN C
75. Chemical form
Please Select
76. Chemical form "other"
Specify
77. Total does
Specify amount
78. Units
Please Select
79. Unit, "other"
Specify
80. Frequency of use
Please Select
81. Frequency of use, "other"
Specify
82. Timing of use
Please Select
83. Timing of use, "other"
Specify

84. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN A

85. Chemical form

Please Select

86. Chemical form "other"

Specify

87. Total dose

Specify amount

88. Dose, units

Please Select

89. Unit, "other"

Specify

90. Frequency of use

Please Select

91. Frequency of use, "other"

Specify

92. Timing of use

Please Select

93. Timing of use, "other"

Specify

94. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

IRON

95. Chemical form

Please Select

96. Chemical form "other"

Specify

97. Total dose

Specify amount

98. Units

Please Select

99. Unit, "other"

Specify

100. Frequency of use
Please Select
101. Frequency of use, "other"
Specify
102. Timing of use
Please Select
103. Timing of use, "other"
Specify
104. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified

ZINC
105. Chemical form
Please Select
106. Chemical form "other"
Specify
107. Total dose
Specify amount
108. Units
Please Select
109. Units, "other"
Specify
110. Frequency of use
Please Select
111. Frequency of use, "other"
Specify
112. Timing of use
Please Select
113. Timing of use, "other"
Specify
114. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified

MAGNESIUM
115. Chemical form
Please Select
116. Chemical form "other"

Specify

117. Total dose

Specify amount

118. Units

Please Select

119. Unit, "other"

Specify

120. Frequency of use

Please Select

121. Frequency of use, "other"

Specify

122. Timing of use

Please Select

123. Timing of use, "other"

Specify

124. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN B1 (thiamine)

125. Chemical form

Please Select

126. Chemical form "other"

Specify

127. Total dose

Specify amount

128. Units

Please Select

129. Unit, "other"

Specify

130. Frequency of use

Please Select

131. Frequency of use, "other"

Specify

132. Timing of use

Please Select

133. Timing of use, "other"

Specify

134. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

VITAMIN B2 (riboflavin)

135. Chemical form

Please Select

136. Chemical form "other"

Specify

137. Total dose

Specify amount

138. Units

Please Select

139. Unit, "other"

Specify

140. Frequency of use

Please Select

141. Frequency of use, "other"

Specify

142. Timing of use

Please Select

143. Timing of use, "other"

Specify

144. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

NIACIN

145. Chemical form

Please Select

146. Chemical form "other"

Specify

147. Total dose

Specify amount

148. Units

Please Select

149. Unit, "other"

Specify

150. Frequency of use

Please Select

151. Frequency of use, "other"

Specify

152. Timing of use
Please Select
153. Timing of use, "other"
Specify
154. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified

SELENIUM
155. Chemical form
Please Select
156. Chemical form "other"
Specify
157. Total dose
Specify amount
158. Units
Please Select
159. Unit, "other"
Specify
160. Frequency of use
Please Select
161. Frequency of use, "other"
Specify
162. Timing of use
Please Select
163. Timing of use, "other"
Specify
164. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified
165. OTHER
1
166. Chemical form
Specify
Not specified
167. Total dose
Specify amount

168. Units
Please Select
169. Unit, "other"
Specify
170. Frequency of use
Please Select
171. Frequency of use, "other"
Specify
172. Timing of use
Please Select
173. Timing of use, "other"
Specify
174. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified
175. OTHER
2
176. Chemical form
Specify
Not specified
177. Total dose
Specify amount
178. Units
Please Select
179. Unit, "other"
Specify
180. Frequency of use
Please Select
181. Frequency of use, "other"
Specify
182. Timing of use
Please Select
183. Timing of use, "other"
Specify
184. Duration of use
Exposure--WEEKS
Exposure--MONTHS
Exposure--YEARS
Not specified
185. OTHER

☐ 3

186. Chemical form

☐ Specify

☐ Not specified

187. Total dose

Specify amount

188. Units

Please Select

189. Unit, "other"

Specify

190. Frequency of use

Please Select

191. Frequency of use, "other"

Specify

192. Timing of use

Please Select

193. Timing of use, "other"

Specify

194. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

☐ Not specified

195. OTHER

☐ 4

196. Chemical form

☐ Specify

☐ Not specified

197. Total dose

Specify amount

198. Units

Please Select

199. Unit, "other"

Specify

200. Frequency of use

Please Select

201. Frequency of use, "other"

Specify

202. Timing of use

Please Select

203. Timing of use, "other"

Specify

204. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

205. OTHER

5

206. Chemical form

Specify

Not specified

207. Total dose

Specify amount

208. Units

Please Select

209. Unit, "other"

Specify

210. Frequency of use

Please Select

211. Frequency of use, "other"

Specify

212. Timing of use

Please Select

213. Timing of use, "other"

Specify

214. Duration of use

Exposure--WEEKS

Exposure--MONTHS

Exposure--YEARS

Not specified

215. Notes on ARM 1

Enlarge Shrink

Submit Data

Form took 12.03125 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 13

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Study Results (Outcomes)

This form is ONLY to be used for studies applying to Key Questions 1 and/or 2.

Study endpoints:
Check all that apply, please be as complete as possible in your answers.

	Primary endpoint	Secondary endpoint	
1. Any cancer	○	○	Clear
2. Cancer other than non-melanoma skin cancer	○	○	Clear
3. Breast cancer	○	○	Clear
4. Colorectal cancer	○	○	Clear
5. Lung cancer	○	○	Clear
6. Prostate cancer	○	○	Clear
7. Gastric cancer	○	○	Clear
8. Myocardial infarction	○	○	Clear
9. Stroke	○	○	Clear
10. Cancer other than non-melanoma skin cancer	○	○	Clear
11. Type II diabetes	○	○	Clear
12. Parkinson's disease	○	○	Clear
13. Dementia	○	○	Clear
14. Cataracts	○	○	Clear
15. Macular degeneration	○	○	Clear
16. Hearing loss	○	○	Clear
17. Osteporosis	○	○	Clear
18. Bone mineral density	○	○	Clear
19. Rheumatiod arthritis	○	○	Clear
20. Osteoarthritis	○	○	Clear
21. Osteopenia	○	○	Clear
22. Non-alcoholic steatohepatitis	○	○	Clear
23. Non-alcoholic fatty-liver disease	○	○	Clear
24. Chronic renal insufficiency	○	○	Clear
25. Chronic nepholithiasis	○	○	Clear
26. HIV infection	○	○	Clear
27. Hepatitis C	○	○	Clear
28. Tuberculosis	○	○	Clear
29. Chronic obstructive pulmonary disease	○	○	Clear

	Define	Primary endpoint	Secondary endpoint
30. Other _____	☐	☐	☐

31. Other
32. Other
33. Other
34. Other
35. Other
36. Other
37. Other
38. Other
39. Other
40. Other
41. Other
42. Other

Study results (disease endpoints):
Do not include BMD, or area of opacity results in this table, a seperate table has been supplied for this data.
Check all that apply, please be as complete as possible in your answers.

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
43. 1.								
44. 2.								
45. 3.								
46. 4.								
47. 5.								
48. 6.								
49. 7.								
50. 8.								
51. 9.								

Study results (Bone Mineral Density (BMD)):
Do not include data on area of opacity in this table, a seperate table has been supplied for this data.
Check all that apply, please be as complete as possible in your answers.

Randomized group	Bone density site	Median IQR change from	Mean change from baseline	Standard deviation	Standard error	95% CI	Difference from placebo (95%	p-value

			baseline					CI)	
52. 1.									
53. 2.									
54. 3.									
55. 4.									
56. 5.									
57. 6.									
58. 7.									
59. 8.									
60. 9.									

Study results (area of opacity (% pixels opaque), cognitive function test results or results from other contour measurements): Do not include data on bone mineral density in this table, a seperate table has been supplied for this data. Check all that apply, please be as complete as possible in your answers.

	Randomized group	Median IQR	Mean change from baseline	Standard deviation	Standard error	95% CI	Difference from placebo (95% CI)	p-value	Com
61. 1.									
62. 2.									
63. 3.									
64. 4.									
65. 5.									
66. 6.									
67. 7.									
68. 8.									
69. 9.									

70. What subgroups were analyzed?

- ☐ Gender (specify)
- ☐ Age (specify)
- ☐ Ethnicity (specify)
- ☐ Other (specify)

71. Subgroup 1

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
72. 1.								
73. 2.								
74. 3.								
75. 4.								
76. 5.								
77. 6.								
78. 7.								

79.
8.

80. Subgroup 2

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
81.	1.							
82.	2.							
83.	3.							
84.	4.							

85. Notes on Efficacy Outcomes

Enlarge Shrink

86. Subgroup 3

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
87.	1.							
88.	2.							
89.	3.							
90.	4.							

91. Notes on Efficacy Outcomes

Enlarge Shrink

92. Subgroup 4

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
93.	1.							
94.	2.							
95.	3.							
96.	4.							

97. Notes on Efficacy Outcomes

Enlarge Shrink

98. Subgroup 5

Enlarge Shrink

Diseease endpoint	Study supplement	Total Number in study	Number of disease events	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--	p-value

			(active/placebo)	(active/placebo)			specify RR, OR, or HR)	
99. 1.								
100. 2.								
101. 3.								
102. 4.								

103. Notes on Efficacy Outcomes

Enlarge Shrink

104. Subgroup 6

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
105. 1.								
106. 2.								
107. 3.								
108. 4.								

109. Notes on Efficacy Outcomes

Enlarge Shrink

110. Subgroup 7

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
111. 1.								
112. 2.								
113. 3.								
114. 4.								

115. Notes on Efficacy Outcomes

Enlarge Shrink

116. Subgroup 8

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
117. 1.								
118. 2.								
119. 3.								
120. 4.								

121. Notes on Efficacy Outcomes

Enlarge Shrink

122. Subgroup 9

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
123. 1.								
124. 2.								
125. 3.								
126. 4.								

127. Notes on Efficacy Outcomes

Enlarge Shrink

128. Subgroup 10

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
129. 1.								
130. 2.								
131. 3.								
132. 4.								

133. Notes on Efficacy Outcomes

Enlarge Shrink

134. Subgroup 11

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
135. 1.								
136. 2.								
137. 3.								
138. 4.								

139. Notes on Efficacy Outcomes

Enlarge Shrink

140. Subgroup 12

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
141. 1.								
142. 2.								
143. 3.								
144. 4.								

145. Notes on Efficacy Outcomes

Enlarge Shrink

146. Subgroup 13

Enlarge Shrink

	Diseease endpoint	Study supplement	Total Number in study (active/placebo)	Number of disease events (active/placebo)	Person years (active/placebo)	Incidence	Unadjusted estimates (point estimate and 95% CI--specify RR, OR, or HR)	p-value
147. 1.								
148. 2.								
149. 3.								
150. 4.								

151. Notes on Efficacy Outcomes

Enlarge Shrink

Submit Data

Form took 3.265625 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 14

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Study Results (Outcomes)

This form is ONLY to be used for studies applying to Key Questions 3 and/or 4.

Types of Outcomes
(Study Endpoints)

1. List ALL safety-related outcomes reported in this study

1.
2.
3.
4.
5.
6.

Criteria for causality (for outcome 1 listed above):

	Yes	No	Not reported	
2. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
3. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
4. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
5. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
6. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
7. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Criteria for causality (for outcome 2 listed above):

	Yes	No	Not reported	
8. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
9. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
10. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
11. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
12. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
13. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Criteria for causality (for outcome 3 listed above):

	Yes	No	Not reported	
14. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
15. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
16. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
17. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
18. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
19. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Criteria for causality (for outcome 4 listed above):

	Yes	No	Not reported	
20. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
21. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
22. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
23. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
24. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
25. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Criteria for causality (for outcome 5 listed above):

	Yes	No	Not reported	
26. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
27. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
28. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
29. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
30. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
31. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Criteria for causality (for outcome 6 listed above):

	Yes	No	Not reported	
32. Did supplement use take place prior to adverse events/effects (i.e., temporal relationships)?	○	○	○	Clear
33. Did the original data reported in this article support a dose-respones relationship?	○	○	○	Clear
34. Did advers effects disappear after discontinuation of supplement use?	○	○	○	Clear
35. Was there evidence that serum levels of nutrients increased after supplementation?	○	○	○	Clear
36. Was there lack of alternative cause for the edverse effects other than supplemetn use?	○	○	○	Clear
37. Did adverse effectrs occur again after re-use of the supplements?	○	○	○	Clear

Study results (note that side effects may be presented as reasons for dropouts).

38. Nutrient	39. Outcome as adverse event/event (i.e., vomiting, hives).	40. Side effects or adverse events reported?	41. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	42. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	43. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply	44. Change in control group answer all that apply	45. Point estimate	46. 95% CI	47. Comment (e.g., adjusted for any factor)
Enlarge Shrink	Enlarge Shrink	Please Select	Enlarge Shrink	Enlarge Shrink	☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	☐ Not applicable ☐ Not reported ☐ Reported	Enlarge Shrink
48. Nutrient	49. Outcome as adverse event/event (i.e., vomiting, hives).	50. Side effects or adverse events reported?	51. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the	52. Number of events in the control group. enter "0" if no adverse effects occurred	53. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply	54. Change in control group answer all that apply	55. Point estimate	56. 95% CI	57. Comment (e.g., adjusted for any factor)
Enlarge Shrink	Enlarge Shrink	Please Select			☐ Mean (95% CI) ☐ Mean (SD)	☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean	☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio	☐ Not applicable ☐ Not reported	Enlarge

			result was not reported Enlarge Shrink	enter "not reported" if the result was not reported Enlarge Shrink	☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	(SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	☐ Not applicable ☐ Not reported			Shrink
58. Nutrient Enlarge Shrink	59. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	60. Side effects or adverse events reported? Please Select	61. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	62. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	63. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	64. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	65. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	66. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	67. Comment (e.g., adjusted for any factor) Enlarge Shrink
68. Nutrient Enlarge Shrink	69. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	70. Side effects or adverse events reported? Please Select	71. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	72. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	73. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	74. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	75. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	76. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	77. Comment (e.g., adjusted for any factor) Enlarge Shrink
78. Nutrient Enlarge Shrink	79. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	80. Side effects or adverse events reported? Please Select	81. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	82. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	83. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	84. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	85. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	86. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	87. Comment (e.g., adjusted for any factor) Enlarge Shrink
88.	89. Outcome	90. Side effects or	91. Number	92.	93. Change in active (nutrient) group	94. Change in control group	95. Point estimate	96. 95% CI	97.	

Nutrient Enlarge Shrink	as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	adverse events reported? Please Select	of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	(e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	Not applicable Not reported Reported	Comment (e.g., adjusted for any factor) Enlarge Shrink
98. Nutrient Enlarge Shrink	99. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	100. Side effects or adverse events reported? Please Select	101. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	102. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	103. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	104. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	105. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	106. 95% CI Not applicable Not reported Reported	107. Comment (e.g., adjusted for any factor) Enlarge Shrink
108. Nutrient Enlarge Shrink	109. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	110. Side effects or adverse events reported? Please Select	111. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	112. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	113. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	114. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	115. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	116. 95% CI Not applicable Not reported Reported	117. Comment (e.g., adjusted for any factor) Enlarge Shrink
118. Nutrient Enlarge Shrink	119. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	120. Side effects or adverse events reported? Please Select	121. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	122. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	123. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median	124. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other	125. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not	126. 95% CI Not applicable Not reported Reported	127. Comment (e.g., adjusted for any factor) Enlarge Shrink

			Enlarge Shrink	Enlarge Shrink	Other Not reported Not applicable	Not applicable Not reported	reported			
128. Nutrient Enlarge Shrink	129. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	130. Side effects or adverse events reported? Please Select	131. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	132. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	133. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	134. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	135. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	136. 95% CI Not applicable Not reported Reported	137. Comment (e.g., adjusted for any factor) Enlarge Shrink
138. Nutrient Enlarge Shrink	139. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	140. Side effects or adverse events reported? Please Select	141. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	142. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	143. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	144. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	145. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	146. 95% CI Not applicable Not reported Reported	147. Comment (e.g., adjusted for any factor) Enlarge Shrink
148. Nutrient Enlarge Shrink	149. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	150. Side effects or adverse events reported? Please Select	151. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	152. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	153. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	154. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	155. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	156. 95% CI Not applicable Not reported Reported	157. Comment (e.g., adjusted for any factor) Enlarge Shrink
158. Nutrient	159. Outcome as adverse event/event (i.e., vomiting, hives).	160. Side effects or adverse events reported? Please Select	161. Number of events in the active (nutrient)	162. Number of events in the control	163. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean	164. Change in control group answer all that apply Mean (95% CI)	165. Point estimate Relative Risk Odds	166. 95% CI Not applicable Not	167. Comment (e.g., adjusted for any factor)

Enlarge Shrink	Enlarge Shrink		group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	(95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	Mean (SD) Mean (SE) Median Other Not applicable Not reported	Ratio Hazard Ratio Not applicable Not reported	reported Reported	Enlarge Shrink
168. Nutrient Enlarge Shrink	169. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	170. Side effects or adverse events reported? Please Select	171. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	172. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	173. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	174. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	175. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	176. 95% CI Not applicable Not reported Reported	177. Comment (e.g., adjusted for any factor) Enlarge Shrink
178. Nutrient Enlarge Shrink	179. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	180. Side effects or adverse events reported? Please Select	181. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	182. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	183. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	184. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	185. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	186. 95% CI Not applicable Not reported Reported	187. Comment (e.g., adjusted for any factor) Enlarge Shrink
188. Nutrient Enlarge Shrink	189. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	190. Side effects or adverse events reported? Please Select	191. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	192. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	193. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported	194. Change in control group answer all that apply Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable	195. Point estimate Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	196. 95% CI Not applicable Not reported Reported	197. Comment (e.g., adjusted for any factor) Enlarge Shrink

				Enlarge Shrink	☐ Not applicable	☐ Not reported			
198. Nutrient Enlarge Shrink	199. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	200. Side effects or adverse events reported? Please Select	201. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	202. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	203. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	204. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	205. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	206. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	207. Comment (e.g., adjusted for any factor) Enlarge Shrink
208. Nutrient Enlarge Shrink	209. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	210. Side effects or adverse events reported? Please Select	211. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	212. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	213. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	214. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	215. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	216. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	217. Comment (e.g., adjusted for any factor) Enlarge Shrink
218. Nutrient Enlarge Shrink	219. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	220. Side effects or adverse events reported? Please Select	221. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	222. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	223. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	224. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	225. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	226. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	227. Comment (e.g., adjusted for any factor) Enlarge Shrink
228. Nutrient Enlarge Shrink	229. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	230. Side effects or adverse events reported? Please Select	231. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not	232. Number of events in the control group. enter "0" if no adverse effects occurred	233. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD)	234. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE)	235. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio	236. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	237. Comment (e.g., adjusted for any factor) Enlarge

			reported" if the result was not reported Enlarge Shrink	enter "not reported" if the result was not reported Enlarge Shrink	☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	☐ Median ☐ Other ☐ Not applicable ☐ Not reported	☐ Not applicable ☐ Not reported		Shrink
238. Nutrient Enlarge Shrink	239. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	240. Side effects or adverse events reported? Please Select	241. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	242. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	243. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	244. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	245. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	246. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	247. Comment (e.g., adjusted for any factor) Enlarge Shrink
248. Nutrient Enlarge Shrink	249. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	250. Side effects or adverse events reported? Please Select	251. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	252. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	253. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	254. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	255. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	256. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	257. Comment (e.g., adjusted for any factor) Enlarge Shrink
258. Nutrient Enlarge Shrink	259. Outcome as adverse event/event (i.e., vomiting, hives). Enlarge Shrink	260. Side effects or adverse events reported? Please Select	261. Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	262. Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported Enlarge Shrink	263. Change in active (nutrient) group (e.g., cholesterol data) answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not reported ☐ Not applicable	264. Change in control group answer all that apply ☐ Mean (95% CI) ☐ Mean (SD) ☐ Mean (SE) ☐ Median ☐ Other ☐ Not applicable ☐ Not reported	265. Point estimate ☐ Relative Risk ☐ Odds Ratio ☐ Hazard Ratio ☐ Not applicable ☐ Not reported	266. 95% CI ☐ Not applicable ☐ Not reported ☐ Reported	267. Comment (e.g., adjusted for any factor) Enlarge Shrink
268.	269. Outcome	270. Side effects or	271.	272.	273. Change in active (nutrient) group	274. Change in control group	275. Point estimate	276. 95% CI	277.

Nutrient	as adverse event/event (i.e., vomiting, hives).	adverse events reported?	Number of events in the active (nutrient) group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	Number of events in the control group. enter "0" if no adverse effects occurred enter "not reported" if the result was not reported	(e.g., cholesterol data) answer all that apply	answer all that apply			Comment (e.g., adjusted for any factor)
Enlarge Shrink	Enlarge Shrink	Please Select	Enlarge Shrink	Enlarge Shrink	Mean (95% CI) Mean (SD) Mean (SE) Median Other Not reported Not applicable	Mean (95% CI) Mean (SD) Mean (SE) Median Other Not applicable Not reported	Relative Risk Odds Ratio Hazard Ratio Not applicable Not reported	Not applicable Not reported Reported	Enlarge Shrink

278. NOTES: Add notes on this study regarding data that did not fit into the above form.

Enlarge Shrink

Submit Data

Form took 14.8125 seconds to render

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Previewing at Level 15

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Quality Review Form
(only for articles that apply to Key Questions 1 and/or 2)

NOTE FOR SECOND REVIEWERS:
All quality reviews should be done independantly. DO NOT follow the serial review instructions as you have for the outcomes data

NOTE: numbers in brackets () are the quality score

Representativeness of the Study Population

1. Did the study describe the setting and population from which the study sample was drawn, and the dates of the study?
Please Select

2. Were detailed inclusion/exclusion criteria provided?
Please Select

3. Was information provided on excluded or non-participating individuals?
Please Select

4.

Does the study describe key characteristics of study participants at enrollment?

Demographics: age, gender, race/ethnicity, education

Medical risk factors:

i. Oncologic (breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric, or any other malignancy, colorectal polyps): family history, medical conditions (e.g. benign prostatic hyperplasia, benign breast disease, inflammatory bowel disease).
ii. Cardiovascular (MI, stroke): family history of CVD, obesity, lipid profile, hypertension, diabetes
iii. Endocrine (type II diabetes): obesity
iv. Neurologic (Parkinson's disease):
Neurologic (Dementia):
v. Age-related sensory loss (cataracts, macular degeneration, hearing loss):
vi. Musculoskeletal (osteoporosis, rheumatoid arthritis, osteoarthritis, osteopenia): women, heredity, sex hormone deficiency (estrogen deficiency in women, testosterone deficiency in men), low body weight, physical inactivity, poor calcium intake, vitamin D deficiency, excessive alcohol drinking
vii. Gastroenterologic (non-alcoholic steatorrheic hepatitis, NAFLD): obesity, type 2 diabetes, elevated total cholesterol or triglyceride.
viii. Renal (chronic renal insufficiency, chronic nephrolithiasis): hypertension, diabetes, African American, hypercalciuria
ix. HIV infection:
Hepatitis C:
TB:
x. Pulmonary: COPD

Lifestyle risk factors: smoking, prior dietary supplement use, diet, physical activities

Use of medication: any medication reported, particularly those used to prevent or treat the outcome of interest
Please Select

Bias and Confounding

5. Was the assignment of patients to study group randomly determined?
Please Select

6.

Was concealment of allocation sequence adequate?
Please Select

* Centralized randomization by telephone; numbered or coded identical containers administered sequentially; on-site computer system which can only be accessed after entering the characteristics of an enrolled participant; sequentially numbered, sealed, opaque envelopes.
** Sealed envelopes but not sequentially numbered or opaque; list of random numbers read by someone entering patient into trial (open list); a trial in which the description suggests adequate concealment, but other features are suspicious (for example: markedly unequal controls and trial groups; stated random, but unable to obtain further details.
*** for example: an open list of random numbers, alternation, date of birth, day of week, case record number, not randomized or unclear.

7.

Did the patient groups have any important differences in key patient characteristics?

Demographics: age, gender, race/ethnicity, education,

i. Oncologic (breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric, or any other malignancy, colorectal polyps): family history, medical conditions (e.g. benign prostatic hyperplasia, benign breast disease, inflammatory bowel disease).
ii. Cardiovascular (MI, stroke): family history of CVD, obesity, lipid profile, hypertension, diabetes
iii. Endocrine (type II diabetes): obesity
iv. Neurologic (Parkinson's disease):
Neurologic (Dementia):
v. Age-related sensory loss (cataracts, macular degeneration, hearing loss):
vi. Musculoskeletal (osteoporosis, rheumatoid arthritis, osteoarthritis, osteopenia): women, heredity, sex hormone deficiency (estrogen deficiency in women, testosterone deficiency in men), low body weight, physical inactivity, poor calcium intake, vitamin D deficiency, excessive alcohol drinking
vii. Gastroenterologic (non-alcoholic steatorrheic hepatitis, NAFLD): obesity, type 2 diabetes, elevated total cholesterol or triglyceride.
viii. Renal (chronic renal insufficiency, chronic nephrolithiasis): hypertension, diabetes, African American, hypercalciuria
ix. HIV infection:
Hepatitis C:
TB:

x. Pulmonary: COPD

Lifestyle Factors: smoking, prior dietary supplement use, diet, physical activities

Use of medication: any medication reported, particularly those used to prevent or treat the outcome of interest

Please Select

8.

Did study report adequate information about the use of vitamin/mineral supplements prior to study enrollment?

Please Select

9.

Did the study groups differ in the use of vitamin/mineral supplements prior to study enrollment?

Please Select

10.

Did the study describe medication use during the study period that may affect the net efficacy of the supplements of interest?

Please Select

11.

Were there efforts made to blind study supplements?

Please Select

12.

Did the study report evidence of success on blinding study subjects?

Please Select

13.

Were diagnoses of clinical outcomes in the present study confirmed by medical charts, pathohistological data or registry?

Please Select

14.

Was interpretation of clinical outcomes performed by two or more independent observers?

Please Select

15.

Was there blinding to clinicians, study participants, outcome assessors and statisticians with regard to group assignment?

Please Select

16.

Were all randomized arms blinded?

Please Select

Description of Study Supplements/Supplementation

17.

How well were the details of the study supplements (including placebo)described? (i.e., types of supplements, chemical forms of supplements, and dosage, frequency, and duration of supplementation)

Please Select

18.

How good was the assessment of adherence to supplemetnations?

Please Select

Adherence and Follow-up

19.

How did the study describe the flow of participants through each stage? For each group, the number of participants randomly assigned, receiving intended intervention, completing the study protocol and analyzed for the primary outcome.

Please Select

20.

How was the participants' adherence to study supplement use?

Please Select

21.

Was there an unintended cross-over between/among randomized groups? (i.e. subjects in one arm taking what was assigned to another arm)

Please Select

22.

Did the study report the numbers or reasons for withdrawals from the study protocol or for participants otherwise lost to follow-up?

Please Select

23.

What was the percentage of participants who withdrew from the study protocol or were lost to follow-up?

Please Select

24.

Did the study stop the intervention earlier than as planned or describe other deviations from the study protocol together with reasons?

Please Select

* no deviations from the protocol OR deviations from the protocol with reasons given did not appear to have affected the estimate of the efficacy
** deviations from the protocol with reasons given BUT may have affected the estimate of the efficacy, e.g. inadequate follow-up
*** deviations from the protocol with no reasons given AND may have affected the efficacy of interest

Statistical Analysis

25.

Was the statistical test of all analyses clearly identified?

Please Select

26.

Was unintended cross-over handled appropriately in the analysis?

Please Select

27.

Was loss-to-follow-up handled appropriately in the analysis?

Please Select

28.

For primary endpoints of the evaluation, does the study report: (The magnitude of difference between groups OR magnitude of the association between outcomes and participant characteristics) AND (an index of variability e.g., test statistic, p value, standard error, confidence interval)?

Please Select

29.

Was adequate adjustment made for potential confounding in the analysis from which the main findings were drawn?

Please Select

* adjusted for all potential confounding factors that differed between groups
** adjusted for some but not all potential confounding factors
*** did not adjust for confounding factors or unclear whether potential confounding factors differed between groups
**** e.g., groups did not differ in important participant characteristics

30.

Did the study report its statistical power?

Please Select

Conflicts of Interest

31.

Did the study report identify the sources of funding and the type and degree of involvement of the funding agency?

Please Select

32. Notes on Quality

Enlarge Shrink

Submit Data

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Previewing at Level 16

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Quality Review Form
(only for SYSTEMATIC REVIEWS)

NOTE FOR SECOND REVIEWERS:
All quality reviews should be done independantly. DO NOT follow the serial review instructions as you have for the outcomes data

NOTE: numbers in brackets () are the quality score

1. Did the authors clearly state the question addressed by the overview at the beginning of the article?
Please Select

2. Did the authors describe the search methods used to find evidence (original research) on the primary question(s)?
Please Select

3. Was the search for evidence reasonably comprehensive?
Please Select

* Search included MEDLINE (or other electronic database), hand-searching of select journals or reference lists, AND query of 1 or more experts.
** Search included MEDLINE (or other electronic database), but did not include hand-searching of journals or reference lists AND/OR did not include a query of experts.
*** Search did not include an electronic database of journals

4. Did the authors report on the criteria they used for deciding which studies to include in the systematic review?
Please Select

5. Were the inclusion criteria appropriate (aimed at avoiding bias in the selection of studies)?
Please Select

6. Were analyses done to see whether efficacy varies according to dose and duration of the supplements, such as dose-response analyses?
Please Select

7. Were analyses done to see whether efficacy varies according to the forms of the dietary supplements?
Please Select

8. Did the authors assess study quality?
Please Select

9. Was the quality assessment done appropriately?
Please Select

* Quality assessment was done using a validated instrument (with citation) or the authors demonstrated validity of their methods
** Authors used their own quality assessment instrument without validation, or another instrument with unknown measurement properties.

10. Did the authors evaluate and consider the differences in defining outcomes across studies? (e.g., overall CVD vs. combination of specific cardiovascular events)
Please Select

11. Did the authors take account of the different ways of reporting outcomes across studies in their analyses?
Please Select

12. Did the authors demonstrate that their methodology was reproducible?
Please Select

* The investigators mostly (>50% of the time) agreed on selection of articles, on quality assessment, AND on the data that was extracted.
** Disagreement occurred the majority of the time either on the selection of articles, quality assessment, or data extraction (but not all 3).
*** Disagreement occurred the majority of the time on the selection of articles, quality assessment, AND data extraction.

13. Did the authors discuss whether variation in the results of the original research may be due to differences in study design or population?
Please Select

* Text or tables provide comparative information on both study design, and population characteristics

14. Were the results of the relevant studies combined appropriately relative to the primary question?
Please Select

* The overview included some assessment of the qualitative and quantitative heterogeneity of study results AND used an accepted pooling method (i.e., more than simple addition).

15. Were the conclusions of the authors supported by the data and/or analysis reported in the overview?
Please Select

Submit Data

Form took 0.515625 seconds to render

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Previewing at Level 17

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Summary Result Form
(for systematic reviews of calcium/vitamin D)

Study aim of the systematic review (check all that apply):

1. To assess:

- [ ] calcium
- [ ] vitamin D

2. In the prevention of:

- [ ] Bone density loss
- [ ] Fracture
- [ ] Colon Cancer
- [ ] Colon polyps
- [ ] Colorectal cancer
- [ ] Other

Years

Months

3. **Exclusion criteria used in this systematic review article:**

Enlarge Shrink

Search Strategies

4. Source databases (check all that apply):

- [ ] Cochrane Library
- [ ] MEDLINE
- [ ] EMBASE
- [ ] Cochrane Controlled Trial Register
- [ ] Cancerlit
- [ ] CABNAR
- [ ] LILACS
- [ ] CINAHL
- [ ] BIOSIS
- [ ] HealthSTAR
- [ ] MANTIS
- [ ] Allied & Complementary Medicine
- [ ] CABHealth
- [ ] TGG Health & Wellness
- [ ] Unpublished Data
- [ ] Hand search based on reference lists of relevant articles
- [ ] Experts' referral
- [ ] Other (list all)

5. Publication dates of included articles:

From (Years)

From (Months)

To (Years)

To (Months)

6. Search terms used (check all that apply):

- [ ] calcium
- [ ] vitamin D
- [ ] osteoporosis
- [ ] post-menopause
- [ ] bone loss
- [ ] fracture
- [ ] cancer
- [ ] polyps
- [ ] colorectal cancer
- [ ] oncologic
- [ ] other

7. **Number of trials included in the review:**

Enlarge Shrink

8. **Total number of trial participants:**

In placebo group

In Calcium alone group

In Vitamin D alone group

In Calcium + vitamin D group

9. **Follow-up periods of the trials included in this systematic review:**

Range____to____ (year)

- [ ] Not Reported

10. **Range of proportion of participants who were lost to follow-up:**

From

To

- [ ] Not Reported

11. **Trial Participants Characteristics:**

Range of mean age: (___to___)

Range of % women: _____% to _____%

Race (range of %)

- [ ] White
- [ ] African-American
- [ ] Hispanic
- [ ] Other (specify)

Baseline BMD

- [ ] Mean (including unit)
- [ ] Median (including unit)

% post-menopausal in women

12. **Chemical forms of vitamins/minerals used in included trials (check all that apply):**

- [ ] Ca1. calcium carbonate
- [ ] Ca2. calcium citrate
- [ ] Ca3. calcium citrate malate
- [ ] Ca4. dibasic calcium phosphate
- [ ] Ca5. unspecified

- [ ] Ca6. other
- [ ] D1. cholecalciferol
- [ ] D2. ergocalciferol
- [ ] D3. unspecified
- [ ] D4. other

13. **Range of doses used in trials:**

- [ ] Calcium (including unit)
- [ ] Vitamin D (including unit)

Aggregate Results on Bone mineral density and bone mineral content

Result 1:

14. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

15. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

16. Number of trials for this result:

Enlarge Shrink

17. Total sample size for this result:

Enlarge Shrink

18. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

19. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Result 2:

20. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

21. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

22. Number of trials for this result:

Enlarge Shrink

23. Total sample size for this result:

Enlarge Shrink

24. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

25. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

Result 3:

26. Group comparison:

- Calcium compared to inactive comparison group
- Vitamin D compared to inactive comparison group
- Calcium + vitamin D compared to inactive comparison group

27. Bone density site:

- Total body
- L-spine (1-2 yrs)
- L-spine (3-4 yrs)
- Combined hip
- 1/3 distal radius
- Other

28. Number of trials for this result:

Enlarge Shrink

29. Total sample size for this result:

Enlarge Shrink

30. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

31. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

Result 4:

32. Group comparison:

- Calcium compared to inactive comparison group
- Vitamin D compared to inactive comparison group
- Calcium + vitamin D compared to inactive comparison group

33. Bone density site:

- Total body
- L-spine (1-2 yrs)
- L-spine (3-4 yrs)
- Combined hip
- 1/3 distal radius
- Other

34. Number of trials for this result:

Enlarge Shrink

35. Total sample size for this result:

Enlarge Shrink

36. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

37. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

Result 5:

38. Group comparison:

- Calcium compared to inactive comparison group
- Vitamin D compared to inactive comparison group
- Calcium + vitamin D compared to inactive comparison group

39. Bone density site:

- Total body
- L-spine (1-2 yrs)
- L-spine (3-4 yrs)
- Combined hip
- 1/3 distal radius
- Other

40. Number of trials for this result:

Enlarge Shrink

41. Total sample size for this result:

Enlarge Shrink

42. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

43. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

Result 6:

44. Group comparison:

- Calcium compared to inactive comparison group
- Vitamin D compared to inactive comparison group
- Calcium + vitamin D compared to inactive comparison group

45. Bone density site:

- Total body
- L-spine (1-2 yrs)
- L-spine (3-4 yrs)
- Combined hip

- [ ] 1/3 distal radius
- [ ] Other

46. Number of trials for this result:

Enlarge Shrink

47. Total sample size for this result:

Enlarge Shrink

48. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

49. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Result 7:

50. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

51. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

52. Number of trials for this result:

Enlarge Shrink

53. Total sample size for this result:

Enlarge Shrink

54. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

55. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Result 8:

56. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

57. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)

- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

58. Number of trials for this result:

Enlarge Shrink

59. Total sample size for this result:

Enlarge Shrink

60. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

61. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Result 9:

62. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

63. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

64. Number of trials for this result:

Enlarge Shrink

65. Total sample size for this result:

Enlarge Shrink

66. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

Result 9:

67. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

68. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)

- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

69. Number of trials for this result:

Enlarge Shrink

70. Total sample size for this result:

Enlarge Shrink

71. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

Result 9:

72. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

73. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

74. Number of trials for this result:

Enlarge Shrink

75. Total sample size for this result:

Enlarge Shrink

76. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

Result 9:

77. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

78. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

79. Number of trials for this result:

Enlarge Shrink
80. Total sample size for this result:

Enlarge Shrink
81. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

Result 9:

82. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

83. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

84. Number of trials for this result:

Enlarge Shrink
85. Total sample size for this result:

Enlarge Shrink
86. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

87. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Result 10:

88. Group comparison:

- [ ] Calcium compared to inactive comparison group
- [ ] Vitamin D compared to inactive comparison group
- [ ] Calcium + vitamin D compared to inactive comparison group

89. Bone density site:

- [ ] Total body
- [ ] L-spine (1-2 yrs)
- [ ] L-spine (3-4 yrs)
- [ ] Combined hip
- [ ] 1/3 distal radius
- [ ] Other

90. Number of trials for this result:

Enlarge Shrink
91. Total sample size for this result:

Enlarge Shrink
92. Weighted mean difference (active group – inactive group):

Weighted mean difference (including unit)

95% CI

P-value for the mean difference

93. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

Aggregate Results on Fractures

94. Fracture Site:

- Vertebral
- Hip
- Nonvertebral (other than hip; specified)

95. Number of trials included for this result:

Enlarge Shrink
96. Total sample size for this result:

Enlarge Shrink
97. Cancer outcome (type in the cancer site):

- colon cancer
- colorectal cancer
- polyps
- other

98. Aggregate efficacy (active vs. inactive groups):

- Relative Risk
- Odds Ratio
- Hazard Ratio

Point estimate

95% confidence interval

- Not Reported (only individual study-results were reported)

99. P-value for test of heterogeneity:

- p>0.05
- p<=0.05
- not reported

100. Fracture Site:

- Vertebral
- Hip
- Nonvertebral (other than hip; specified)

101. Number of trials included for this result:

Enlarge Shrink
102. Total sample size for this result:

Enlarge Shrink

103. Cancer outcome (type in the cancer site):

- [ ] colon cancer
- [ ] colorectal cancer
- [ ] polyps
- [ ] other

104. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate

95% confidence interval

- [ ] Not Reported (only individual study-results were reported)

105. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

106. Fracture Site:

- [ ] Vertebral
- [ ] Hip
- [ ] Nonvertebral (other than hip; specified)

107. Number of trials included for this result:

Enlarge Shrink

108. Total sample size for this result:

Enlarge Shrink

109. Cancer outcome (type in the cancer site):

- [ ] colon cancer
- [ ] colorectal cancer
- [ ] polyps
- [ ] other

110. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate

95% confidence interval

- [ ] Not Reported (only individual study-results were reported)

111. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

112. Fracture Site:

- [ ] Vertebral
- [ ] Hip
- [ ] Nonvertebral (other than hip; specified)

113. Number of trials included for this result:

Enlarge Shrink

114. Total sample size for this result:

Enlarge Shrink

115. Cancer outcome (type in the cancer site):

- [ ] colon cancer
- [ ] colorectal cancer
- [ ] polyps
- [ ] other

116. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate

95% confidence interval

- [ ] Not Reported (only individual study-results were reported)

117. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

118. Fracture Site:

- [ ] Vertebral
- [ ] Hip
- [ ] Nonvertebral (other than hip; specified)

119. Number of trials included for this result:

Enlarge Shrink

120. Total sample size for this result:

Enlarge Shrink

121. Cancer outcome (type in the cancer site):

- [ ] colon cancer
- [ ] colorectal cancer
- [ ] polyps
- [ ] other

122. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate

95% confidence interval

- [ ] Not Reported (only individual study-results were reported)

123. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

124. Fracture Site:

Vertebral

Hip

Nonvertebral (other than hip; specified)

125. Number of trials included for this result:

Enlarge Shrink

126. Total sample size for this result:

Enlarge Shrink

127. Cancer outcome (type in the cancer site):

colon cancer

colorectal cancer

polyps

other

128. Aggregate efficacy (active vs. inactive groups):

Relative Risk

Odds Ratio

Hazard Ratio

Point estimate

95% confidence interval

Not Reported (only individual study-results were reported)

129. P-value for test of heterogeneity:

p>0.05

p<=0.05

not reported

130. Fracture Site:

Vertebral

Hip

Nonvertebral (other than hip; specified)

131. Number of trials included for this result:

Enlarge Shrink

132. Total sample size for this result:

Enlarge Shrink

133. Cancer outcome (type in the cancer site):

colon cancer

colorectal cancer

polyps

other

134. Aggregate efficacy (active vs. inactive groups):

Relative Risk

Odds Ratio

Hazard Ratio

Point estimate

95% confidence interval

Not Reported (only individual study-results were reported)

135. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

136. Fracture Site:

- [ ] Vertebral
- [ ] Hip
- [ ] Nonvertebral (other than hip; specified)

137. Number of trials included for this result:

Enlarge Shrink

138. Total sample size for this result:

Enlarge Shrink

139. Cancer outcome (type in the cancer site):

- [ ] colon cancer
- [ ] colorectal cancer
- [ ] polyps
- [ ] other

140. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate

95% confidence interval

- [ ] Not Reported (only individual study-results were reported)

141. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Submit Data

Form took 1.96875 seconds to render

Previewing Only: You cannot submit data from this form

Previewing at Level 18

Refid: 1, Cosman, F., Nieves, J., Zion, M., Woelfert, L., Luckey, M., and Lindsay, R., Daily and cyclic parathyroid hormone in women receiving alendronate, *N Engl J Med*, 353(6), 2005, p.566-75
State: Excluded, Level: 1

Submit Data

Summary Result Form
(for systematic reviews *other than* calcium/vitamin D)

Study aim of the systematic review (check all that apply):

1. To assess:

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] calcium/magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

2. In the prevention of:

- [ ] Oncologic (specify)
- [ ] Cardiovascular (specify)
- [ ] Endocrine (specify)
- [ ] Neurologic (specify)
- [ ] Age-related sensory loss (specify)
- [ ] Musculoskeletal (specify)
- [ ] Gastroenterologic (specify)
- [ ] Renal (specify)
- [ ] Infectious (specify)
- [ ] Pulmonary (specify)

Comments

3. **Exclusion criteria used in this systematic review article:**

Enlarge Shrink

Search Strategies

4. Source databases (check all that apply):

- [ ] Cochrane Library

- [ ] MEDLINE
- [ ] EMBASE
- [ ] Cochrane Controlled Trial Register
- [ ] Cancerlit
- [ ] CABNAR
- [ ] LILACS
- [ ] CINAHL
- [ ] BIOSIS
- [ ] HealthSTAR
- [ ] MANTIS
- [ ] Allied & Complementary Medicine
- [ ] CABHealth
- [ ] TGG Health & Wellness
- [ ] Unpublished Data
- [ ] Hand search based on reference lists of relevant articles
- [ ] Experts' referral
- [ ] Other (list all) _____

Comments _____

5. Search terms used (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] calcium/magnesium
- [ ] beta-carotene
- [ ] selenium
- [ ] cancer
- [ ] cardiovascular disease
- [ ] other (specify) _____

6. Publication dates of included articles:

FROM (year):

TO (year):

Comments

7. **Number of trials included in the review:**

Enlarge Shrink

Total number of trial participants:

8. In Placebo group:

Enlarge Shrink

9. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] calcium/magnesium
- [ ] beta-carotene
- [ ] selenium
- [ ] Not applicable

Comments

10. Follow-up *range* of periods of the trials included in this systematic review:

From ____to_____(year):

- [ ] Not Reported

Comments

11. **Range of proportion of participants who were lost-to-follow up:**

From:

To:

- [ ] Not Reported

Comments

12. **Trial Participants Characteristics:**

Range of mean age: (___to___)

Range of % women: _____% to _____%

Race (range of %)

- [ ] White
- [ ] African-American
- [ ] Hispanic
- [ ] Other (specify)

Comments

13. **Health Status:**

- [ ] All trials included apparent healthy individuals
- [ ] Some trials included diseased individuals

Comments

14. **Chemical forms of folic acid used in included trials (check all that apply):**

- [ ] F1: Folic acid

- [ ] F2: unspecified
- [ ] F3: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

15. **Chemical forms of vitamin B6 used in included trials (check all that apply):**

- [ ] B6_1: Pyridoxine hydrochloride
- [ ] B6_2: Pyridoxol 5' phosphate
- [ ] B6_3: Pyridoxine alpha-ketoglutarate
- [ ] B6_4: unspecified
- [ ] B6_5: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

16. **Chemical forms of vitamin E used in included trials (check all that apply):**

- [ ] E_1: d-alpha-tocopherol
- [ ] E_2: d-alpha-tocopherol acetate
- [ ] E_3: d-alpha-tocopherol succinate
- [ ] E_4: dl-alpha-tocopherol
- [ ] E_5: dl-alpha-tocopherol acetate
- [ ] E_6: dl-alpha-tocopherol succinate
- [ ] E_7: d-beta-tocopherol
- [ ] E-8: d-gamma-tocopherol
- [ ] E_9: d-delta-tocopherol
- [ ] E_10: unspecified
- [ ] E_11: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

17. **Chemical forms of vitamin C used in included trials [4] (check all that apply):**

- [ ] C_1: Ascorbic acid
- [ ] C_2: L-Ascorbic acid
- [ ] C_3: Sodium Ascorbate
- [ ] C_4: Unspecified
- [ ] C_5: Other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

18. **Chemical forms of beta-carotene used in included trials (check all that apply):**

- [ ] A_1: Beta-carotene
- [ ] A_2: Retinyl acetate
- [ ] A_3: Retinyl palmitate
- [ ] A_4: Retinol
- [ ] A_5: Unspecified
- [ ] A_6: Other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

19. **Chemical forms of iron used in included trials (check all that apply):**

- [ ] Fe_1: Ferrous fumarate
- [ ] Fe_2: Ferrous sulfate
- [ ] Fe_3: Ferrous citrate
- [ ] Fe_4: Ferrous glycinate
- [ ] Fe_5: Iron carbonyl
- [ ] Fe_6: Ferrous gluconate
- [ ] Fe_7: Unspecified
- [ ] Fe_8: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

20. **Chemical forms of zinc used in included trials (check all that apply):**

- [ ] Z_1: Zinc acetate
- [ ] Z_2: Zinc gluconate
- [ ] Z_3: Zinc oxide
- [ ] Z_4: Zinc pyrithione
- [ ] Z_5: Zinc sulfate
- [ ] Z_6: Zinc citrate
- [ ] Z_7: Zinc taurinate
- [ ] Z_8: Zinc monomethionine
- [ ] Z_9: Zinc picolinate
- [ ] Z_10: unspecified
- [ ] Z_11: Other (Specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

21. **Chemical forms of magnesium used in included trials (check all that apply):**

- [ ] Mg_1: Magnesium carbonate
- [ ] Mg_2: Magnesium chloride
- [ ] Mg_3: Magnesium hydroxide
- [ ] Mg_4: Magnesium oxide
- [ ] Mg_5: Magnesium trisilicate
- [ ] Mg_6: Magnesium chloride hexahydrate
- [ ] Mg_7: Magnesium citrate
- [ ] Mg_8: Magnesium taurinate
- [ ] Mg_9: Magnesium aspartate
- [ ] Mg_10: Magnesium lactate gluconate
- [ ] Mg_11: Magnesium gluconate
- [ ] Mg_12: Unspecified
- [ ] Mg_13: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

22. **Chemical forms of vitamin B1 used in included trials (check all that apply):**

- [ ] B1_1: Thiamine hydrochloride
- [ ] B1_2: Thiamine carboxylase

- [ ] B1_3: Thiamine mononitrate
- [ ] B1_4: unspecified
- [ ] B1_5: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

23. **Chemical forms of vitamin B2 used in included trials (check all that apply):**

- [ ] B2_1: Riboflavin
- [ ] B2_2: Riboflavin 5' phosphate
- [ ] B2_3: unspecified
- [ ] B2_4: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

24. **Chemical forms of niacin used in included trials (check all that apply):**

- [ ] N_1: Niacin
- [ ] N_2: Niacinamide
- [ ] N_3: unspecified
- [ ] N_4: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

25. **Chemical forms of selenium used in included trials (check all that apply):**

- [ ] S_1: Selenium sulfide
- [ ] S_2: L-selenomethionine
- [ ] S_3: Sodium selenate
- [ ] S_4: selenium yeast
- [ ] S_5: Selenite
- [ ] S_6: Unspecified
- [ ] S_7: other (specified)
- [ ] Range of doses used in trials (including units):
- [ ] Not Applicable

Comments

Aggregate Efficacy Results

Result 1

26. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

27. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

28. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

29. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 2

30. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

31. In vitamin/mineral group (check all that apply):

- [ ] iron

- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

32. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

33. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 3

34. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

35. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid

- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

36. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

37. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 4

38. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

39. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin

- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

40. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

41. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 5

42. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

43. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C

- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

44. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

45. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 6

46. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

47. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A

- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

48. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

49. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 7

50. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

51. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1

- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

52. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

53. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

Result 8

54. Type of outcome:

- [ ] CVD incidence
- [ ] CVD mortality
- [ ] Total mortality
- [ ] Cataract incidence
- [ ] Cancer incidence (specify site)
- [ ] Cancer mortality (specify site)
- [ ] Non-fatal myocardial infarction
- [ ] fatal myocardial infarction
- [ ] fatal and non-fatal myocardial infarction
- [ ] Other (specify)
- [ ] Not reported

Comments

55. In vitamin/mineral group (check all that apply):

- [ ] iron
- [ ] vitamin B2
- [ ] folic acid/B12
- [ ] folic acid
- [ ] vitamin E
- [ ] zinc
- [ ] niacin
- [ ] folic acid/B6
- [ ] vitamin B6
- [ ] vitamin C
- [ ] magnesium
- [ ] vitamin B12
- [ ] vitamin A
- [ ] vitamin B1
- [ ] magnesium
- [ ] beta-carotene
- [ ] selenium

Comments

56. Aggregate efficacy (active vs. inactive groups):

- [ ] Relative Risk
- [ ] Odds Ratio
- [ ] Hazard Ratio

Point estimate (active compared to inactive)

95% confidence interval

- [ ] Not reported (only individual study-results were reported)

Comments

57. P-value for test of heterogeneity:

- [ ] p>0.05
- [ ] p<=0.05
- [ ] not reported

Comments

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Evidence Table 1a. Characteristics of the studies on the efficacy of multivitamins in preventing chronic disease

Study name	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
Linxian General Population Trial [64,66]	Groups of placebo, AB, AC, AD, BC, BD, CD, ABCD where A: Retinol palmitate 10000 IU + Zinc oxide 45 mg, B: Riboflavin 5.2 mg + Niacin 40 mg, C: Ascorbic acid 180 mg + Molybdenum Yeast complex 30 µg, D: Beta-carotene 15 mg + Selenium yeast 50 µg + alpha-tocopherol 60 mg	RCT; Factorial design	1986-1991	Not 40-69; history of stomach or esophageal cancer; debilitating disease; does not live in one of 4 communes in Linxian	29584	5.25 years (total)	Linxian province, China	Community
Wang, 1994[68]				Not 40-69; history of cancer; did not live in one of two villages in Rencun commune; did not complete 1st (1987) and end-of-trial (2nd 1991) cytology exam.	391 (in 1991)			

Evidence Table 1a. Characteristics of the studies on the efficacy of multivitamins in preventing chronic disease (continued)

Study name	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
Linxian cataract Study [65]	Groups of placebo, AB, AC, AD, BC, BD, CD, ABCD where A: Retinol palmitate 10000 IU + Zinc oxide 45 mg, B: Riboflavin 5.2 mg + Niacin 40 mg, C: Ascorbic acid 180 mg + Molybdenum Yeast complex 30 µg, D: Beta-carotene 15 mg + Selenium yeast 50 µg + alpha-tocopherol 60 mg	RCT; Factorial design	1985-1991	Not 40-69; cancer; did not live in Linxian province.	5390	6 years (total)	Linxian province, China	Community
SU.VI.MAX [69,70]	Vitamin C+ vitamin E+ beta carotene+ selenium+ zinc.	RCT; placebo controlled	1994-2002 [69]	Disease was expected to hinder participation or threaten 5-year survival; participant was taking any supplement offered in this study; participant had extreme beliefs or behavior regarding diet.	12741	8 years (total), 7.5 years (median).	France	Community
			1994-1995 [70]	Not 45-60 years old; female; cancer; not free of "severe health problems"; any use study supplements.	5141 (males)	8.9 years (median)	France	Community

Evidence Table 1a. Characteristics of the studies on the efficacy of multivitamins in preventing chronic disease (continued)

Study name	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
REACT [72]	Beta-carotene + vitamin C+ vitamin E.	RCT; placebo controlled	1990-1995	History of iritis or amblyopia; glaucoma or elevated intraocular pressure; ocular corticosteroid use or glaucoma therapy; participation in other anti-cataract trial within last year; regular use of antioxidants.	297	3 years (total), 2.8 years (mean).	Boston, USA; Oxford and Bradford, UK.	Clinical: outpatient eye clinic
ARED [73,75]	Beta-carotene+ vitamin C+ vitamin E.	RCT; placebo controlled	1992-2001	History of cancer with a poor 7-year prognosis; major cardiovascular or cerebrovascular event within the last year; hemachromatosis; persons bilaterally aphakic or pseudophakic were ineligible for AMD Category 1.	4596 [75] 3509 [73]	9 years (total), 6.3 years (mean).	USA (multiple centers)	Clinical and community

Evidence Table 1a. Characteristics of the studies on the efficacy of multivitamins in preventing chronic disease (continued)

Study name	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
ARMD [74]	Beta-carotene; vitamin E; vitamin C; citrus bioflavenoid complex; quercitin; rutin; zinc; selenium; taurine; N-acetyl cysteine; glutathione; vitamin B2; chromium.	RCT; Placebo controlled	NR	Did not have a one-time decrease of visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease; eye findings not consistent with loss of macular reflex; former prisoner of war; chronic alcoholic with tobacco/nutritional amblyopia or gastrointestinal absorption disorder.	71	3 years (total)	USA (multiple centers)	Clinical
MONMD [71]	Beta-carotene; vitamin E; vitamin C; citrus bioflavenoid complex; quercitin; rutin; zinc; selenium; taurine; N-acetyl cysteine; glutathione; vitamin B2; chromium.	RCT; Placebo controlled	NR	Did not have a one-time decrease of visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease; eye findings not consistent with loss of macular reflex; former prisoner of war; chronic alcoholic with tobacco/nutritional amblyopia or gastrointestinal absorption disorder; prior use vitamins >1 year.	84	3 years (total)	USA (multiple centers)	Clinical

SU.VI.MAX. (SUppléments en VItamines et Minéraux AntioXydants); REACT (Roche European American Cataract Trial); AREDS (Age-Related Eye Disease Study); ARMD (Age-Related Macular Degeneration).

Evidence Table 1b. Characteristics of the intervention in the studies of the efficacy of multivitamins/minerals in the prevention of chronic disease

Study name	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
Linxiana General Population study[66]	Placebo			NS	5 years
	Vitamin A	Retinol palmitate	10000 IU/NS		
	Zinc	Zinc oxide	45 mg/NS		
	Vitamin B2	Riboflavin	5.2 mg/NS		
	Niacin	Niacin	40 mg/NS		
	Vitamin C	Ascorbic acid	180 mg/NS		
	Molybdenum	Yeast complex	30 µg/NS		
	Beta-carotene	NS	15 mg/NS		
	Selenium	Selenium yeast	50 µg/NS		
	Vitamin E	alpha-tocopherol	60 mg/NS		
Linxian General Population Study[64]	Placebo		NS	NS	5.25 years
	Vitamin A + zinc	Retinol palmitate, zinc oxide	5000 IU/daily, 22.5 mg/daily		
	Riboflavin + niacin	Riboflavin , niacin	3.2 mg/1x/day, 40 mg/1x/day		
	Vitamin C + molybdenum	Ascorbic acid, molybdenum	120 mg/1x/day, 30 mcg/1x/day		
	Vitamin E + selenium + beta-carotene	d-alpha-tocopherol, selenium yeast, beta-carotene	30 mg/1x/day, 50 mcg/1x/day, 15 mg/1x/day		
Linxian General Population Study[68]	Placebo 1			NS	5.25 years
	Vitamin A	Retinol palmitate	5000 IU/daily		
	Zinc	Zinc oxide	22.5 mg/daily		
	Vitamin B2	Riboflavin	3.2 mg/1x/day		
	Niacin	Niacin	40 mg/1x/day		
	Vitamin C	Ascorbic acid	120 mg/1x/day		
	Other Chemical	Molybendum	30 mcg/1x/day		
	Vitamin E	d-alpha-tocopherol	30 mg/1x/day		
	Selenuim	Selenium yeast	50 mcg/1x/day		
	Other Chemical	beta-carotene	15 mg/1x/day		
Linxian Cataract Study[65]	Placebo		NS	NS	6 years
	Calcium	Dibasic calcium phosphate	324 mg/NS		
	Folic Acid	Folic aci	800 mcg/NS		
	Vitamin B6	Pyridoxine hydrochloride	6 mg/NS		
	Vitamin B12	Cyanocobalamin	18 mcg/NS		
	Vitamin D	NS	800 IU/NS		
	Vitamin E	2-ambo-alpha-tocopherol	60 IU/NS		
	Vitamin C	Ascorbic acid	180 mg/NS		
	Vitamin A	Acetate	10000 IU/NS		
	Iron	Ferrous fumarate	54 mg/NS		
	Zinc	Zinc sulfate	45 mg/NS		

Evidence Table 1b. Characteristics of the intervention in the studies of the efficacy of multivitamins/minerals in the prevention of chronic disease (continued)

Study name	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
Linxian Cataract Study (cont'd)	Magnesium	Magnesium oxide	200 mg/NS		
	Vitamin B1	Thiamine mononitrate	5 mg/NS		
	Vitamin B2	Riboflavin	5.2 mg/NS		
	Niacin	Niacinamide	40 mg/NS		
	Selenuim	Sodium selenate	50 mcg/NS		
	Beta-carotene	beta-carotene	15 mg/1x/day		
	Biotin	Biotin	90 mcg/1x/day		
	Calcium	Pantothenic acid/calcium pantothenate	20 mg/1x/day		
	Phosphorus and calcium	Phophorous/dibasic calcium phosphate	250 mg/1x/day		
	Iodine	Iodine/potassium iodide	300 mg/1x/day		
	Copper	Cupric oxide	6 mg/1x/day		
	Potassium	Potassium chloride	15.4 mg/1x/day		
	Chloride	Potassium chloride	14 mg/1x/day		
	Chromium	Chromium chloride	30 mcg/1x/day		
	Molybendum	Sodium molybdate	30 mcg/1x/day		
	Manganese	Manganese sulfate	15 mg/1x/day		
SU.VI.MAX [69]	Placebo		NS	NS	7.5 years
	Vitamin E	NS	30 mg/1x/day		
	Vitamin C	Ascorbic acid	120 mg/1x/day		
	Vitamin A	beta-carotene	6 mg/1x/day		
	Zinc	Zinc gluconate	20 mg/1x/day		
	Selenuim	Selenium yeast	100 mcg/1x/day		
SU.VI.MAX [70]	Placebo		NS	NS	8 years
	Vitamin E	a-tocopherol	30 mg/1x/day		
	Vitamin C	NS	120 mg/1x/day		
	Vitamin A	beta-carotene	6 mg/1x/day		
	Zinc	NS	20 mg/1x/day		
	Selenuim	Selenium yeast	100 mcg/1x/day		

Evidence Table 1b. Characteristics of the intervention in the studies of the efficacy of multivitamins/minerals in the prevention of chronic disease (continued)

Study name	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
REACT [72]	Placebo			With meals	3 years
	Vitamin E	all rac-alpha-tocopherol acetate	200 mg/3x/day		
	Vitamin C	Ascorbic acid	250 mg/3x/day		
	Vitamin A	beta-carotene	6 mg/3x/day		
ARED [75]	Placebo		NS	NS	6.3 years
	Vitamin E	dl-alpha-tocopherol acetate	200 IU/2x/day/ (2 tablets in the morning, 2 in the evening)	With meals	
	Vitamin C	Ascorbic acid	250 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Vitamin A	beta-carotene	7.5 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Zinc	Zinc oxide	40 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Copper	Cupric copper	2 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Combination above supplements				
ARED [73]	Placebo		NS	NS	6.3 years
	Vitamin E	dl-alpha-tocopherol acetate	200 IU/2x/day (2 tablets in the morning, 2 in the evening)	With meals	
	Vitamin C	Ascorbic acid	250 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Vitamin A	beta-carotene	7.5 mg/2x/day (2 tablets in the morning, 2 in the evening)		
	Zinc	Zinc oxide	40 mg/2x/day (2 tablets in the morning, 2 n the evening)		
MONMD [74]	Placebo	Starch	NS	NS	18 months
	Vitamin E	NS	200 IU/1x/day		
	Vitamin C	NS	750 IU/1x/day		
	Vitamin A	beta-carotene	20000 IU/1x/day		
	Zinc	Zinc picolinate	12.5 mg/1x/day		
	Selenuim	Unspecified	60 mcg/1x/day		

SU.VI.MAX. (SUppléments en VItamines et Minéraux AntioXydants); REACT (Roche European American Cataract Trial); AREDS (Age-Related Eye Disease Study); ARMD (Age-Related Macular Degeneration); NS = Not specified; mg = milligram; mcg = microgram; IU = international unit

Evidence Table 1c. Characteristics of participants in studies of the efficacies of multivitamins

Study name	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
Linxian General Population Study [66]	Median (female) 51; median (male): 53; range: 44-60.	16271 (55); ethnicity NR	Current (female): 3254 (20); current (male): 8929 (67)	Current (female): (10); current (male): (40).	Median BMI (female): 21.9; median BMI (male): 21.6.	NR
Linxian General Population Study [64]	<50: 12425 (42%); 50-59: 10354 (35%); ≥60: 6804 (23%).	16271 (55); ethnicity NR	Never: 20709 (70); ever smoked for >6 months: 8875 (30).	Never: 22780 (77); any use in past 12 months: 6804 (23).	NR	NR
Wang,1994	53	196 (50); ethnicity NR	Current: 141 (36.0).	Current: 145 (37.0).	NR	NR
Linxian Cataract Study [65]	57.5	2872 (53.3); ethnicity NR	Ever smoked for >6 months: 1748 (32.4).	NR	NR	NR
SU.VI.MAX [69]	Women: 46.6 (6.6); men: 51.3 (4.7).	7713; ethnicity NR	Never (women, placebo): (54.8); never (women, intervention): (54.6); never (men, placebo): (34.5); never (men, intervention): (33.7); former (women, placebo): (29.1); former (women, intervention) (28.9); former (men, placebo): (50.2); former (men, intervention): (50.9); current (women, placebo): (16.1); current (women, intervention): (16.5); current (men, placebo): (15.3); current (men, intervention): (15.4).	NR	Placebo (women): 22.9 (3.0); intervention (women): 22.8 (0.5); placebo (men): 25.2 (3.0); intervention (men): 25.2 (3.0).	NR
SU.VI.MAX [70]	51.3 (4.6)	0 (0) ; ethnicity NR	Current: 4818 (15.4)	NR	BMI≥27 (placebo): 25.23%; BMI≥27 (supplement): 25.21%.	NR
REACT [72]	UK: 67.55 (8.47); US: 64.2 (8.49).	UK: 33 (47.1); US 52 (59.2); ethnicity NR	Never (UK): 13 (18.8); never (US): 15 (17.1).	NR	NR	NR

Evidence Table 1c. Characteristics of participants in studies of the efficacies of multivitamins (continued)

Study name	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
ARED [75]	Median: 56	2551 (56); Caucasian, 4412 (96); Latino 185 (4)	Former: 2184 (48); current: 345 (7.5).	NR	NR	Multivitamins or a supplement containing a study compound: 2528 (55); Centrum: 1548 (66).
ARED [73]	Median: 69	2021 (56); Caucasian, 3483 (96); Latino 153 (3)	Former: 1751 (49); current: 298 (8.0).	NR	NR	Multivitamin or supplement containing a study compound: 2047 (57); Centrum: 2418 (67).
MONMD [71]	68.6-72.4	5 (6)	NR	0.69-1.00 ounce/day	NR	No one used >1 year at entry

SU.VI.MAX. (SUppléments en VItamines et Minéraux AntioXydants); REACT (Roche European American Cataract Trial); AREDS (Age-Related Eye Disease Study); ARMD (Age-Related Macular Degeneration); BMI = Body mass index; NR (not recorded); UK = United Kingdom; US = United States

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease

Study name	Disease endpoint	Study supplement *	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer								
Linxian General Population Study [64]	Total cancer incidence	Retinol + zinc	Total 29,584	Total 1298		RR 1.00 (0.89-1.11)		
		Riboflavin + niacin				RR 0.95 (0.85-1.06)		
		Vitamin C + molybdenum				RR 1.06 (0.95-1.18)		
		Beta-carotene +selenium+ alpha-tocopherol				RR 0.93 (0.83-1.03)		
	Gastric cancer incidence	Retinol + zinc		Total 539		RR 0.96 (0.81-1.14)		
		Riboflavin + niacin				RR 1.04 (0.88-1.23)		
		Vitamin C + molybdenum				RR 1.10 (0.92-1.30)		
		Beta-carotene +selenium+ alpha-tocopherol				RR 0.84 (0.71-1.00)		
	Esophageal cancer incidence	Retinol + zinc		Total 640		RR 1.07 (0.92-1.25)		
		Riboflavin + niacin				RR 0.86 (0.74-1.01)		
		Vitamin C + molybdenum				RR 1.06 (0.91-1.24)		
		Beta-carotene +selenium+ alpha-tocopherol				RR 1.02 (0.87-1.19)		
	Esophageal/cardia incidence	Retinol + zinc		Total 1075		RR 1.05 (0.93-1.19)		
		Riboflavin + niacin				RR 0.94 (0.83-1.06)		
		Vitamin C + molybdenum				RR 1.06 (0.94-1.20)		
		Beta-carotene +selenium+ alpha-tocopherol				RR 0.94 (0.84-1.06)		
	Total cancer death	Retinol + zinc		Total 792		RR 0.97 (0.85-1.12)		
		Riboflavin + niacin				RR 0.98 (0.85-1.13)		
		Vitamin C + molybdenum				RR 1.06 (0.92-1.21)		

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement *	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer (continued)								
Linxian General Population Study [64]	Total cancer death	Beta-carotene +selenium+ alpha-tocopherol		Total 792		RR 0.87 (0.75-1.00)		
	Stomach cancer death	Retinol + zinc		Total 331		RR 1.03 (0.83-1.28)		
		Riboflavin + niacin				RR 1.00 (0.81-1.24)		
		Vitamin C + molybdenum				RR 1.09 (0.88-1.36)		
		Beta-carotene+selenium+ alpha-tocopherol				RR 0.79 (0.64-0.99)		
	Esophageal cancer death	Retinol + zinc		Total 360		RR 0.93 (0.76-1.15)		
		Riboflavin + niacin				RR 0.90 (0.73-1.11)		
		Vitamin C + molybdenum				RR 1.05 (0.85-1.29)		
		Beta-carotene+selenium+ alpha-tocopherol				RR 0.96 (0.78-1.18)		
	Esophageal/gastric cardia death	Retinol + zinc		Total 613		RR 1.04 (0.89-1.22)		
		Riboflavin + niacin				RR 0.95 (0.81-1.11)		
		Vitamin C + molybdenum				RR 1.06 (0.90-1.24)		
		Beta-carotene+selenium+ alpha-tocopherol				RR 0.90 (0.77-1.05)		

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer (continued)								
Linxian General Population Study[68]	Esophageal and gastric cancer and dyaplasia	Retinol + zinc	197/194	28/32		OR 0.83 (0.47-1.46)		Adjusted for age, gender, smoking, and alcohol use
		Riboflavin + niacin	194/197	34/26		OR 1.39 (0.79-2.44)		
		Ascorbic acid + molybdenum	206/185	37/23		OR 1.61 (0.91-2.86)		
		Beta-carotene + selenium + alpha-tocopherol	177/214	25/35		OR 0.83 (0.47-1.46)		
	Esophageal and gastric cancer	Retinol + zinc	197/194	13/18		OR 0.61 (0.29-1.31)		
		Riboflavin + niacin	194/197	18/13		OR 1.46 (0.68-3.11)		
		Ascorbic acid + molybdenum	206/185	21/10		OR 1.99 (0.90-4.41)		
		Beta-carotene + selenium + alpha-tocopherol	177/214	12/19		OR 0.79 (0.36-1.69)		
SU.VI.MAX[70]	Prostate cancer	Vitamin C + vitamin E + beta-carotene + selenium + zinc	2522/2512	49/54		0.88 (0.60-1.29)	0.73	
			2293/2270	18/33		0.52 (0.29-0.92)	0.009	In men with initial PSA<3.0 µg/L
			149/143	31/19		1.54 (0.87-2.72)	0.43	In men with initial PSA≥3.0 µg/L
SU.VI.MAX[69]	Cancer	Vitamin C + vitamin E + beta-carotene + selenium + zinc	6364/6377	267/295		RR 0.90 (0.76-1.06)	0.19	
			3844/3869 women only	179/171		RR 1.04 (0.85-1.29)	0.53	
			2520/2508 men only	88/124		RR 0.69 (0.53-0.91)	0.008	

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cardiovascular Disease								
Linxian General Population Study [66]	Stroke deaths	Retinol + zinc + riboflavin + niacin	Total 29,584	66/77	3.5/4.1 per 1000	RR 0.85 (0.61-1.18)		
		Retinol + zinc + vitamin C + molybdenum		71/77	3.8/4.1 per 1000	RR 0.91 (0.66-1.27)		
		Retinol + zinc + beta-carotene +selenium+ alpha-tocopherol		55/77	2.9/4.1 per 1000	RR 0.71 (0.50-1.00)		
		Riboflavin + niacin + vitamin C + molybdenum		60/77	3.2/4.1 per 1000	RR 0.78 (0.55-1.09)		
		Riboflavin + niacin + beta-carotene + selenium + alpha-tocopherol		58/77	3.1/4.1 per 1000	RR 0.75 (0.53-1.05)		
		Vitamin C + molybdenum + beta-carotene + selenium+ alpha-tocopherol		67/77	3.6/4.1 per 1000	RR 0.86 (0.62-1.20)		
		retinol + zinc + riboflavin + niacin + vitamin C + molybdenum + beta-carotene + selenium + alpha-tocopherol		69/77	3.7/4.1 per 1000	RR 0.88 (0.64-1.22)		
		Retinol + zinc				RR 0.99 (0.84-1.18)		
		Riboflavin + niacin				RR 0.94 (0.79-1.11)		
		Vitamin C + molybdenum				RR 1.04 (0.88-1.24)		
		Beta-carotene + selenium + alpha-tocopherol vs. placebo				RR 0.91 (0.76-1.07)		

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cardiovascular Disease (continued)								
SU.VI.MAX [69]	Ischemic cardiovascular disease	Vitamin C + vitamin E + beta-carotene + selenium + zinc	6364/6377	134/137		RR 0.97 (0.77-1.20)	0.8	
Eye Disease								
Linxian Cataract Study [65]	Prevalence of nuclear cataracts	Retinol + zinc	1628/ 1621		0.120/ 0.151	OR 0.77 (0.58-1.02)		
		Riboflavin + niacin	1623/ 1626		0.107/ 0.169	OR 0.59 (0.45-0.79)		OR 0.99 (0.62-1.59) in those aged 55-64, OR 0.45(0.31-0.64) in those aged 65-74
		Vitamin C + molybdenum	1654/ 1595		0.121/ 0.150	OR 0.78 (0.59-1.04)		
		Beta-carotene + selenium + alpha-tocopherol	1617/ 1632		0.146/ 0.125	OR 1.19 (0.90-1.59)		
	Prevalence of cortical cataracts	Retinol + zinc	1628/ 1621		0.342/ 0.325	OR 1.08 (0.92-1.27)		
		Riboflavin + niacin	1623/ 1626		0.342/ 0.325	OR 1.08 (0.92-1.27)		
		Vitamin C + molybdenum	1654/ 1595		0.325/ 0.342	OR 0.92 (0.79-1.09)		
		Beta-carotene + selenium + alpha-tocopherol	1617/ 1632		0.330/ 0.338	OR 0.96 (0.82-1.13)		
	Prevalence of posterior subcapsular cataracts	Retinol + zinc	1628/ 1621		0.008/ 0.013	OR 0.59 (0.31-1.14)		
		Riboflavin + niacin	1623/ 1626		0.016/ 0.006	OR 2.64 (1.31-5.35)		
		Vitamin C + molybdenum	1654/ 1595		0.011/ 0.009	OR 1.25 (0.65-2.38)		
		Beta-carotene + selenium + alpha-tocopherol	1617/1632		0.013/ 0.008	OR 1.56 (0.81-3.00)		

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Eye Disease (continued)								
REACT [72]	Anterior % pixel opaque†	Beta-carotene + vitamin C + vitamin E	81/77	Not applicable		Mean ± 95% CI Placebo: baseline 5.0 ± 1.4, last 8.3 ± 2.2, mean change from baseline: 3.3 ± 1.4; supplement: baseline 5.7± 1.6, last 7.3± 2.0 mean change from baseline: 1.7± 1.0; Difference from placebo: -1.6	.05	Unfavorable changes in secondary outcomes were smaller in the active supplement group, but none was significantly different from placebo group.
AREDS [73] cataract	Total lens event	Vitamin C + vitamin E + beta-carotene	2286/2310	756/785 (in 5 years)		OR 0.97 (0.84-1.11)	0.55	Adjustments for several potential confounders did not materially alter results
	Cataract surgery	Vitamin C + vitamin E + beta-carotene	2286/2310	675 in total		OR 0.94 (0.77-1.14)	0.41	
	Severe lens event	Vitamin C + vitamin E + beta-carotene	2286/2310	991 in total		OR 0.92 (0.76-1.12)	0.27	
	Nuclear event	Vitamin C + vitamin E + beta-carotene	4331	1674 in total		OR 0.98 (0.84-1.14)	0.71	Analysis of antioxidants only vs. placebo yielded similar results
		Antioxidants only (vitamin C + vitamin E+ beta-carotene)	2715	1027 in total		OR 1.00 (0.82-1.22)	0.97	
	Cortical event	Vitamin C + vitamin E + beta-carotene	4329	1058 in total		OR 0.99 (0.82-1.19)	0.84	
		Antioxidants only (vitamin C + vitamin E+ beta-carotene)	2715	625 in total		OR 0.91 (0.71-1.15)	0.29	
	Posterior subcapsular event	Vitamin C + vitamin E + beta-carotene	4329	888 in total		OR 0.94 (0.78-1.14)	0.39	
		Antioxidants only (vitamin C + vitamin E+ beta-carotene)	2715	535 in total		OR 0.91 (0.70-1.17)	0.33	

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Eye Disease (continued)								
AREDS [73] cataract (continued)	Lens event in eyes without opacities	Vitamin C + vitamin E + beta-carotene	823	NR		OR 0.85 (0.55-1.33)	NR	Among those with no or minimal opacity in at least one eye at enrollment
	Loss of visual acuity score of 15 letters or more	Antioxidants only (vitamin C + vitamin E+ beta-carotene)	537/580	Total 172		OR 1.03 (0.63-1.66)	0.89	Among those without age-related macular degeneration at enrollment
AREDS [75] age-related macular degene-ration	Progression to advanced AMD (among participants in AMD categories 2,3,4)	Antioxidants vs. no antioxidants	Total 3609	Total 803		OR 0.87(0.70-1.09)	0.12	Analysis adjusted for sex, age, race, and category, and smoking status at enrollment did not materially alter size or direction of estimates
		Zinc vs. no zinc				OR 0.82 (0.66-1.03)	0.02	
		Antioxidants				OR 0.80 (0.59-1.09)	0.07	
		Zinc				OR 0.75 (0.55-1.03)	0.02	
		Antioxidants + zinc				OR 0.72 (0.52-0.98)	0.007	
	Loss of visual acuity score of >=15 letters from baseline (among participants in AMD categories 2,3,4)	Antioxidants vs. no antioxidants	Total 3597	Total 1197		OR 0.90 (0.74-1.09)	0.14	
		Zinc vs. no zinc				OR 0.88 (0.73-1.07)	0.09	
		Antioxidants				OR 0.88 (0.67-1.15)	0.22	
		Zinc				OR 0.87 (0.66-1.13)	0.17	
		Antioxidants + zinc				OR 0.79 (0.60-1.04)	0.03	
	Progression to advanced AMD (among participants in AMD categories 3,4)	Antioxidants vs. no antioxidants	Total 2556	Total 775		OR 0.83 (0.66-1.06)	0.05	
		Zinc vs. no zinc				OR 0.79 (0.69-0.99)	0.009	
		Antioxidants				OR 0.76 (0.55-1.05)	0.03	
		Zinc				OR 0.71 (0.52-0.99)	0.008	
		Antioxidants + zinc				OR 0.66 (0.47-0.91)	0.001	

Evidence Table 1d. Results of studies of the efficacy of multivitamins/minerals in preventing chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Eye Disease (continued)								
AREDS [75] age-related macular degene-ration (continued)	Loss of visual acuity score of >=15 letters from baseline (among participants in AMD categories 3,4)	Antioxidants vs. no antioxidants	Total 2549	Total 1022		OR 0.86 (0.70-1.07)	0.07	
		Zinc vs. no zinc				OR 0.84 (0.68-1.04)	0.04	
		Antioxidants				OR 0.85 (0.63-1.14)	0.16	
		Zinc				OR 0.83 (0.62-1.11)	0.10	
		Antioxidants + zinc				OR 0.73 (0.54-0.99)	0.008	
MONMD [74]	Macular degeneration	Beta-carotene + vitamin E+vitamin C+ citrus bioflavenoid complex+ quercitin+ rutin+ zinc+ selenium+ taurine+ N-acetyl cysteine+ glutathione+ vitamin B2+ chromium	39/32	Not applicable				Acuity of left eyes, dist VA (logMAR): from 0.17 to 0.19 (active arm), from 0.26 to 0.35 (placebo arm); difference from placebo=-0.7(p=0.03) Acuity of left eyes, near VA (M print): from 0.77 M to 0.89 M (active arm), from 1.29 M to 2.03 M (placebo arm); difference from placebo=-.62(p=0.07)

* comparisons were made between groups receiving the combination of the listed nutrients and the groups receiving combinations of placebo/nutrients other than the nutrients listed, unless otherwise specified.
† primary endpoint
‡ secondary endpoint
SU.VI.MAX. (SUppléments en VItamines et Minéraux AntioXydants); MONMD = Multicenter ophthalmic and nutritional age-related macular degeneration study; REACT (Roche European American Cataract Trial); AREDS (Age-Related Eye Disease Study); OR = odds ratio; RR = relative risk; 95% CI = 95 confidence interval; PSA = prostate-specific antigen; py = person-years; AMD = age-related macular degeneration.

Evidence Table 1e. Total mortality in studies multivitamins/minerals used to prevent chronic disease

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Linxian General Population Study [66]	Total mortality	Retinol + zinc + riboflavin + niacin	29,584 (total)	265/280	14.1/15.0 per 1000 py	RR 0.94 (0.79-1.11)	NR	
		Retinol + zinc + vitamin C + molybdenum		296/280	15.8/15.0 per 1000 py	RR 1.05 (0.89-1.24)		
		Retinol + zinc + beta-carotene +selenium+ alpha-tocopherol		250/280	13.3/15.0 per 1000 py	RR 0.89 (0.75-1.05)		
		Riboflavin + niacin + vitamin C + molybdenum		268/280	14.3/15.0 per 1000 py	RR 0.95 (0.81-1.13)		
		Riboflavin + niacin + beta-carotene +selenium+ alpha-tocopherol		263/280	14.0/15.0 per 1000 py	RR 0.93 (0.79-1.11)		
		Vitamin C + molybdenum + beta-carotene + selenium+ alpha-tocopherol		249/280	13.2/15.0 per 1000 py	RR 0.88 (0.74-1.05)		
		Retinol + zinc + riboflavin + niacin + vitamin C + molybdenum + beta-carotene + selenium + alpha-tocopherol		256/280	13.6/15.0 per 1000 py	RR 0.91 (0.76-1.07)		
		Retinol + zinc		NR	NR	RR 1.00 (0.92-1.09)		
		Riboflavin + niacin				RR 0.98 (0.90-1.06)		
		Vitamin C + molybdenum				RR 1.01 (0.92-1.10)		
		Beta-carotene +selenium+ alpha-tocopherol				RR 0.91 (0.84-0.99)		

Evidence Table 1e. Total mortality in studies multivitamins/minerals used to prevent chronic disease (continued)

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Linxian General Population Study [71]	Total mortality In men	Retinol + zinc	NR	NR	NR	1.03	NR	Confidence intervals not reported; Age and sex difference are not statistically significant
		Riboflavin + niacin				0.96		
		Vitamin C + molybdenum				0.93		
		Beta-carotene +selenium+ alpha-tocopherol				0.93		
	Total mortality In women	Retinol + zinc				0.97		
		Riboflavin + niacin				0.99		
		Vitamin C + molybdenum				1.12		
		Beta-carotene +selenium+ alpha-tocopherol				0.89		
	Total mortality In those aged <55 years	Retinol + zinc				0.96		
		Riboflavin + niacin				1.02		
		Vitamin C + molybdenum				0.90		
		Beta-carotene +selenium+ alpha-tocopherol				0.87	<.05	
	Total mortality In those aged ≥55 years	Retinol + zinc				1.02	NR	
		Riboflavin + niacin				0.96		
		Vitamin C + molybdenum				1.05		
		Beta-carotene +selenium+ alpha-tocopherol				0.93		
SU.VI.MAX [69]	Total mortality	Vitamin C + vitamin E + beta-carotene + zinc +selenium vs. placebo	6364/6377	76/98	NR	RR 0.77 (0.57-1.00)	.09	

Evidence Table 1e. Total mortality in studies multivitamins/minerals used to prevent chronic disease.

Study name	Disease endpoint	Study supplement*	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence or prevalence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
AREDS [73] cataract study	Total mortality	Vitamin C + vitamin E + beta-carotene	2370/2387	251/240		RR 1.06 (0.84-1.33)	.53	
		vitamin C + vitamin E+ beta-carotene only vs. placebo	2965	313		RR 1.05 (0.78-1.40)	.68	
AREDS [75] age-related macular degene-ration		Vitamin C + vitamin E + beta-carotene	1833/1807	216/194		RR 1.10 (0.85-1.42)	.35	
		Zinc vs. no zinc	1792/1848	178/232		RR 0.79 (0.61-1.02)	.02	
		Vitamin C + vitamin E + beta-carotene vs. placebo	945/903	125/107		RR 1.12 (0.80-1.57)	.39	
		Zinc vs. placebo	904/903	87/107		RR 0.81 (0.56-1.17)	.14	
		Vitamin C + vitamin E + beta-carotene + zinc vs. placebo	888/903	91/107		RR 0.87 (0.60-1.25)	.32	
REACT [72]		Beta-carotene + vitamin C + vitamin E vs. placebo	81/77	9/3		NR	NR	

* comparisons were made between groups receiving the combination of the listed nutrients and the groups receiving combinations of placebo/nutrients other than the nutrients listed, unless otherwise specified.

CI = confidence interval; SU.VI.MAX. = SUppléments en VItamines et Minéraux AntioXydants; RR = relative risk; AREDS = Age-Related Eye Disease Study; REACT = Roche European American Cataract Trial; NR = not reported.

Evidence Table 2a. Characteristics of the interventions in studies of the safety of multivitamin supplements

Author, year	Study design	Control arm (duration of use)	INTERVENTION ARMS				
			Nutrient/supplement	Chemical form(s)	Dose/frequency of use	Timing of use	Duration of use
Chylack, 2002[72]	RCT	Placebo-corn oil (3 years)	Multivitamin (beta-carotene, vitamin C, vitamin E)	All-rac alpha-tocopherol acetate; ascorbic acid; beta-carotene	200 mg; 250 mg; 6 mg	3x per day (with meals)	3 years
ARED, 2001a, b[73,75]	RCT	Placebo (6.3 years)	Multivitamin (vitamin E, vitamin C, vitamin A, zinc, copper)	Dl-alpha-tocopherol acetate; ascorbic acid; beta-carotene; zinc oxide; cuprix oxide	200 IU; 250 mg; 7.5 mg; 40 mg; 1 mg	2 pills in the morning, 2 in the evening, with meals	6.3 years
			Multivitamin (vitamin E, vitamin C, vitamin A)	Dl-alpha-tocopherol acetate; ascorbic acid; beta-carotene	200 IU; 250 mg; 7.5 mg		
			Zinc, copper	Zinc oxide; cupric oxide	40 mg; 1 mg		
Richer, 1996[74]	RCT	Placebo (starch), (18 months)	Multivitamin (Vitamin E, Vitamin C, Vitamin A, Zinc, Vitamin B2, Selenuim, citrus bioflavonoid complex; quercitin (bioflavonoid); biberry extract (bioflavonoid); rutin (bioflavonoid); taurine; n-acetyl cysteine; l-glutathione; chromium)	NS; NS; betacarotene; Zinc picolinate; NS; NS; NS; NS; NS; NS; NS;taurine; n-acetyl cysteine; l-glutathione	200 IU; 750 IU; 20000 IU; 12.5 mg; 25 mg; 60 mcg; 125 mg; 50 mg; 5 mg; 50 mg; 100 mg; 100 mg; 100mg; 5 mg	2x per day	18 months
Xuan, 1991 [78]	RCT		Vitamin A; beta-carotene; vitamin E; selenium	Retinol; beta-carotene; d-alpha-tocopherol; selenium yeast	25,000 IU, 30 mg; 50 mg; 800 IU; 400 mcg	1x per day	6 months
Ohtake [79]	Case report		Multivitamin (Calcium, Vitamin D, Vitamin C), laxatives and aspirin	Calcium lactate; NS; ascorbic acid	1000 mg; 250 IU; 6000 mg	1x per day	10 years
Grouhi, 2000[80]	Case report		Multivitamin (Calcium, Vitamin E, Vitamin C, niacin, selenium), echinacia; barley green; licorice root; Chinese herbs; B complex	NS; NS; NS; niacin; NS	100 mg; 800 IU; 300 mg; 240 mg (niacin comes from multivitamin (40mg), B-complex (40mg) and anti-nausea drug(150mg)); 200 mcg	NS	NS
Gulati, 1999[81]	Case report		Multivitamin/minerals (Vitamin E Vitamin C Vitamin A Zinc Vitamin B2 Selenuim + copper)	Vitamin E acetate; NS; vitamin A acetate; NS; NS; selenium dioxide monohydrate; copper sulfate	NS	1x per day	NS

Evidence Table 2b. Results of studies with information on clinical adverse effects of multivitamin supplements in the prevention of chronic diseases

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Chylack, 2002[72]	Vitamins A, C, E	Intercurrent illness	107	84	NR	NS	
		Deaths/serious events	9 deaths (2 from coronary thrombosis, lead from renal cell cancer, throat cancer, carcinomatosis, esophagitis, sudden death, aneurysm, pulmonary fibrosis)	3 deaths (coronary thrombosis, bile duct cancer, lung cancer)		0.07 for deaths	
		Skin yellowing	6	NR			
ARED, 2001a[73]	Antioxidants	Hospitalizations (due to mild to moderate symptoms)	173 (7.3%)	221(9.3%)	NR	0.01	
		Primary adverse effect (caused by skin, subcutaneous tissue problems)	56 (2.4%)	21(.9%)		<0.001	
		Change in skin color	203 (8.6%)	146 (6.1%)		<0.001	
		Chest pain	467 (19.8%)	541 (22.8%)		0.01	
		Mortality	251	240	1.06 (0.84-1.33)	0.53	Similar results for analysis of antioxidants only vs. placebo

Evidence Table 2b. Results of studies with information on clinical adverse effects of multivitamin supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
ARED, 2001b[75]	Antioxidants	Yellow skin	151 (8.3%) in antioxidant arm	106 (6.0%) in non antioxidant arms	NR	0.008	
		Hospitalizations due to infections	29 (1.6%) in antioxidant arms	15 (0.8%) in non antioxidant arns	NR	0.04	
		Mortality	NR	NR	1.10 (0.85-1.42)	0.35	Similar results when comparing antioxidants vs. placebo.
		Skin and subcutaneous tissue conditions	41 (2.2%)	18 (1.0)%	NR	0.003	
	Zinc	Anemia	236 (13.2%) in zinc arms	187 (10.2%) in non zinc arms	NR	0.004	
		Genitourinary hospitalizations (eg, unspecified urinary tract infection, prostatic hyperplasia in men, stress incontinence in women)	134 (7.5%) in zinc arms	90 (4.9%) in non zinc arms		0.001	
		Hospitalizations for mild/moderate symptoms (e.g. chest pain, fever)	173 (9.7%) in zinc arms	143 (7.8%) in non zinc arms		0.04	
		Circulatory adverse experience	16 (0.9%)	5 (0.3%)			

Evidence Table 2b. Results of studies with information on clinical adverse effects of multivitamin supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Richer, 1996[74]	Beta-carotene; vitamin E; vitamin C; bioflavonoid; zinc picolinate; selenium; taurine; n-acetyl cysteine; l-glutathione; vitamin B2; chromium	Diffuse whole body maculopapular rash	1	NR	NR	0.06 for interation between time and caPsule within Patients	
		Transient diarrhea	NR				In the article, Appendix 3 showed changes in several labs, and none of which were significant, Appendix 4 showed the mean scores for diarrhea, constipation, nausea/vomiting, and dyspeptic symptoms, none of which differed between the arms.
		Diarrhea, constipation, nausea/vomiting, dyspeptic symptoms					

Evidence Table 2b. Results of studies with information on clinical adverse effects of multivitamin supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Xuan, 1991 [78]	Vitamin E, selenium	See comments	See comments	See comments	NR		Symptoms (muscle cramps, diarrhea, decreased appetite, runny nose, joint pain, lip chapping, yellowing, broken nails, hair loss, tingling headache, lethargy) were generally improved by the intervantion.
		Stroke	1 (vitamin E + selenium)	1 (placebo)			
Ohtake, 2005 [79]	Ascorbic acid; calcium lactate; vitamin D, laxatives; laxatives	Severe proximal tubular dysfunction, calcified lesion, hypokalemic nephropathy	1	0	NR		Case took ascorbic acid of 6000 mg/day, vitamin D, calcium lactate and laxatives; hypokalemic nephropathy probably was due to long-term use of laxatives, but the calcified lesion probably was due to massive oxalate load after excessive ingestion of vitamin C.
Grouhi, 2000 [80]	Niacin	Pseudoallergic toxic reaction	1	NA	NA		

Evidence Table 2b. Results of studies with information on clinical adverse effects of multivitamin supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Gulati, 1999[81]	Vitamin A acetate; vitamin E acetate; vitamin C; vitamin B2; copper sulfate; zinc sulfate; selenium dioxide monohydrate	Fixed drug eruption	1	0	NA		

NR = Not reported; NS = Not significant; NA = Not applicable

Evidence Table 2c. Results of Studies with information on lipid profiles associated with the use of multivitamin supplements

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Change in active group (indicate mean (95% CI)), mean (SD), mean (SE), median or other measurements	Change in inactive group (indicate mean (95% CI)), mean (SD), mean (SE), median or other measurements	Statistical significance (p-value)	Comment
Sacco, 2003[181]	Vitamin E	Lipid profiles: Cholesterol (mM), LDL (mM), HDL (mM), triglycerides (mM)	NA	NA	Mean (SD) pre/post: Cholesterol 4.97 (1.09)/4.73 (0.87); LDL 3.44 (0.88)/3.06 (0.96l); HDL 1.44 (0.42)/1.23 (0.37); TG 0.84 (0.15)/0.92 (0.28)	Mean (SD) pre/post: Cholesterol 4.68 (0.84)/4.60 (0.80); LDL 2.40 (0.53)/2.84 (0.79) HDL 1.01 (0.3)/1.22 (0.48) TG 1.44 (0.99)/1.18 (0.55)		All values not significantly different from the mean level of the 50 volunteers
	Vitamin C				Mean (SD) pre/post: Cholesterol 5.23 (0.97)/5.30 (1.00); LDL 2.82 (0.65)/3.17(0.72); HDL 1.58 (0.41)/1.50 (0.79); TG 1.31 (1.00)/1.33 (0.79)	Mean (SD) pre/post: Cholesterol 4.68 (0.84)/4.60 (0.80); LDL: 2.40 (0.53)/2.84 (0.79); HDL: 1.01 (0.3)/1.22 (0.48); TG: 1.44 (0.99)/1.18 (0.55)		
	Beta-Carotene				Mean (SD) pre/post: Cholestrol 4.83 (0.65)/4.87 (0.55); LDL 2.88 (0.24)/3.14 (0.52); HDL 1.28 (0.21)/1.12 (0.22); TG 1.01 (0.41)/1.29 (0.96)	Mean (SD) pre/post: Cholesterol 4.68(0.84)/4.60 (0.80); LDL 2.40 (0.53)/2.84 (0.79); HDL 1.01 (0.30)/1.22 (0.48); TG 1.44 (0.99)/1.18 (0.55)		
	Combined				Mean (SD) pre/post: Cholestrol 5.04 (1.32)/4.98 (1.27); LDL 2.97 (1.75)/3.19 (0.34); HDL 1.39 (0.34)/1.30 (0.37); TG 1.06 (0.75)/1.08 (0.89)	Mean (SD) pre/post: Cholesterol 4.68 (0.84)/4.60 (0.80); LDL 2.40 (0.53)/2.84 (0.79); HDL 1.01 (0.30)/1.22 (0.48); TG 1.44 (0.99)/1.18 (0.55)		

NA = Not applicable; NR = Not Reported; LDL = low-density lipoprotein; HDL = high-density lipoprotein; SD = Standard Deviation; SE = Standard Error.

Evidence Table 2d. Assessment of the likelihood that reported adverse effect were caused by use of a multivitamin/mineral supplement

Author, year	Nutrient	Adverse effect	Temporal relationship	Dose-response relationship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supplement use	Lack of alternative cause	Recurrence after reuse of supplement
Chylack, 2002[72]	Vitamins A, C, E	Intercurrent illness	Yes	NR	NR	Yes	NR	NR
		Deaths/serious events						
		Skin yellowing						
ARED, 2001a[73]	Antioxidants	Hospitalizations (due to mild to moderate symptoms)	Yes	NR	NR	Yes	NR	NR
		Primary adverse effect (caused by skin, subcutaneous tissue problems)						
		Change in skin color						
		Chest pain						
ARED, 2001b [75]	Antioxidants	Yellow skin	Yes	NR	NR	Yes	NR	NR
		Hospitalizations due to infections						
		Skin and subcutaneous tissue conditions						
	Zinc	Anemia	Yes	NR	NR	Yes	NR	NR
		Genitourinary hospitalizations						
		Hospitalizations for mild/moderate symptoms (e.g. chest pain, fever)						
		Circulatory adverse experience						
Richer, 1996 [74]	Beta-carotene; vitamin E; vitamin C; bioflavonoid; zinc picolinate; selenium; taurine; n-acetyl cysteine; l-glutathione; vitamin B2;chromium	Diffuse whole body maculopapular rash	Yes	NR	NR	Yes	No	NR
		Transient diarrhea	Yes	NR	NR	Yes	Yes	NR
		Cholesterol	No	NR	NR	Yes	NR	NR
		Diarrhea, constipation, nausea/vomiting, dyspeptic symptom	Yes	NR	NR	Yes	NR	NR

Evidence Table 2d. Assessment of the likelihood that reported adverse effect were caused by use of a multivitamin/mineral supplement (continued)

Author, year	Nutrient	Adverse effect	Temporal relationship	Dose-response relationship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supplement use	Lack of alternative cause	Recurrence after reuse of supplement
Xuan, 1991 [78]	Vitamin E, selenium	Stroke	Yes	NR	NR	Yes	NR	NR
Ohtake, 2005 [79]	Ascorbic acid; calcium lactate; vitamin D, laxatives; laxatives	Severe proximal tubular dysfunction, calcified lesion, hypokalemic nephropathy	NR	No	Yes	NR	NR	NR
Grouhi, 2000 [80]	Niacin	Pseudoallergic toxic reaction	NR	Yes	NR	Yes	Yes	NR
Gulati, 1999 [81]	Vitamin A acetate; vitamin E acetate; vitamin C; vitamin B2; copper sulfate; zinc sulfate; selenium dioxide monohydrate	Fixed drug eruption	NR	NR	NR	No	NR	NR

NR = Not reported

Evidence Table 3a. Characteristics of the studies on the efficacy of vitamin A and/or beta-carotene (singly or paired) in preventing chronic disease

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
ATBC							
ATBC, 1994[97]	RCT; Factorial design	1985-1988	Not 50-69; female; any cancer except non-melanoma skin; chronic renal insufficiency; liver cirrhosis; chronic alcoholism; medical condition limiting participation; severe angina; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses	29133	6.1 years (median)	Finland	Community
Albanes, 1996[98]		1985-1993	Not 50-69; female; any previous or current cancer; symptomatic CV disease, CHD or major ischemic change in their ECG; atrophic gastritits at baseline or after 3-yr follow-up; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettes/day at entry; anti-coagulant use	1344	5-8 years (total), 3.9 years (median, Helsinki), 5.8 years (median, outside Helsinki)		
Rautalahti, 1999[99]		1985-1993	Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; nonsmokers)	29133	5-8 years (total), 6.1 years (media		
Varis, 1998[90]		1985-1993	Not 50-69; female; any previous or current cancer; symptomatic CV disease, CHD or major ischemic change in their ECG; atrophic gastritits at baseline or after 3-yr follow-up; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettes/day at entry; anti-coagulant use	1344	5-8 years (total), 3.9 years (median, Helsinki), 5.8 years (median, outside Helsinki)		
Rapola, 1996[106]		1985-1993	MI; any history of CHD at baseline and same criteria as general ATBC trial	22265	4.7 years (median)		

Evidence Table 3a. Characteristics of the studies on the efficacy of vitamin A and/or beta-carotene (singly or paired) in preventing chronic disease (continued)

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
ATBC (continued)							
Leppala, 2000 [107]		1985-1993	Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettes/day at entry; anti-coagulant use	28519	6.0 years (median)		
Teikari, 1997 [109]		1985-1993	Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; nonsmokers)	1828	6.6 years (median)		
CARET							
Omenn, 1996a [105]	RCT; Placebo controlled	1985-1993	Asbestos arm: not 45-74 years old in pilot period or 45-69 yrs in vanguard; smoking arm: not 50-69 yrs, male; any history of cancer except non-melanoma skin cancer in past 5 years; NASH; NAFLD; asbestos arm: no chest X-ray evidence of asbestos interstitial lung disease or not greater than or equal to 5 years high risk trade, SGOT or alkaline phosphate greater than 2.5x and 1.5x 95th percentile of normal, respectively, history of liver disease in past 12 months, any beta-carotene supplementation; smoking arm: < 20 pack-year smoking history, current or quit in past 6 years; smoking arm: premenopausal; asbestos arm: < 15 years since first occupational exposure.	1845	8 years (total)	Seattle, Washington; Portland, Oregon; San Francisco, CA; Baltimore, MD; New Haven Conn; Irvine, CA.	Clinical and community
Omenn, 1996b [93]		1985-1995		18314	4 years (mean), 3.7 years (median).		Asbestos arm: recruited from physicians' clinics, worker's compensation programs, labor unions, lawyers, Navy Medical Asbestos Surveillance Program, union. Smoking arm: Insurance and AARP mailing lists.
Gooodman, 2004 [94]	RCT (Post-intervention follow up)	1985-1996		17140	5.9 years (total)		Clinical and community
NCSP							
Green, 1999 [84]	RCT; Factorial design	1992-1996	Skin cancer	809	4.5 years (total)	Australia	Community

Evidence Table 3a. Characteristics of the studies on the efficacy of vitamin A and/or beta-carotene (singly or paired) in preventing chronic disease (continued)

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
SCP							
Greenberg, 1996[85]	RCT; Parallel arms	1983-1993	85 years old or greater; any cancer other than nonmelanoma skin cancer diagnosed during the prior 5 years; debilitating cardiovascular conditions; known genetic predisposition to cancer; had not had at least one biopsy proved basal cell or squamous cell skin cancer treated after January 1, 1980; medical conditions that would limit participation in the study.	1720	8.2 years (median)	USA	Clinical
PHS							
Cook, 2000[104]	RCT; Factorial design	1982-1995	Female; cancer; MI; stroke; current use of vitamin A supplements; taking aspirin.	22071	12.9 years (mean)	USA	Physician rosters
Frieling, 2000[86]							
Liu, 1999[108]			Female; cancer; MI; stroke; type II diabetes	21468	12.9 years (mean)		Physician rosters
Hennikens, 1996[95]			Female; cancer except nonmelanoma skin cancer; MI; stroke; transient cerebral ischema	22071	12 years (mean)		Physician rosters
WHS							
Lee, 1999[96]	RCT; Factorial design	1993-1996	Male; cancer; MI; stroke; serious illness that might preclude participation; participants in the Nurses Health Study; taking supplements of vitamin A, E, or beta-carotene more than once per week; taking aspirin or aspirin containing medications and not willing to forego use; NSAID more than once a week and not willing to forego use; taking anticoagulants; taking corticosteroids.	39876	4.1 years (median)	USA (nation-wide)	Health professionals

Evidence Table 3a. Characteristics of the studies on the efficacy of vitamin A and/or beta-carotene (singly or paired) in preventing chronic disease (continued)

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
Linxian General Population Study							
Mark, 1998[66]	RCT; factorial design	1986-1991	Not 40-46 years old; history of cancer; history of debilitating diseases.	29584	5 years (total)	Linxian province, China	Community
Blot, 1993[64]			Not 40-69; stomach or esophageal; debilitating disease; does not live in one of 4 communes in Linxian		5.25 years (total)		

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; NSCP = Nambour Skin Cancer Prevention Trial; SCP = Skin Cancer Prevention Study; PHS = Physicians Health Study; WHS = Womens Health Study.

Evidence Table 3b. Characteristics of the intervention in the studies of the efficacy of vitamin A and/or beta-carotene in the prevention of chronic disease

Author, year	Control arm	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
ATBC						
ATBC, 1994[97]	Placebo	Vitamin E; beta-carotene	dl-alpha-tocopherol acetate; beta-carotene	50 mg/1x/day; 20 mg/1x/day	NS	6.1 years median
Albanes, 1996[98]						5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
Rautalahti, 1999[99]						6.1 years
Varis, 1998[90]						5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
Rapola, 1996[106]						4.7 years median
Leppala, 2000 [107]						6 years median
Teikari, 1997[109]						5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
CARET						
Omenn, 1996a[105]	Placebo	Vitamin A	Retinol in pilot phase (1985-1988) then retinyl palmitate in Vanguard (1988-1996)	25000 IU/1x/day	NS	Max 8 years
Omenn, 1996b[93]		Vitamin A	Retinyl palmitate	25000 IU/1x/day		10 years; Until endpoint (NS)
Gooodman, 2004[94]		Vitamin A; beta-carotene		25000 IU/1x/day; 30 mg/1x/day		10 years; Until endpoint (NS)

Evidence Table 3b. Characteristics of the intervention in the studies of the efficacy of vitamin A and/or beta-carotene in the prevention of chronic disease (continued)

Author, year	Control arm	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
NSCP						
Green, 1999[84]	Placebo	Beta-carotene	Beta-carotene	30 mg/1x/day	With meals	4.5 years
SCP						
Greenberg, 1996[85]	Placebo	Beta-carotene	Beta-carotene	50 mg/1x/day	NS	4.3 years
PHS						
Cook, 2000[104]	Placebo	Beta-carotene	Beta-carotene	50 mg/every other day	NS	12.9 years (mean)
Frieling, 2000[86]						12.9 years (mean)
Liu, 1999[108]						12 years
Hennikens, 1996[95]						12 years (mean)
WHS						
Lee, 1999[96]	Placebo	Beta-carotene	Beta-carotene	50 mg/every other day	NS	2.1 years
Linxian General Population Study						
Mark, 1998[66]	Placebo	Vitamin A; zinc	Retinol palmitate; zinc oxide	10,000 IU/NS; 45 mg/NS	NS	5 years
		Vitamin B2; niacin	Riboflavin; niacin	5.2 mg/NS; 40 mg/NS		
		Vitamin C; molybdenum	Ascorbic acid; yeast complex	180 mg/NS; 30 µg/NS		
Blot, 1993[64]	Placebo	Vitamin A; zinc	Retinol palmitate; zinc oxide	5000 IU/daily; 22.5 mg/daily	NS	5.25 years
		Vitamin B2; niacin	Riboflavin; niacin	3.2 mg/1x/day; 40 mg/1x/day		
		Vitamin C; molybdenum	Ascorbic acid; yeast complex	12 mg/NS; 30 µg/NS		

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; NSCP = Nambour Skin Cancer Prevention Trial; SCP = Skin Cancer Prevention Study; PHS = Physicians Health Study; WHS = Women Health Study; NS = Not specified; mg = milligram; mcg = microgram; IU = international unit; µg

Evidence Table 3c. Characteristics of participants in studies of the efficacies of Vitamin A and/or beta-carotene (singly or in nutrient pairs)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
ATBC						
ATBC, 1994[97]	Median: 57; range: 50-69.	0 (0); ethnicity NR	Current: 29133 (100)	Mean intake (grams/day): 11.0.	26.0	NA
Albanes, 1996[98]	Median: 57; range: 50-69.		Current: 29133 (100)	Mean intake (grams/day): 11.0.	26.0	
Rautalahti, 1999[99]	57.7		Current: (100.0)	Mean intake (grams/day): 18.0.	26.3	
Varis, 1998[90]	58.8		Current: 1344 (100)	Mean intake (grams/day): 8.9.	NR	
Rapola, 1996[106]	Median: 56.9		Current: 22269 (100)	NR	26.0	
Leppala, 2000[107]	Mean: 57.7		Current: 28519 (100)	Mean intake (grams/day): 18.0.	26.3	
Teikari, 1997[109]	64.8		Current: 1828 (100)	Mean intake (grams/day): 12.5.	25.5	
CARET						
Omenn, 1996a[105]	NR	Gender, NR; ethnicity NR	NR	NR	NR	NR
Omenn, 1996b[93]	58	6289 (34.3); Caucasian, 17067 (93.2); African-American, 530 (2.9); Latino 275 (1.5)	Never: 132 (0.7); former: 7174 (39.2); current: 11008 (60.1).	Never: 6121 (33.4).		
Gooodman, 2004[94]	62	6007 (35); Caucasian, 15988 (93.3)	Never: 116 (0.7); former: 8988 (52.4); current: 8036 (46.9).	NR		
NSCP						
Green, 1999[84]	48.8	913 (56.3); ethnicity NR	NR	NR	NR	NR

Evidence Table 3c. Characteristics of participants in studies of the efficacies of Vitamin A and/or beta-carotene (singly or in nutrient pairs) (continued)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
SCP						
Greenberg, 1996[85]	63.2	532 (31); ethnicity NR	Never: 625 (36.3); former: 780 (45.3); current: 315 (18.3).	NR	BMI <23: 461 (26.8); BMI 23-27: 813 (47.3); BMI>27: 466 (27.1).	NR
PHS						
Cook, 2000[104]	53.0 (9.5); range: 40-84.	0 (0); ethnicity NR	Never: 11036 (50); former: 8608 (39); current 2428 (11.0).	Rare: 3222 (14.6%); monthly: 2428 (11.0); weekly: (49.5); daily: 5518 (25.0).	24.9	Current multivitamin use: 4304 (19.5).
Frieling, 2000[86]						
Liu, 1999[108]						
Hennikens, 1996[95]						
WHS						
Lee, 1999[96]	53.9 (7.1)	39876 (100); Caucasian, 37802 (94.8); Latino, 917 (2.3),; Asian, 558 (1.4)	Never: 20377 (51.1); former: 14355 (36); current: 5224 (13.1).	Never: 17984 (45.1).	26.0; BMI>27.3: 13119 (32.9%).	Vitamin C use: 3788 (9.5); current regular multivitamin use: 11644 (29.2).
Linxian General Population Study						
Mark, 1998[66]	Median (female) 51; median (male): 53; range: 44-60.	16271 (55); ethnicity NR	Current (female): 3254 (20); current (male): 8929 (67).	Current (female): (10); current (male): (40).	Median BMI (female): 21.9; median BMI (male): 21.6.	NR
Blot, 1993[64]	<50: 12425 (42%); 50-59: 10354 (35%); ≥60: 6804 (23%).		Never: 20709 (70); ever smoked for >6 months: 8875 (30).	Never: 22780 (77); any use in past 12 months: 6804 (23).	NR	

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; NSCP = Nambour Skin Cancer Prevention Trial; SCP = Skin Cancer Prevention Study; PHS = Physicians Health Study; WHS = Womens Health Study; BMI = Body Mass Index; NR not reported

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease.

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer								
				ATBC				
ATBC, 1994[97]	Lung cancer	Beta-carotene	14564/ 14564	474/402	56.3/47.5 per 10000 py	RR 1.18 (1.03-1.36)	.01	
	Lung cancer mortality	Beta-carotene		302/262	35.6/30.8 per 10000 py	RR 1.08 (1.01-1.16)	.02	
Albanes, 1996[98]	Lung cancer	Beta-carotene vs. no beta-carotene	14560/ 14573	482/412	58.0/41.2 per 10000 py	RR 1.16 (1.02-1.33)	.01	RR 1.39, 95% CI 1.03-1.88 in those aged 65-69; RR 1.25, 95% CI 1.07-1.46 in those smoker 20+ cigarettes/day; RR 1.23, 95% CI 1.04-1.47 in those who always inhale cigarette smoke; RR 1.17, 95% CI 1.03-1.34 in those exposed to asbestos; RR 1.40, 95% CI 1.10-1.78 in those with dietary intake <8.1 mg/d; RR 1.35, 95% CI 1.01-1.81 in those drank ethanol >11 g/d; RR 1.33, 95% CI 1.01-1.73 in those with baseline serum α-tocopherol 11.6-13.1 mg/L; Non significant findings for lng cancer in the subgroups defined by baseline dietary intake of β-carotene, vitamin C, or retinol, and by serum β-carotene or retinol.
Albanes, 2000[102]	Colorectal cancer	Beta-carotene	7282/7287	39/37	NR	RR 1.06 (0.68-1.66)		
		Beta-carotene vs. no beta-carotene	14560/ 14573	69/66		RR 1.05 (0.75-1.47)	.78	P-value from log-rank test
		Alpha-tocopherol +beta-carotene	7278/7287	30/37		RR 0.82 (0.50-1.31)		
	Colorectal cancer mortality	Beta-carotene vs. no beta-carotene	14564/ 14569	22/24		RR 1.01 (0.56-1.79)		

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease.

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer (continued)								
ATBC (continuted)								
Malila, 1999 [100]	Colorectal Adnomas	Beta-carotene vs. no beta-carotene	7761/7777	81/56	NR	RR 0.98 (0.71-1.35)	.89	P-value from log-rank test ; results did not change after excluding 15 cases with a prior history of polyps (RR 0.96)
Heinonen, 1998[101]	Prostate cancer	Beta-carotene	7282/7287	80/67	NR	RR 1.20 (0.87-1.66)		
		Alpha-tocopherol +beta-carotene	7278/7287	56/67		RR 0.84 (0.59-1.20)		
		Beta-carotene vs. no beta-carotene	14560/ 14573	136/110		RR 1.23 (0.96-1.59)		
	Prostate cancer mortality	Beta-carotene vs. no beta-carotene	14560/ 14573	33/29		RR 1.15 (0.70-1.89)		
Rautalahti, 1999[99]	Pancreatic cancer	Beta-carotene vs. no beta-carotene	14573/ 14560	38/51	0.45/0.60 per 1000 py	RR 0.75 (0.49-1.14)		
	Carcinoma of the pancreas	Beta-carotene	7282/7287	12/26	NR	RR 0.46 (0.23-0.92)		
	Pancreatic cancer mortality	Beta-carotene vs. no beta-carotene	14573/ 14560	35/48	NR	RR 0.81 (0.53-1.26)		
Varis, 1998[90]	Gastric dysplasia, carcinoma, or carcinoid	Beta-carotene	329/333	13/18	NR	NR		
		Alpha-tocopherol + beta-carotene	361/333	19/18				
		Beta-carotene vs. no beta-carotene	690/654	32/31		RR 0.98 (0.59-1.62)		Adjusted RR 1.13 (0.65-1.95)
CARET								
Omenn, 1996a [105]	Lung Cancer	Retinyl palmitate + beta-carotene	9420/8894	229/159	5.9/4.6 per 1000	RR 1.28 (1.04-1.57)	.02	
	Lung cancer mortality		9420/8894	NR		RR 1.46 (1.07-2.00)	.02	
	Leukemia		9420/8894	18/8		RR 2.18 (0.95-5.03)	.06	
	Mesothelioma		9420/8894	14/9		RR 1.52 (0.66-3.52)	.32	
	Breast Cancer		3208/3081	59/65		RR 0.78 (0.55-1.12)	.18	
	Colorectal cancer		9420/8894	56/50		RR 1.02 (0.70-1.50)	.91	
	Head/neck cancer		9420/8894	32/22		RR 1.26 (0.73-2.19)	.41	
	Lymphoma		9420/8894	13/13		RR 0.91 (0.42-1.98)	.81	
	Prostate cancer		9420/8894	161/139		RR 1.01 (0.80-1.27)	.95	
	Bladder cancer		9420/8894	42/36		RR 1.08 (0.69-1.70)	.73	

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active/inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer (continued)								
CARET (continued)								
Omenn, 1996b [93]	Lung Cancer	Retinyl palmitate + beta-carotene	9420/8894	Total 388, Con-firmed: 286	Total 5.4 per 1000 py; Active: con-firmed: 5.92 per 1000 py; Placebo 4.62 per 1000 py	RR 1.28 (1.04-1.57)	.02	
	Lung Cancer death			NR		RR 1.46 (1.07-2.0)		
	Mesothelioma			14/9		NR		Described as "no statistically significant effect"
Goodman, 1993 [92]	Lung Cancer	Active group follow up (had received vitamin A and beta-carotene)	8744/8396	376/311		RR 1.12 (0.97-1.31)	.13	
	Lung cancer mortality	Active group follow up (had received vitamin A and beta-carotene)		294/227		RR 1.20 (1.01-1.43)		
NCSP								
Green, 1999 [84]	Basal-cell carcinoma	Beta-carotene	820/801	102/93	3954/3806 per 100,000	RR 1.04 (0.73-1.27)		Data based on persons with and without a history of skin cancer
	Squamous-cell carcinoma	Beta-carotene		40/28	1508/1146 per 100,000	RR 1.35 (0.84-2.19)		
PHS								
Frieling, 2000 [86]	Nonmelanoma skin cancer	Beta-carotene	10941/ 10943	1786/1821		RR 0.98 (0.92-1.05)		Adjusted for age and aspirin use
	Basal cell carcinoma		10941/ 10943	1574/1598		RR 0.99 (0.92-1.06)		
	Squamous cell carcinoma		10941/ 10943	340/352		RR 0.97 (0.84-1.13)		
Hennikens, 1996 [95]	All cancer	Beta-carotene	11036/11035	1273/1293		RR 0.98 (0.91-1.06)	.65	
	All cancer mortality			386/380		RR 1.02 (0.89-1.18)	.76	

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cancer (continued)								
				SCP				
Greenberg, 1996[85]	Cancer deaths	Beta-carotene		38/44	NR	HR 0.86 (0.56-1.32)	.48, adjusted .41	Adjusted for age, sex, center, quetelet index, smoking; adjusted HR 0.83 (0.54-1.29)
Cook, 2000[104]	Non-melanoma skin cancer	Beta-carotene	11036/ 11035	1314/1353		RR 1.0 (0.9-1.0)	.41	
	Prostate cancer			551/566		RR 1.0 (0.9-1.1)	.62	
	Colon cancer			128/139		RR 0.9 (0.7-1.2)	.48	
	Rectal cancer			42/37		RR 1.1 (0.7-1.8)	.58	
	Lung cancer			85/93		RR 0.9 (0.7-1.2)	.54	
	Lymphoma			89/85		RR 1.0 (0.8-1.4)	.77	
	Leukemia			36/45		RR 0.8 (0.5-1.2)	.31	
	Melanoma			68/77		RR 0.9 (0.6-1.2)	.45	
	Brain cancer			25/33		RR 0.8 (0.5-1.3)	.29	
	Bladder cancer			62/41		RR 1.5 (1.0-2.2)	.04	
	Stomach cancer			20/21		RR 0.9 (0.5-1.8)	.87	
	Thyroid cancer			19/2		RR 9.5 (2.2-40.7)	.003	
	All cancer incidence			1314/1353		RR 1.0 (0.9-1.0)	.41	
	All cancer mortality			414/406		RR 1.0 (0.9-1.2)	.71	
				WHS				
Lee, 1999[96]	All cancers not non-melanoma skin cancer	Beta-carotene	19939/ 19937	378/369		RR 1.03 (0.89-1.18)	.73	Adjusted for age, randomized aspirin assignment, and randomized vitamin E assignment.
	Cancer mortality			31/28		RR 1.11 (0.67-1.85)	.69	
				Linxian General Population Study				
Blot, 1993[64]	Gastric cancer incidence	Retinol + zinc				RR 0.96 (0.81-1.14)		
	Esophageal cancer incidence					RR 1.07 (0.92-1.25)		
	Stomach cancer death					RR 1.03 (.83-1.28)		
	Stomach cancer incidence					RR 1.02 (.85-1.24)		
	Total cancer incidence					RR 1.00 (.89-1.11)		

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active/ inactive)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer (continued)								
ATBC								
Rapola, 1996[106]	Angina	Beta-carotene vs. no beta-carotene	11348/ 11119	1020/963	21.2/20.0 per 1000 py	RR 1.05 (0.97-1.16)		
		Beta-carotene alone	5602/5549	548/487	22.8/20.2 per 1000 py	RR 1.13 (1.00-1.27)		
		Alpha-tocopherol + beta-carotene	5548/5549	472/487	19.6/20.2 per 1000 py	RR 0.96 (0.85-1.09)		
Cardiovascular Disease								
ATBC (continued)								
Leppala, 2000 [107]	Intracerebral hemorrhage	Beta-carotene vs. no beta-carotene	14246/ 14273	69/43	8.4/5.2 per 10000 yr	RR 1.62 (1.10-2.36)	.01	
	Death from Intracerebral hemorrhage			29/21	3.5/2.5 per 10000 yr	RR 1.39(0.79-2.44)	.25	
	Subarachoid hemorrhage			45/40	5.5/4.9 per 10000 yr	RR 1.13 (0.74-1.73)	.57	
	Death from Subarachoid hemorrhage			15/23	1.8/2.8 per /61/1 per 10000 yr	RR 0.65 (0.34-1.25)	.20	
	Cerebral infarction			415/392	50.7/47.6 per 10000 yr	RR 1.07 (0.93-1.22)	.36	
	Death from Cerebral infarction			35/30	4.3/3.6 per 10000 yr	RR 1.17 (0.72-1.91)	.52	
	All strokes			554/503	67.7/61.1 per 10000 yr	RR 1.29 (0.94-1.76)	.11	
	Death from all strokes			82/78	10.0/9.5 per 10000 yr	RR 1/06 (0.78-1.44)	.72	
CARET								
Omenn, 1996b[93]	CV death	Vitamin A + beta-carotene	9420/8894		NR	RR 1.26 (0.99-1.61)		ICD codes 459 and 798, by 9th revision

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active /inactive)	Unadjusted estimates (95% CI)	P-value	Comment
Cardiovascular Disease (continued)								
				SCP				
Greenberg, 1996[85]	CV deaths	Beta-carotene		68/59	NR	HR 1.15 (0.81-1.63), adjusted HR 1.16 (0.82-1.64)	0.44, Adjusted 0.41	Adjusted for age, sex, center, quetelet index, smoking; Persons with baseline serum β-carotene in the highest quartile had the lower risk of CV death [RR 0.52 (0.34-0.95)]
				PHS				
Liu, 1999[108]	Type 2 DM	Beta-carotene	10756/ 10712	396/402	NR	RR 0.98 (0.85-1.12)	NR	
Hennekens, 1996[95]	MI	Beta-carotene	11036/11035	468/489	NR	RR 0.96 (0.84-1.09)	.50	
	Stroke			367/382		RR 0.96 (0.83-1.11)	.60	
	All CV events			967/972		RR 1.00 (0.91-1.09)	.90	
	Death; CV causes			338/313		RR 1.09 (0.93-1.27)	.28	
				PHS				
Liu, 1999[108]	Type 2 DM	Beta-carotene	10756/ 10712	396/402	NR	RR 0.98 (0.85-1.12)	NR	
Hennekens, 1996[95]	MI	Beta-carotene	11036/11035	468/489	NR	RR 0.96 (0.84-1.09)	.50	
	Stroke			367/382		RR 0.96 (0.83-1.11)	.60	
	All important CV events			967/972		RR 1.00 (0.91-1.09)	.90	
	Death from CV causes			338/313		RR 1.09 (0.93-1.27)	.28	
				WHS				
Lee, 1999[96]	MI	Beta-carotene	19939/ 19937	42/50		RR 0.84 (0.56-1.27)	.41	
	Stroke			61/43		RR 1.42 (0.96-2.10)	.08	
	All important CV events combined			116/102		RR 1.14 (0.87-1.49)	.34	
	Death from CV causes			14/12		RR 1.17 (0.54-2.53)	.69	
				Linxian General Population Study				
Mark, 1998[66]	Stroke deaths	Retinol + zinc				RR 0.99 (0.84-1.18)	NA	

Evidence Table 3d. Results of studies of the efficacy of vitamin A and/or beta-carotene in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ inactive)	Number of disease events (active/ inactive)	Incidence of disease endpoint (active /inactive)	Unadjusted estimates (95% CI)	P-value	Comments
Eye Disease								
				ATBC				
Teikari, 1997[109]	Nuclear cataract	Beta-carotene	469/428	55/51	NA	OR 0.9 (0.5-1.6)		All ORs adjusted
		Alpha-tocopherol + beta-carotene	475/428	65/51		OR 1.2 (0.7-2.1)		
	Cortical cataract	Beta-carotene	469/428	102/86		OR 1.2 (0.8-1.9)		
		Alpha-tocopherol + beta-carotene	475/428	108/86		OR 1.3 (0.8-1.9)		
	Posterior subcapsular cataract	Beta-carotene	469/428	21/25		OR 0.7 (0.3-1.5)		
		Alpha-tocopherol + beta-carotene	475/428	34/25		OR 1.1 (0.5-2.2)		
Teikari, 1997 [110]	ARM	Beta-carotene vs. no beta-carotene	491/450	141/128	NA	1.04 (0.74-1.47)		
				Linxian General Population Study				
Sperduto, 1993[65]	Nuclear cataracts	Retinol and zinc			NA	OR 0.77 (0.58-1.02)		
	Posterior subcapsular cataracts					OR 0.59 (0.31-1.14)		
	Cortical cataracts					OR 1.08 (0.92-1.27)		

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; NSCP = Nambour Skin Cancer prevention Trial; SCP = Skin Cancer prevention Study; PHS = Physicians Health Study; WHS = Women's Health Study; OR = odds ratio; RR = relative risk; HR = hazard ratio; 95% CI = 95 confidence interval; CV = cardiovascular; cum = cumulative; MI = myocardial infraction; DM = diabetes mellitus; ARM = age-related maculopathy; ANOVA = analysis of variance; py = person-year

Evidence Table 3e. Total mortality in studies of vitamin A and/or beta-carotene used to prevent chronic disease

Author, year	Study supplement	Total number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence per 1000 person-years (active/placebo)	Unadjusted estimates (point estimate and 95% CI)	P-value	Comments
ATBC							
ATBC, 1994[97]	Beta-carotene	14573/14560	NR	NR	RR 1.08 (1.01-1.16)	.02	
SCP							
Greenberg, 1996[85]	Beta-carotene	NR	146/139	NR	HR 1.05 (0.83-1.32)	.71	Adjusted for age, sex, center, quetelet index, smoking.
WHS							
Omenn, 1996b[93]	Beta-carotene	19939/19937	59/55	NR	RR 1.07 (0.74-1.56)	.7	Adjusted for age, randomized aspirin assignment, and randomized vitamin E assignment.
CARET							
Omenn, 1996b[93]	Vitamin A; beta-carotene.	9420/8894	NR	14.45/11.91	RR 1.17 (1.03-1.33)	.02	
Gooodman, 2004[94]	Vitamin A; beta-carotene.	8744/8396	1225/1047	NR	RR 1.08 (0.99-1.17)	.07	
Linxian General Population Study							
Mark, 1998[66]	Retinol + zinc		265/280	14.1/15.0 per 1000 py	RR 0.94, CI (0.79-1.11)		
	Retinol + zinc vs. placebo		296/280	15.8/15.0 per 1000 py	RR 1.05, CI (0.89-1.24)		
	Retinol + zinc				RR 1.00 (.92-1.09)	NA	

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; SCP = Skin Cancer prevention Study; WHS = Womens Health Study; CI = confidence interval; RR = relative risk; AREDS = Age-Related Eye Disease Study; NR = not reported; HR = hazard ratio; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial; CARET = Beta Carotene and Retinol Efficacy Trial.

Evidence Table 3f. Characteristics of the studies on the efficacy of vitamin E (singly or paired) in preventing chronic disease

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
ATBC							
Varis, 1998[90]	RCT; Factorial design	1985-1993	Not 50-69; female; any previous or current cancer; symptomatic CV disease, CHD or major ischemic change in their ECG; atrophic gastritits at baseline or after 3-yr follow-up; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettess/day at entry; anti-coagulant use.	1344	5-8 years (total), 3.9 years (median, Helsinki), 5.8 years (median, outside Helsinki).	Finland	Community
Albanes, 1996[98]			Not 50-69; female; any previous or current cancer; symptomatic CV disease, CHD or major ischemic change in their ECG; atrophic gastritits at baseline or after 3-yr follow-up; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettess/day at entry; anti-coagulant use.	1344	5-8 years (total), 3.9 years (median, Helsinki), 5.8 years (median, outside Helsinki).		
Albanes, 2000[102]			Not 50-69; female; not smoking 5 or more cigarettess/day at entry; cancer; serious illness; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses (>20 mg, >20000 IU, or >6mg); anti-coagulant use.	29133	5-8 years (total)		
ATBC, 1994[97]			Not 50-69; female; any cancer except non-melanoma skin; chronic renal insufficiency; liver cirrhosis; chronic alcoholism; medical condition limiting participation; severe angina; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses.	29133	6.1 years (median)		
Rautalahti, 1999[99]			Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; nonsmokers).	29133	5-8 years (total), 6.1 years (median).		
Heinonen, 1998[101]			Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettess/day at entry	29133	5-8 years (total), 6.1 years (median).		
Rapola, 1996[106]			MI; any history of CHD at baseline and same criteria as general ATBC trial.	22269	4.7 years (median)		

Evidence Table 3f. Characteristics of the studies on the efficacy of vitamin E (singly or paired) in preventing chronic disease (continued)

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
ATBC (continued)							
Lappala,2000[107]			Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; not smoking 5 or more cigarettes/day at entry; anti-coagulant use	28519	6.0 years (median)		
Teikari, 1997[109]			Not 50-69; female; cancer; serious diseases; vitamin E, vitamin A, and/or beta carotene in excess of predefined doses; nonsmokers).	1828	6.6 years (median)		
WHS							
Lee, 2005[87]	RCT, factorial design	1992-2004	All cancers except nonmelanoma skin cancer; all other major chronic disease; vitamin A , vitamin E, beta-carotene, aspirin, or NSAID use greater than once weekly; history of adverse effects from aspirin; use of anticoagulants; use of corticosteroids.	39876	10.1 years (mean)	USA (nation-wide)	Health care professsionals
Lee, 1999[96]	RCT, placebo controlled trial	1993-1999	Male; <45 years; cancer; coronary disease or cerebrovascular disease	39876	4.1 years (median)	USA (nation-wide)	Women health study
PPP							
DeGaetano, 2001[112]	RCT; factorial design	1994-1998	Disease with poor short-term prognosis; history of vascular events or or disease; chronic use of vitamin E, antiinflammatory agents, anticoagulants, aspirin; predictable psychological or logistical difficulties affecting compliance.	4495	3.6 years (mean)	Italy	Clinical
Sacco, 2003[181]				1031	3.7 years (median)		
VECAT							
McNeil, 2004[113]	RCT; placebo controlled trial	1995-2000	MI or type II diabetes in the previous 6 months; prior cataract surgery; advanced cataract in both eyes; glaucoma; major psychiatric illness; uncontrolled hypertension; terminal illness; continued use of vitamin E supplements; vitamin E sensitivity; long-term steroid or anti-coagulation treatment; bilateral intraocular pressure >22; inadequate pupillary dilation (<6.5mm).	1193	4 years (total)	Melbourne, Australia	Clinical and community

Evidence Table 3f. Characteristics of the studies on the efficacy of vitamin E (singly or paired) in preventing chronic disease+ (continued)

Author, year	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
CARET							
Goodman, 2004[94]	RCT (Post-inter-vention follow up)	1985-1996	Asbestos arm: not 45-74 years old in pilot period or 45-69 yrs in vanguard; smoking arm: not 50-69 yrs, male; any history of cancer except non-melanoma skin cancer in past 5 years; NASH; NAFLD; asbestos arm: no chest X-ray evidence of asbestos interstitial lung disease or not greater than or equal to 5 years high risk trade, SGOT or alkaline phosphate greater than 2.5x and 1.5x 95th percentile of normal, respectively, history of liver disease in past 12 months, any beta-carotene supplementation; smoking arm: < 20 pack-year smoking history, current or quit in past 6 years; smoking arm: premenopausal; asbestos arm: < 15 years since first occupational exposure.	17140	5.9 years (total)	Seattle, Washington; Portland, Oregon; San Francisco, CA; Baltimore, MD; New Haven Conn; Irvine, CA.	Clinical and community

ATBC = Alpha-tocopherol Beta-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; WHS = Womens Health Study; PPP = Primary prevention Project; VECAT = Vitamin E and Cataract Randomized Controlled Trial.

Evidence Table 3g. Characteristics of the intervention in the studies of the efficacy of vitamin E in the prevention of chronic disease

Author, year	Control arm	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
ATBC						
Varis, 1998[90]	Placebo	Vitamin E; beta-carotene	dl-alpha-tocopherol; beta-carotene	50 mg/1x/day; 20 mcg/1x/day	NS	5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
Albanes, 1996[98]						5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
Albanes, 2000[102]	Placebo	Vitamin E; beta-carotene	dl-alpha-tocopherol; beta-carotene	50 mg/1x/day; 20 mcg/1x/day	NS	5-8 years
ATBC, 1994[97]						6.1 years median
Rautalahti, 1999[99]						6.1 years
Heinonen, 1998[101]						6.1 years median
Rapola, 1996[106]						4.7 years median
Lappala,2000[107]						6.0 years median
Teikari, 1997[109]						5.1 years; 3.9 years (Helsinki) and 5.4 years (outside)
WHS						
Lee, 2005[87]	Placebo	Vitamin E	alpha-tocopherol	600 IU/every other day	NS	10.1 years
Lee, 1999[96]	Placebo	beta-carotene	NS	50mg/every other day	NS	2.1 years median
PPP						
DeGaetano, 2001[112]	Placebo	Vitamin E	synthetic alpha tocopherol	300 mg/1x/day	NS	3.6 months (mean)
Sacco, 2003[181]		Vitamin E	alpha tocopherol			3.7 years
VECAT						
McNeil, 2004[113]	Placebo	Vitamin E	d-alpha-tocopherol	335 mg/1x/day	NS	4 years
CARET						
Goodman, 2004[94]	Placebo	Vitamin A; beta-carotene		25000 IU/1x/day; 30 mg/1x/day	NS	10 years; Until endpoint (NS)

ATBC = Alpha-tocopherol Beta-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; WHS = Womens Health Study; PPP = Primary prevention Project; VECAT = Vitamin E and Cataract Randomized Controlled Trial; NS = Not specified; mg = milligram; mcg = microgram; IU = international unit; µg = microgram

Evidence Table 3h. Characteristics of participants in studies of the efficacies of Vitamin E (singly or in nutrient pairs)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
ATBC						
Varis, 1998[90]	64.8	0 (0); ethnicity NR	Current: 1828 (100)	Mean intake (grams/day): 12.5.	25.5	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Albanes, 1996[98]	Median: 56.9	0 (0); ethnicity NR	Current: 22269 (100)	NR	26.0	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Albanes, 2000[102]	57.2	0 (0); ethnicity NR	Current: 29133 (100)	Mean intake (grams/day): 11.0	26.0	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
ATBC, 1994[97]	64.2 (7.5)	534 (51.8); ethnicity NR	Former: 257 (25.2); current: 168 (16.5).	NR	29.0	NR
Rautalahti, 1999[99]	53.0 (9.5); range: 40-84.	0 (0); ethnicity NR	Never: 11036 (50); former: 8608 (39); current 2428 (11.0).	Rare: 3222 (14.6%); monthly: 2428 (11.0); weekly: (49.5); daily: 5518 (25.0).	24.9	Current multivitamin use: 4304 (19.5).
Heinonen, 1998[101]	57.2	0 (0); ethnicity NR	Current: 29133 (100)	Mean intake (grams/day): 11.0	26.0	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Rapola, 1996[106]	Median: 57; range: 50-69.	0 (0); ethnicity NR	Current: 29133 (100)	Mean intake (grams/day): 11.0	26.0	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Lappala,2000[107]	57.7	0 (0); ethnicity NR	Current: 28519 (100)	Mean intake (grams/day): 18.1	26.3	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Teikari, 1997[109]	Median: 57; range: 50-69.	0 (0); ethnicity NR	Current: 29133 (100)	Mean intake (grams/day): 11.0.	26.0	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
WHS						
Lee, 2005[87]	58.8	0 (0); ethnicity NR	Current: 1344 (100)	Mean intake (grams/day): 8.9.	NR	Vitamin E: 0 (0); vitamin A: 0 (0); beta-carotene: 0 (0).
Lee, 1999[96]	NA	39876 (100); ethnicity NR	NA	NA	NA	NA

Evidence Table 3h. Characteristics of participants in studies of the efficacies of Vitamin E (singly or in nutrient pairs) (continued)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
PPP						
DeGaetano, 2001[112]	Median: 48	(50); ethnicity NR	Current: (36)	Current: (37.0)	NR	NR
Sacco, 2003[181]	64.4 (7.6)	1912 (42); ethnicity NR	Former: 1080 (24); current: 667 (15).	NR	27.6	NR
VECAT						
McNeil, 2004[113]	65.7	670 (56); ethnicity NR	Current: 24 (2); ever: 577(48)	NA	>=27: 468 (39)	Vitamin E: 289 (24)
CARET						
Goodman, 2004[94]	62	6007 (35); Caucasian, 15988 (93.3)	Never: 116 (0.7); former: 8988 (52.4); current: 8036 (46.9).	NR	NR	NR

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; WHS = Womens Health Study; PPP = Primary prevention Project; VECAT = Vitamin E and Cataract Randomized Controlled Trial; BMI = Body Mass Index; NR = not reported

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease.

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ non-active)	Number of disease events (active/ non-active)	Incidence of disease endpoint (active/ non-active)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer								
				ATBC				
Varis, 1998[90]	Gastric dysplasia, carcinoma, or carcinoid	Alpha-tocopherol	321/333	13/18	NR	NR		
		Alpha-tocopherol + beta-carotene	361/333	19/18				
		Alpha-tocopherol vs. no alpha-tocopherol	682/662	32/31		RR 1.00 (0.60-1.66)		Adjusted RR 0.98 (0.57-1.69)
Albanes, 1996[98]	Lung cancer	Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	444/450	53.2/54.5 per 10000 person years	RR 0.99 (0.87-1.13)	.86	No effect of α-tocopherol in subgroups defined by age, cigarettes smoking, years of cigarette smoking, cigarette smoke inhalation, asbestos exposure, dietary intake of vitamin E, β-carotene, vitamin C, retinol, or alcohol as ethanol, and serum levels of α-tocopherol, β-carotene, and retinol
Albanes, 2000[102]	Colorectal cancer	Alpha-tocopherol vs. placebo	7286/7287	29/37	NR	RR 0.79 (0.48-1.28)		
		Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	59/76	NR	RR 0.78 (0.55-1.09)	.15	P-value from log-rank test
		Alpha-tocopherol + beta-carotene	7278/7287	30/37	NR	RR 0.82 (0.50-1.31)		
	Colorectal cancer mortality	Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	22/24	NR	RR 0.92 (0.51-1.64)		
ATBC, 1994[97]	Lung cancer	Alpha-tocopherol	14564/ 14564	433/443	51.3/52.4 per 10000 person year	RR 0.98 (0.86-1.12)	.8	
	Lung cancer mortality	Alpha-tocopherol	14564/ 14564	285/279	33.6/32.6 per 10000 person year	RR 1.03		Confidence interval NR

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/non-active)	Number of disease events (active/non-active)	Incidence of disease endpoint (active/ non-active)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer (continued)								
ATBC (continued)								
Rautalahti, 1999[99]	Pancreatic cancer	Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	51/38	0.60/0.45 per 1000 person year	RR 1.34 (0.88-2.05)		
	Carcinoma of the pancreas	Alpha-tocopherol	7286/7287	25/26	NR	RR 0.94 (0.56-1.67)		
	Pancreatic cancer mortality	Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	49/34	NR	RR 1.11 (0.72-1.72)		
Malila, 1999 [100]	Colorectal Adnomas	Alpha-tocopherol vs. no alpha-tocopherol	7768/7770	81/56	NR	RR 1.66 (1.19-2.32)	.003	Results did not change after excluding 15 cases with a prior history of polyps (RR 1.63)
Heinonen, 1998[101]	Prostate cancer	Alpha-tocopherol	7286/7287	43/67	NR	RR 0.64 (0.44-0.94)		
		Alpha-tocopherol + beta-carotene	7278/7287	56/67	NR	RR 0.84 (0.59-1.20)		
		Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	99/147	NR	RR 0.68 (0.53-0.88)	.002	
	Prostate Cancer mortality	Alpha-tocopherol vs. no alpha-tocopherol	14564/ 14569	23/39	NR	RR 0.59 (0.35-0.99)		
WHS								
Lee, 2005[87]	Total invasive cancer	Vitamin E	19937/ 19939	1437/1428	NR	RR 1.01 (0.94-1.08)	.87	
	Breat cancer			616/614		RR 1.00 (0.90-1.12)	.95	
	Lung cancer			107/98		RR 1.09 (0.83-1.44)	.52	
	Colon cancer			107/107		RR 1.00 (0.77-1.31)	.99	
	Cancer death			308/275		RR 1.12 (0.95-1.32)	.17	

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ non-active)	Number of disease events (active/ non-active)	Incidence of disease endpoint (active/ non-active)	Unadjusted estimates (95% CI)	P-value	Comment
Cardiovascular Disease								
				ATBC				
Rapola, 1996[106]	Angina	Alpha-tocopherol vs. no alpha-tocopherol	11118/ 11351	948/1035	19.6/21.5 per 1000 py	RR 0.91 (0.83-0.99)		
		Alpha-tocopherol alone	5570/5549	476/487	19.7/20.2 per 1000 py	RR 0.97 (0.85-1.10)		
		Alpha-tocopherol + beta-carotene	5548/5549	472/487	19.6/20.2 per 1000 py	RR 0.96 (0.85-1.09)		
Lappala, 2000 [107]	Intracerebral hemorrhage	Alpha-tocopherol vs.no alpha-tocopherol	14238/ 14281	57/55	7.0/6.7 per 10000 py	RR 1.04 (0.72-1.51)	.84	
	Death from Intracerebral hemorrhage			31/19	3.8/2.3 per 10000 py	RR 1.64 (0.93-2.90)	.09	
	Subarachoid hemorrhage			51/34	6.2/4.1 per 10000 py	RR 1.50 (0.97-2.32)	.07	
	Death from Subarachoid hemorrhage			28/10	3.4/2.1 per 10000 py	RR 2.81 (1.37-5.79)	.005	
	Cerebral infarction			373/434	45.5/52.8 per 10000 py	RR 0.86 (0.75-0.99)	.03	
	Death from Cerebral infarction			29/36	3.5/4.4 per 10000 py	RR 0.81 (0.49-1.32)	.39	
	All strokes			509/548	62.1/66.6 per 10000 py	RR 0.93 (0.83-1.05)	0.25	
	Death from all strokes			90/70	11.0/8.5 per 10000 py	RR 1.29 (0.94-1.76)	0.11	

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ non-active)	Number of disease events (active/ non-active)	Incidence of disease endpoint (active/ non-active)	Unadjusted estimates (95% CI)	P-value	Comments
Cardiovascular Disease (continued)								
				WHS				
Lee, 2005[87]	Combined first major CV event	Vitamin E	19937/ 19939	482/517	NR	RR 0.93 (0.82-1.05)	0.26	
	MI			196/195		RR 1.01 (0.82-1.23)	0.96	
	Nonfatal MI			184/181		RR 1.02 (0.83-1.25)	0.87	
	Fatal MI			12.0/14		RR 0.86 (0.40-1.85)	0.70	
	Stroke			241/246		RR 0.98 (0.82-1.17)	0.82	
	Nonfatal stroke			220/222		RR 0.99 (0.82-1.19)	0.93	
	Fatal stroke			21/24		RR 0.88 (0.49-1.57)	0.66	
	Ischemic stroke			194/197		RR 0.99 (0.81-1.20)	0.88	
	Hemorrhagic stroke			44/48		RR 0.92 (0.61-1.38)	0.68	
	Cardiovascular death			106/140		RR 0.76 (0.59-0.98)	0.03	
				PPP				
DeGaetano, 2001[112]	CV deaths, nonfatal MI and non-fatal stroke	Vitamin E		56/53		RR 1.07 (0.74-1.56)		
	Total CV events/ diseases			158/170		RR 0.94 (0.77-1.16)		
	CV Deaths			22/26		RR 0.86 (0.49-1.52)		
	Non-CV deaths			50/42		RR 1.21 (0.80-1.81)		
	All MI			22/25		RR 0.89 (0.52-1.58)		
	Non-fatal MI			19/18		RR 1.01 (0.56-2.03)		
	All Stroke			22/18		RR1.24 (0.66-2.31)		
	Nonfatal Stroke			20/13		RR 1.56 (0.77-3.13)		
	TIA			33/35		RR 0.96 (0.60-1.53)		
	PAD			16/30		RR 0.54 (0.30-0.99)	.043	
	Revascularization procedures			27/22		RR 1.25 (0.71-2.18)		
	Angina pectoris			66/55		RR 1.22 (0.86-1.73)		

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/non-active)	Number of disease events (active/non-active)	Incidence of disease endpoint (active/non-active)	Unadjusted estimates (95% CI)	P-value	Comments
Cardiovascular Disease (continued)								
Sacco, 2003[182]	CV deaths, nonfatal MI and non-fatal stroke	Vitamin E vs. placebo In persons with type 2 diabetes	509/522	22/20		RR 1.13 (0.62-2.04)		No significant effects in persons without diabetes at baseline except a reduction in the risk of peripheral artery disease (RR 0.37, 95% CI 0.14-0.96)
	Total CV events			51/61		RR 0.86 (0.60-1.22)		
	CV deaths			10/8		RR 1.28 (0.51-3.22)		
	Non CV deaths			13/14		RR 0.95 (0.45-2.01)		
	All MI			7/8		RR 0.90 (0.33-2.46)		
	All stroke			8/11		RR 0.75 (0.30-1.83)		
	Angina pectoris			14/15		RR 0.93 (0.45-1.90)		
	TIA			6/11		RR 0.54 (0.21-1.43)		
	PAD			10/14		RR 0.71 (0.32-1.58)		
	Revascularisation procedure			9/9		RR 1.00 (0.40-2.48)		

Evidence Table 3i. Results of studies of the efficacy of vitamin E in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/non-active)	Number of disease events (active/ non-active)	Incidence of disease endpoint (active/non-active)	Unadjusted estimates (95% CI)	P-value	Comments
Eye Disease								
				VECAT				
McNeil, 2004[113]	Cortical cataract	Vitamin E	442/442	19/22	4.5%/5%	0.9(0.5-1.6)	0.75	Incidence of cataract
	Nuclear cataract		480/486	62/59	12.9%/12.1%	1.1(0.8-1.5)	0.77	
	Posterior subcapsular cataract		479/486	8/17	1.7%/3.5%	0.5(0.2-1.1)	0.08	
	Any cataract		409/430	70/72	17.1%/16.7%	1.0(0.8-1.4)	0.92	
	Cortical cataract		156/147	26/27	16.7%/18.4%	0.9(0.5-1.6)	0.76	Progression of lens opacities
	Nuclear cataract		501/503	57/60	11.4%/11.9%	0.9(0.7-1.3)	0.84	
	Posterior subcapsular cataract		18/18	5/2	28%/10%	2.5(0.6-11.2)	0.20	
	Any cataract		504/508	83/85	16.5%/16.7%	1.0(0.7-1.3)	0.93	
				ATBC				
Teikari, 1997[109]	Nuclear cataract	Alpha-tocopherol	456/428	51/51	NA	OR 0.8 (0.4-1.4)		Adjusted OR
		Alpha-tocopherol + beta-carotene	475/428	65/51		OR 1.2 (0.7-2.1)		
	Cortical cataract	Alpha-tocopherol	456/428	90/86		OR 0.9 (0.6-1.4)		
		Alpha-tocopherol + beta-carotene	475/428	108/86		OR 1.3 (0.8-1.9)		
	Posterior subcapsular cataract	Alpha-tocopherol	456/428	25/25		OR 0.9 (0.4-1.8)		
		Alpha-tocopherol + beta-carotene	475/428	34/25		OR 1.1 (0.5-2.2)		
Teikari, 1998 [110]	Age-related maculopathy	Alpha-tocopherol vs. no alpha-tocopherol	492/447	148/121		OR 1.13 (0.81-1.59)		

ATBC = Alpha-tocopherol Bata-carotene Prevention Study; CARET = Beta-carotene and Retinol Efficacy Trial; WHS = Women's Health Study; PPP = Primary prevention Project; VECAT = Vitamin E and Cataract Randomized Controlled Trial; OR = odds ratio; 95% CI = 95 confidence interval; py = person years; CV = cardiovascular; cum = cumulative; PSA = prostate-specific antigen; MI = myocardial infraction; ANOVA = analysis of variance; TIA = Transient ischemic attacks; PAD = peripheral artery disease

Evidence Table 3j. Total mortality in studies of vitamin E used to prevent chronic disease

Author, year	Study supplement	Total number in study (active/ placebo)	Number of disease events (active/ placebo)	Person years (active/ placebo)	Incidence per 1000 person-years (active/placebo)	Unadjusted estimates (point estimate and 95% CI)	P-value
ATBC, 1994[97]	Alpha-tocopherol vs. placebo	14564/14564	NR	NR	NR	RR 1.02 (0.95-1.09)	0.6
Lee, 2005[87]	Vitamin E	19937/19939	636/615	NR	NR	1.04 (0.93-1.16)	0.53
DeGaetano, 2001[112]	Vitamin E	2231/2264	72/68	NR	NR	RR 1.07 (0.77-1.49)	NR
Sacco, 2003[181]	Vitamin E	509/522	23/22	NR	NR	RR 1.07 (0.61-1.90)	NR

CI = confidence interval; RR = relative risk; NR = not reported; WHS = Women's Health Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial; PPP = Primary Prevention Project.

Evidence Table 3k. Characteristics of the studies on the efficacy of selenium, B vitamins, or other single nutrients (singly or paired) in preventing chronic disease

Author, year	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
NCP								
Calrk, 1996[133] Calrk, 1998[134]	Selenium	RCT; Placebo controlled	1983-1993	History of 2 or more BCC or 1 SCC of the skin, with 1 of these carcinomas occurring within the prior year; liver or kidney disease history; internal malignancies treated within the previous 5 years; life expectancy not greater than 5 years; female; no non-melanoma skin cancer; life expectancy not greater than 5 years; reported internal malignancies treated within the previous 5 years	974-1312	10 years (total), 6.4 years (mean).	Eastern USA	Clinical
Reid, 2002[135]				Not having valid baseline plasma selenium value collected on day of randomization +/-4 days; no noncutaneous malignancy within previous 5 years.	1250	13 years (total), 7.9 years (mean)	Eastern USA	Clinical
Duffield-Lillico, 2002[136]				History of 2 or more BCC or 1 SCC of the skin, with 1 of these carcinomas occurring within the prior year; liver or kidney disease history; internal malignancies treated within the previous 5 years; life expectancy not greater than 5 years; Not having valid baseline plasma selenium value collected on day of randomization +/-4 days; no noncutaneous malignancy within previous 5 years; not NPC participant; female; Initial blood not drawn within first 4 days of randomization; history of prostate cancer	927-1250	13 years (total), selenium 7.6 years (mean), placebo 7.3 years (mean), 7.4 years (mean).	Eastern USA	Clinical

Evidence Table 3k. Characteristics of the studies on the efficacy of selenium, B vitamins, or other single nutrients (singly or paired) in preventing chronic disease (continued)

Author, year	Nutrient(s)	Study design	Study period	Exclusion criteria	Total sample size enrolled	Mean/ median follow-up time	Study site	Recruitment setting
Linxian General Populatiton Study								
Mark, 1998[66]	Vitamin A + zinc; riboflavin + niacin; vitamin C + molyb-denum	RCT; Factorial design	1986-1991	Not 40-46 years old; history of cancer; history of debilitating diseases.	29584	5 years (total)	Linxian province, China	Community
Sperduto, 1993[64]				Not 40-69; stomach or esophageal; debilitating disease; does not live in one of 4 communes in Linxian	29584	5.25 years (total)		
Other Study								
Yu, 1991[139]				Not in Qidong county; Not HBVsAg carrier; Abnormal liver function; not a member of family with hereditary predisposition to cancer	226-2474	2-4 years (total)	Qidong County, China	Community

NPC = Nutritional Prevention of Cancer Study Group; ARED = Age-related Eye Disease Study Group.

Evidence Table 3l. Characteristics of the intervention in the studies of the efficacy of other nutrients in the prevention of chronic disease

Author, year	Contorl Arm	Interventnion	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
NPC						
Clark, 1996[133]	Placebo	Selenium	Selenium yeast	NS	NS	4.3 years
Clark, 1998[134]	Placebo	Selenium	Selenium yeast	NS	NS	4.4 years
Reid, 2002[135]	Placebo	Selenium	Selenium yeast	200 mcg/1x/day	NS	7.9 years
					NS	
Duffield-Lillico, 2002[136]	Placebo		Yeast	NS	NS	NS
		Selenium	Selenium yeast	200 mcg/1x/day	NS	NS
Duffield-Lillico, 2003[137]	Placebo		Yeast	NS	NS	NS
		Selenium	Selenium yeast	200 mcg/1x/day	NS	NS
Linxian General Population Study						
Mark, 1998[66]	Placebo	Placebo 1			NS	5 years
		Vitamin A	Retinol palmitate	10000 IU/NS		
		Zinc	Zinc oxide	45 mg/NS		
		Vitamin B2	Riboflavin	5.2 mg/NS		
		Niacin	Niacin	40 mg/NS		
		Vitamin C	Ascorbic acid	180 mg/NS		
		Molybdenum	Yeast complex	30 mg/NS		
Sperduto, 1993[64]	Placebo 1					
		Vitamin A	Retinol palmitate	5000 IU/daily	NS	5.25 years
		Zinc	Zinc oxide	22.5 mg/daily		
		Vitamin B2	Riboflavin	3.2 mg/1x/day		
		Niacin	Niacin	40 mg/1x/day		
		Vitamin C	Ascorbic acid	120 mg/1x/day		
		Molybdenum	Molybendum	30 mcg/1x/day		

Evidence Table 3l. Characteristics of the intervention in the studies of the efficacy of other nutrients in the prevention of chronic disease (continued)

Author, year	Contorl Arm	Interventnion	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
ARED						
AREDS, 2001b[75]	Placebo 1			NS	NS	6.3 years
		Vitamin E	Dl-alpha-tocopherol acetate	200 IU/2x/day (2 tablets in the morning, 2 in the evening)	With meals	
		Vitamin C	Ascorbic acid	250 mg/2x/day (2 tablets in the morning, 2 in the evening)		
		Vitamin A	Beta-carotene	7.5 mg/2x/day (2 tablets in the morning, 2 in the evening)		
		Zinc	Zinc oxide	40 mg/2x/day (2 tablets in the morning, 2 n the evening)		
		Selenium	Selenium yeast	200 mcg/1x/day		4.5 years
Other Study						
Yu, 1991[139]	Placebo 1		Trial 2 control group (plain yeast tablet)	NS	NS	4 years
	Placebo 2		Trial 3 control group (placebo, undefined)	NS	NS	2 years
		Selenium	Selenium yeast	200 mcg/1x/day	NS	2-4 years

NPC = Nutritional Prevention of Cancer Study Group; ARED = Age-related Eye Disease Study Group; NS = Not specified; mg = milligram; mcg = microgram; IU = international unit.

Evidence Table 3m. Characteristics of participants in studies of the efficacies of selenium, B vitamins or other nutrients (singly or in nutrient pairs)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
NPC						
Clark, 1996[133]	63.2; range: 18-80.	332 (25.3); ethnicity, NR	Never: 428 (32.6); former: 514 (39.2); current: 369 (28.2).	NR	NR	NR
Clark, 1998[134]	63.8	0 (0); ethnicity, NR	NR	NR	NR	
Reid, 2002[135]	63.2 (10.0)	316 (25.0); ethnicity, NR	Never: 398 (31.8); former: 497 (39.8); current: 355 (28.4).	Mean drinks/week: 12.9.	NR	
Duffield-Lillico, 2002[136]	63.2; range: 18-80. selenium: 63.4 (10.2); placebo 63 (9.9)	332 (25.3); ethnicity, NR	Never: 428 (32.6); former: 514 (39.2); current: 369 (28.2).	NR	25.5	
Duffield-Lillico, 2003[137]	64.4; selenium: 64.9 (8.8); placebo 63.7 (9.4)	0 (0); ethnicity, NR	Never: 213 (23); former: 431 (46.5); current: 283 (30.5).	NR	25.9	
Linxian General Population Study						
Mark, 1998[66]	Median (female) 51; median (male): 53; range: 44-60.	16271 (55); ethnicity, NR	Current (female): 3254 (20); current (male): 8929 (67).	Current (female): (10); current (male): (40).	Median BMI (female): 21.9; median BMI (male): 21.6.	NR
Sperduto, 1993[64]	<50: 12425 (42%); 50-59: 10354 (35%); ≥60: 6804 (23%).		Never: 20709 (70); ever smoked for >6 months: 8875 (30).	Never: 22780 (77); any use in past 12 months: 6804 (23).	NR	

Evidence Table 3m. Characteristics of participants in studies of the efficacies of selenium, B vitamins or other nutrients (singly or in nutrient pairs) (continued)

Author, year	Mean age (SD), and/or range	Women, n (%); Ethnicity, n (%)	Smokers, n (%)	Alcohol consumption, n (%)	Mean BMI in kg/m2	Prior supplement use, type (%)
ARED						
AREDS, 2001b[75]	Median: 69	2021 (56); Caucasian, 3483 (96); African-American, 153 (3)	Former: 1751 (49); current: 298 (8.0).	NR	NR	Multivitamin or supplement containing a study compound: 2047 (57); Centrum: 2418 (67).
Other Study						
Yu, 1991[139]	Range: 21-63; Range: 15-75	NR; Asian (100)	NR	NR	NR	

NPC = Nutritional Prevention of Cancer Study Group; ARED = Age-related Eye Disease Study Group; BMI = Body Mass Index; NR = not reported.

Evidence Table 3n. Results of studies of the efficacy of other single or paired nutrients in preventing chronic disease.

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer								
NPC								
Clark, 1996[133]	Lung cancer	Selenium	653/659	17/31		HR 0.56 (0.31-1.01)	.05	Lung cancer mortality
	Prostate cancer			13/35		HR 0.35 (0.18-.65)	.001	
	Colorectal cancer			8/19		HR 0.39 (0.17-0.90)	.03	
	Head and neck			6/8		HR 0.77 (0.27-2.24)	.64	
	Bladder			8/6		HR 1.27 (0.44-3.67)	.66	
	Esophageal			2/6		HR 0.30 (0.06-1.49)	.14	
	Breast			9/3		HR 2.95 (0.80-10.9)	.11	
	Other specific carcinomas			5/9		HR 0.54 (0.18-1.62)	.27	
	Total carcinomas			59/104		HR 0.54 (0.39-0.75)	<.001	
	Melanomas			8/8		HR 0.92 (0.34-2.45)	.87	
	Leukemia/ lymphomas			8/5		HR 1.50 (0.49-4.60)	.48	
	Other specific non-carcinomas			3/3		HR 0.99 (0.20-4.94)	.99	
	Total non-carcinomas			19/16		HR 1.16 (0.60-2.27)	.65	
	Total cancer			77/119		HR 0.61 (0.46-0.82)	<.001	
	Total cancer mortality			29/57		HR 0.48 (0.31-0.76)	.001	
	Lung cancer mortality			12/25		HR 0.47 (0.23-0.93)	.03	
	Other carcinoma mortality			15/25		HR 0.56 (0.30-1.07)	.08	
Clark, 1998[134]	Prostate cancer	Selenium	479/495	13/35		RR 0.37	.002	

Evidence Table 3n. Results of studies of the efficacy of other single or paired nutrients in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer (continued)								
NPC (continued)								
Reid, 2002[135]	All lung cancer	Selenium	621/629	25/35	0.063/0.085	RR 0.70 (0.40-1.21); HR 0.74 (0.44-1.24)	.18 for RR; .26 for HR	Earlier publication from this trial (1983-1993 only showed RR 0.54 (0.30-0.98); this study adds 3 years of follow-up.
Duffield-Lillico, 2003[136]	Prostate Cancer	Selenium	621/629	22/42		RR 0.51 (0.29-0.87)	.009	
	Lung Cancer			25/35		RR 0.7 (0.4-1.21)	.18	
	Colorectal Cancer			9/19		RR 0.46 (0.19-1.08)	.055	
	Cancer mortality			40/66		RR 0.59 (0.39-0.89)	.008	
	Head and neck cancer			9/7		RR1.27 (0.42-4.01)	.65	
	Bladder cancer			10/8		RR 1.24 (0.44-3.61)	.66	
	Esophageal cancer			2/5		RR 0.39 (0.04-2.41)	.28	
	Breast			11/6		RR 1.82 (0.62-6.01)	.24	
	Other specific carcinomas			6/9		RR 0.66 (0.19-2.07)	.44	
	Melanomas			11/9		RR 1.21 (0.46-3.3)	.68	
	Leukemia/ lymphomas			40/66		RR 1.32 (0.4-4.61)	.62	
Duffield-Lillico, 2002[137]	Prostate cancer	Seleniu	457/470	22/42		RR 0.51 (0.29-0.88)	.009	

Evidence Table 3n. Results of studies of the efficacy of other single or paired nutrients in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value	Comments
Cancer (continued)								
Linxian General Population Study								
Blot, 1993[67]	Gastric cancer incidence	Retinol + zinc	539 total			RR 0.96 (0.81-1.14)		
		Riboflavin + niacin				RR 1.04 (0.88-1.23)		
		Vitamin C + molybdenum				RR 1.10 (0.92-1.30)		
	Esophageal cancer incidence	Retinol + zinc	640 total			RR 1.07 (0.92-1.25)		
		Riboflavin + niacin				RR 0.86 (0.74-1.01)		
		Vitamin C + molybdenum				RR 1.06 (0.91-1.24)		
	Stomach cancer death	Retinol + zinc	331 total			RR 1.03 (0.83-1.28)		
		Riboflavin + niacin				RR 1.00 (0.81-1.24)		
		Vitamin C + molybdenum				RR 1.09 (0.88-1.36)		
	Stomach cancer incidence (noncardia)	Retinol + zinc	331 total			RR .73 (0.49-1.08)		
		Riboflavin + niacin				RR .92 (0.63-1.35)		
		Vitamin C + molybdenum				RR 1.21 (0.82-1.78)		
Other studies								
Yu, 1991[139]	Primary liver cancer	Selenium	1444/1030	10/16	0.69% vs 1.26%		<.05	In Hep B carriers,

Evidence Table 3n. Results of studies of the efficacy of other single or paired nutrients in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value	Comments
Cardiovascular Disease								
NPC								
Clark, 1996[133]	CVD and cerebro-vascular diseases mortality			47/46		HR 0.96 (0.64-1.44)	.83	
	All other causes mortality			32/26		HR 1.16 (0.69-1.95)	.57	
	Respiratory disease mortality			14/11		HR 1.26 (0.57-2.77)	.57	
	All cause mortality			108/129		HR 0.79 (0.61-1.02)	.07	
Linxian General Population Study								
Mark, 1998[66]	Stroke deaths	Retinol + zinc + riboflavin + niacin			NA	RR .85 (.61-1.18)	NA	
		Retinol + zinc + vitamin C + molybdenum				RR .91 (.66-1.27)		
		Riboflavin + niacin, vitamin C + molybdenum				RR .78 (.55-1.09)		
		Retinol + zinc				RR .99 (.84-1.18)		
		Riboflavin + niacin				RR .94 (.79-1.11)		
		Vitamin C + molybdenum				RR 1.04 (.88-1.24)		

Evidence Table 3n. Results of studies of the efficacy of other single or paired nutrients in preventing chronic disease. (continued)

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value	Comments
Eye Disease								
Linxian Cataract Study								
Sperduto, 1993[64]	Cortical cataracts	Retinol + zinc				OR 1.08 (0.92-1.27)		
		Riboflavin + niacin				OR 1.08 (0.92-1.27)		
		Vitamin C + molybdenum				OR .92 (0.79-1.09)		

NPC = Nutritional Prevention of Cancer Study Group; ARED = Age-related Eye Disease Study Group; OR = odds ratio; RR = relative risk; HR = hazard ratio; 95% CI = 95 confidence interval; MVM = cum = cumulative; ANOVA = analysis of variance; py = person-years; AMD = age-related macular degeneration

Evidence Table 3o. Total mortality in studies of the efficacy of other single or paired nutrients in preventing chronic disease

Author, year	Disease endpoint	Study supplement	Total Number in study (active/ placebo)	Number of disease events (active/ placebo)	Incidence of disease endpoint (arm1/arm2)	Unadjusted estimates (95% CI)	P-value
Clark, 1996[133]	All cause mortality			108/129		HR 0.79 (0.61-1.02)	.07
Mark, 1998[66]	Total mortality	Retinol + zinc			NA	RR 1.00 (.92-1.09)	NA
		Riboflavin + niacin				RR .98 (.90-1.06)	
		Vitamin C + molybdenum				RR 1.01 (.92-1.10)	

NPC = Nutritional Prevention of Cancer Study Group

Evidence Table 3p. Systematic reviews on calcium and/or vitamin D: supplement information.

Author, Year	Study aim	Trials included, n	Publication yrs (range of dates)	Supplements/ other therapies in treated groups	Chemical forms	Range of daily doses	Types of comparison groups
Prevention of Bone Loss							
Shea, 2004[47]	Assess effects of calcium supplementation on bone loss and postmenopausal women.	10	1978-1998	Calcium Vitamin D: - In 2 trials, (n=140), vitamin D given to both treatment & control groups. Exercise: In 2 trials (n=121), exercise prescribed for both treatment & control groups	Calcium carbonate, Calcium gluconate ± lactate Calcium citrate ± malate, Calcium (salt form not stated. Vitamin D forms not stated.	Ca carbonate 500-2000 mg Ca gluconate ± lact 1000 mg Ca citrate ± malate 500-1000mg Ca(no salt) 500-1000mg Vitamin D 300,000 IU at start of 1.5 yr study (=~550 IU/day) Vitamin D 400 IU	Placebo Vitamin D - given simultaneously to both treatment & control groups in equal dose Exercise -
Papadimitri-opoulos, 2004[49]	vitamin D in preventing osteoporosis in postmenopausal women with bone density in the normal or near-normal range.	25 total trials -10 of which involved vitamin D doses ≤ 2000 IU/day ("standard vit D"). Of these 10 trials, 4 measured BMD fracture reduction ± BMD changes, and 6 monitored BMD changes only.	1980-1999	Vitamin D ± calcium	Cholecalciferol (vitamin D_3); Calcium salts not described	Cholecalciferol 300-2000 IU; Calcium 377 mg-1000 mg;	Placebo; Calcium
Mackerras, 1997[52]	Separate analyses of first- and second-year effects of calcium of bone mineral density in postmenopausal women	8	1987-1995	Calcium; Milk Powder	calcium carbonate, calcium citrate malate, lactogluconate, lactate-gluconate, combination, milk powder	Ca carbonate 500-2000 mg; Ca lactate gluconate 1000-2000 mg; Ca citrate maleate 500 mg Ca in milk powder 1000 mg	Placebo; Placebo + exercise

Evidence Table 3p. Systematic reviews on calcium and/or vitamin D: supplement information. (continued)

Author, Year	Study aim	Trials included, n	Publication yrs (range of dates)	Supplements/ other therapies in treated groups	Chemical forms	Range of daily doses	Types of comparison groups
Prevention of Bone Loss & Fractures							
Shea, 2004[47]	Assess effects of calcium supplementation on bone loss and fractures in postmenopausal women.	5	1978-1998	Calcium Vitamin D	Calcium carbonate, Calcium gluconate Calcium citrate Calcium (salt form not stated); Vitamin D formulations not described.	Ca carb 1000-2000 mg Ca gluc 1000 mg Calcium 1000 mg Calcium citrate 1600 mg	Placebo
Papadimitri-opoulos, 2004[49]	vitamin D in preventing osteoporosis in postmenopausal women	25 total trials, 10 eligible for our review. 4 of these 10 evaluiated fracture reduction.	1980-1999	Vitamin D ± calcium	Cholecalciferol (vitamin D_3); Neither calcium nor phosphate salt forms described	Cholecalciferol 400 - 800 IU Calcium 300-1200 mg; Phosphate 600 mg	Placebo; Calcium
Avenell, 2005[143]	Vitamin D for preventing fractures associated with involutional and post-menopausal osteoporosis	Of total 38 trials, 11 eligible for our review (involved rx with vitamin D in doses <2000 IU (upper limit advised by the Food & Nutrition Board.	1983-2005	Vitamin D ± calcium	Cholecalciferol (vitamin D_3); Ca carbonate; Tricalcium phosphate; Calcium lactate; Calcium	Cholecalciferol 400-1000 IU; Calcium salts to provide 500-1200 mg;	Placebo (single & double); Calcium

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Bone Loss													
Shea, 2004[47]	Inclusison: RCT; PMP women >45 yrs old with amenorrhea ≥ 6 months; Treatment in which intervention was calcium supplementation or usual dietary calcium intake; Vit D supplementation ≤400 IU/day & equivalent in Rx & control grps. Exclusion: Males Calcium <400mg/d; Vit D rx >400 IU/d and/or that differed between rx & pbo groups; Trial duration <1 yr; BMD measured only at ultra-distal forearm site; BMD measurement by technique other than SPA, DPA, or DXA; Failure of contacted authors of eligible studies to provide re-quested data; A priori selected out-comes not included	745	497	629	69	47	71	52	0	374	46-72.1 (0.6)	100	It was explained in paper that baseline BMD for groups was not pooled because of heterogen eity in technique s used to measure BMD. Rather calc-ulations of BMD changes were based on % change from baseline

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Bone Loss (continued)													
Papadimitri-opoulos, 2004[49]	Inclusion: PMP women >45 yrs old with amenorrhea ≥ 6 mos; included studies with interventions of vitamin D ± calcium and control grp intakes of vitamin D ≤100 IU/day ± calcum. Exclusion: Males; Women < 45 y/o and/or amenorrheic < 6 mos; vitamin D daily intake ≤ 400 IU/d; follow-up < 1 year;BMD (g/cm or g/cm2) not measured by single-photon absorptiometry, dual-photon absroptiometry, or dual x-ray absroptiometry in at least 1 of several designated sites (femoral neck, total hip, trochanter, lumbar spine, total body ,or combined forearm); reporting total number of fractures for a group as opposed to reporting fracture results on individual patients; studies that compared different types or doses of vitamin D	445	511	373	387	NA	578	NA	0	275	49.9-71.5	100	Calcu-lations were made for each bone density site (rather than pooling results); measurem ents of % change in BMD from baseline were used to calculate weighted mean dif-ferences in BMD between Rx & control groups

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Bone Loss (continued)													
Mackerras, 1997[52]	Inclusion: PMP women; any indication that study was randomized. Exclusion: report not in English; less than 2 years of follow-up; no group received calcium supplement or dairy products; no randomized control group; no intention-to-treat analysis reported and/or reconstructable from the data given; a crossover study using subjects as their own controls; obviously nonrandomized studies; combination therapy arms involving calcium and another drug with known strong effects on bone; not postmenopausal women	999	387	612	34 Aloia study)	75	36	35	352	352	51-66	100	

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Fractures													
Shea, 2004[47]	Inclusion: PMP women >45 years old with amenorrhea ≥ 6 months; Vit D supplementation ≤400 IU & same in Rx & control groups Exclusion: Males; calcium <400mg/d; vit D rx >400 IU/d and/or that differed between rx & pbo groups; trial duration <1 yr; BMD measured only at ultra-distal forearm site; BMD measurement by technique other than SPA, DPA, or DXA; Failure of contacted authors of eligible studies to provide requested data; A priori selected outcomes not included	270	279	270	0	0	0	0	279	279	50(2.8) to 73.5 (7.1)	100	

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Fractures (continued)													
Papadimitri-opoulos, 2004[49]	Inclusion: PMP women >45 yrs old with amenorrhea ≥ 6 mos; Included studies with interventions of vitamin D ± calcium and control grp intakes of vitamin D ≤100 IU/day ± calcum. Exclusion: Males; women < 45 y/o and/or amenorrheic < 6 mos; vitamin D daily intake ≤ 400 IU/d; follow-up < 1 year; BMD (g/cm or g/cm2) not measured by single-photon absorp-tiometry, dual-photon absroptiometry, or dual x-ray absoroptiometry in at least 1 of several designated sites (femoral neck, total hip, trochanter, lumbar spine, total body ,or combined forearm); reporting total number of fractures for a group as opposed to reporting fracture results on individual patients; studies that compared different types or doses of vitamin D.	2892	2888	123	1636 re-ceived vit D to-gether with ca 1200 mg and phos-phate 600 mg per day	0	2210	0	2765	2765	49.9 to 84.0	100	

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Author, Year	Inclusion/ exclusion criteria	Treat-ment, n	Con-trols, n	Ca alone, n	Ca + Vit D, n	Ca + exer-cise, n	Vit D alone, n	Exer-cise alone, n	Dietary calcium intake/ fall pre-vention, couseling	PBO Total	Range of mean ages (SD)	Women (%)	Comments
Prevention of Fractures (continued)													
Avenell, 2005[143]	Inclusion; Men & PMP women ≥ age 65; either community-living & institutionalized; Included trials whose subjects had previous fractures and neurologic disorders impairing mobility (e.g. Parkinson's); Included both randomized & pseudorandomized trials Exclusion; Women and men younger than 65 years of age; cognitive impairment;cancer within previous 10 yr of type likely to metastasize to bone; life expectancy <6 months; trials in which subjects were on glucocor- ticoid Rx; interventions that included agents other than vitamin D & calcium; disorders (e.g. nephrolithiasis, hyperparathyroidism) or drugs (e.g. bisphosphonates, HRT, vitamin D >200 IU/day) known to affect bone metabolism	12653	15485	3918	9935	0	2718	0	7042	7042	52.7-85	65	Random-ization and blinding not always clear(as for Chapuy 2004, Larsen)

Evidence Table 3q. Systematic reviews on calcium and/or vitamin D: participant characteristics (continued)

Ca = calcium; vit = vitamin; PBO = placebo; SD = standard deviation; RCT = randomized controlled trial; PMP = post-menopausal; BMD = bone mineral density; SPA = single-photon absorbency; DPA = double-photon absorbency; DXA = dual x-ray absorbency

Evidence Table 3r. Systematic reviews on calcium and/or vitamin D for prevention of bone loss and fractures: efficacy measures

Author, year	Out-come	Inter-vention	BMD Measurements				Fracture Risk				Comments
			BMD Site	Trials (n)	WMD (95% CI) [1]	Hetero-geneity p-value	FX Site	Trials (n)	Weighted RR[2]	Hetero-geneity p-value	
Shea, 2004[47]	Effect of calcium on BMD & FXs in PMP women. Follow-up 1 to 4 yr	Calcium 500-2000 mg/d ± Vit. D_3	L-spine (2 y)	9 (845)	1.66 (0.92, 2.39) p<0.01	0.02	Vert.	5 (576)	0.79 (0.55, 1.13) p= 0.14	0.40	Hetero-geneity of BMD differences not explained by primary vs secondary studies, loss to follow-up, type or dose of Ca or by BMD site. Lack of uniformity of outcome measures problematic.
			L-spine (3-4 y)	2 (218)	1.13 (-0.11, 2.38) p=0.07	0.71	Non-Vert.	2 (222)	0.86 (0.43, 1.72) p=0.66	0.54	
			Combined hip	8 (830)	1.64 (0.70, 2.57) p<0.01	0.04					
			1/3 distal radius	6 (615)	1.91 (0.33, 3.50) p=0.02	<0.01					
			Total body	4 (358)	2.05 (0.24, 3.86) p=0.03	<0.01					
Papadimi-triopoulos, 2004[49]	Effect of Vit. D on BMD & FXs in pmp women. Follow-up 1 to 5 yr	Vit. D_3, 300-2000 IU/day ± Ca	L-spine (1 y)	4 (563))	0.86 (0.17, 1.54) p=0.01	0.10	Vert.	1 (160)	0.33 (0.01, 8.05) p= 0.49	NA	Potential causes of heterog. Include variable Ca use in treated & controls & population-dependent D effects. OH-vit D forms more potent.
			L-spine (2-5 y)	4 (608)	-0.40 (-2.06, 1.25) p=0.63	<0.00	Non-Vert.	3 (5399)	0.78 (0.55, 1.09) p=0.15	0.05	
			Femoral neck (1-5 y)	5 (862)	0.98 (0.10, 1.85) p=0.03	0.22					
			Combined forearm (1-2 y)	5 (597)	-0.48 (-1.18, 0.22) p=0.18	0.42					
			Total body (1-3 y)	3 (508)	0.40 (-0.25, 1.05) p=0.23	<0.01					

Evidence Table 3r. Systematic reviews on calcium for prevention of bone loss (upper panel) and vitamin D for prevention of falls (lower panel): efficacy measures (continued)

Author, year	Out-come	Inter-vention	Year-by-year differences in rate of bone loss[1]				Comments
			BMD Site	First yr (95% CI)	Second yr (95% CI)	2 yr total	
Mackerras, 1997[52]	Year-by-year effect of calcium on BMD in postme no-pausal women. Follow-up 2 to 3 yr.	Calcium, 500-2000 mg/d ± Vit. D_3 400 IU/d	L-spine	1.9 (0.9, 2.8) p<0.001	0.00 (-1.2, 1.1) p=1.0	1.9 (0.8, 2,9) p=0.001	
			Femoral neck	2.2 (1.0, 3.5) p=0.001	0.1 (-1.4, 1.6) p=0.9	2.3 (1.0, 3.6) p=0.001	
			Trochante	2.9 (1.5, 4.2) p<0.001	-0.4 (-2.0, 1.3) p=0.7	2.5 (1.1, 3.9) p=0.001	
			Distal forearm	0.9 (-1.2, 3.1) p=0.04	1.1 (-1.6, 3.7) p=0,04	1.9 (-0.3, 4.3) p=0.09	
			Proximal forearm	2.1 (0.8, 3.4) p=0.002	0.5 (-1.0, 2.1) p=0.5	2.6 (1.3, 4.0) p=<0.001	

Evidence Table 3r. Systematic reviews on calcium for prevention of bone loss (upper panel) and vitamin D for prevention of falls (lower panel): efficacy measures (continued)

Author, year	Outcome	Inter-venttion	Trials (n)	Corrected pooled odds ratio for prevention of falls by vitamin D supplementation	Pooled risk difference		Comment
Bischoff-Ferrari 2004 [145]	Effect of vitamin D on falls in older persons. Follow-up 3 to 14 mos.	Vit. D_3, 400-800 IU/day or active vitamin D (calcitriol or alpha calcidiol ± Ca 800-1200/day	5 (1237)	0.78 (95% CI 0.64-0.92)	7% (95% CI 2%-12%; p=0.007) NNT 15 (95% CI 8-53)		No statistically significant heterogeneity. Effect sizes similar for studies using active vit D & D_3 ± Ca, and in community or institution-dwellers. Pooled odds ratios ranged from 0.77-0.83 for variable Ca regimens or no Ca.
			Subgroup analyses				
			Trials using vitamin D_3 400-800 IU/day (active vitamin D trials excluded)		Trials using only vitamin D_3 800 IU/day (400 IU/day vitamin D trial excluded)		
			No. of trials (n)	Corrected odds ratio of falling	No. of trials (n)	Corrected odds ratio of falling	
			3 (613)	0.83 (95% CI 0.65,1.06)	2 (259)	0.65 (95% CI 0.40,1.00)	

Evidence Table 3r. Systematic reviews on calcium for prevention of bone loss (upper panel) and vitamin D for prevention of falls (lower panel): efficacy measures (continued)

Author, year	Outcome	Inter-venttion	FX Site	Daily Vitamin D dose	Trials (n)	Weighted RR[2] (95% CI)	Hetero-geneity p-value	Pooled Risk Difference	Comment
Bischoff-Ferrari 2005[40]	Effect of vitamin D in prevention of hip and nonvertebral fractures in older persons. Follow-up. 1.5 to 5 yrs	Vit. D_3 400-800 IU/day ± calcium, 500-1200 mg/d	Hip	400-800 IU	5 (9294)	0.88 (0.69, 1.13)	0.09		Meta-regression revealed an inverse relationship between serum 25OH Vit. D (during follow-up) and reduction in hip fracture risk. Optimal fracture prevention appeared to occur with achieved mean 25OH Vit. D levels of 100 nmol/L. These results suggest that doses higher than 700-800 IU/d may be needed for people with low baseline 25OH D.
			Hip	700-800 IU	3 (5572)	0.74 (0.61, 0.88)	0.74	2% (95% CI, 1%-4%) p<0.001 (for treatment 2-5 y)	
			Hip	400 IU	2 (3722)	1.15 (0.88,1.50)	0.68		
			Any non-vert.	400-800 IU	7 (9820)	0.83 (0.70, 0.98)	0.07		
			Any non-vert.	700-800 IU	5 (6098)	0.77 (0.68, 0.87)	0.41	4% (95% CI, 2%-5%) p=0.02 (for treatment 1-5 y)	
			Any non-vert.	400 IU	2 (3722)	1.03 (0.86, 1.24)	0.36		

Evidence Table 3r. Systematic review on vitamin D ± calcium for prevention of fractures in elderly people: efficacy measures (continued)

Author, year	Inter-vention	Fracture Risk								
		Hip			Vertebral			Non-vertebral		
		# Trials (n)	Weighted RR[2] (95% CI)	Hetero-geneity p-value	# Trials (n)	Weighted RR[2] (95% CI)	Hetero-geneity p-value	# Trials (n)	Weighted RR[2] (95% CI)	Hetero-geneity p-value
Avenell, 2005[143]	Vit. D vs placebo or control	7 (18668)	1.17 (0.98, 1.41) p=0.09	0.67	4 (5698)	1.13 (0.50, 2.55) p=0.8	0.08	8 (18903)	0.99 (0.91, 1.09) p=0.90	0.09
	Vit. D vs Ca	2 (2739)	1.08 (0.72, 1.51) p=0.7	0.21	3 (2997)	2.76 (1.27-6.00) p=0.01	0.72	3 (2997)	1.02 (0.84, 1.22) p=0.9	0.36
	Vit. D + Ca vs placebo or control	7 (10376)	0.81 (0.68, 0.96) p=0.02	0.66	2 (2708)	0.34 (0.01, 8.34) p=0.50	N/A	7 (10376)	0.87 (0.78, 0.97 p=0.01	0.39
	Vit. D + Ca vs Ca	3 (6866)	0.81 (0.60, 1.10) p=0.20	0.50	2 (2681)	0.14 (0.01-2.77) p=0.2	N/A	4 (3061)	0.96 (0.79, 1.16) p=0.6	0.34

[1]Weighted mean difference (WMD) in BMD (treated group – control group) using percentile change from baseline
[2]Aggregate estimate (Relative Risk (RR), 95% confidence interval (CI)) of risk of event with vs without supplement
Abbreviations: BMD, bone mineral density; FX, fracture; pmp, postmenopausal; IU, international unit; Vert., vertebral; NA, not applicable

Evidence Table 3s. Randomized controlled trials on the efficacy of calcium and/or vitamin D in preventing chronic disease that were not included in previous systematic reviews: characteristics of studies

Author, year	Study name	Nutrient(s)	Study period	Total sample size enrolled	Mean/ median follow-up time	Mean participant age	Women, n (%)
Jackson, 2006[146]	WHI	Calcium/ Vitamin D	1993-1998	36,282	7	62.4	36,282 (100)
Wactawski-Wende, 2006[152]	WHI	Calcium/ Vitamin D	1993-1998	36,282	7	62.4	36,282 (100)
Meier, 2004[147]		Calcium/ Vitamin D	NS	55	Planned 2 years	56.2	29 (52.7)
Hunter, 2000[148]		Calcium/ Vitamin D	NS	158	Planned 2 years	58.7	158 (100)
Storm, 1998[149]		Calcium	NS	60	Planned 2 years	71	60 (100)

Evidence Table 3t. Randomized controlled trials on the efficacy of calcium and/or vitamin D in preventing chronic disease that were not included in previous systematic reviews: characteristics of the intervention.

Author, year	Intervention	Chemical form	Dose/Frequency of use	Timing of use	Duration of use
Jackson, 2006[146]	Placebo			2 x/day	Until censoring (Mean duration 7.0 years)
	Calcium	Calcium Carbonate	500 mg		Until censoring (Mean duration 7.0 years)
	Vitamin D	Vitamin D3	200 IU		Until censoring (Mean duration 7.0 years)
Wactawski-Wende, 2006[152]	Placebo			2 x/day	Until censoring (Mean duration 7.0 years)
	Calcium	Calcium Carbonate	500 mg		Until censoring (Mean duration 7.0 years)
	Vitamin D	Vitamin D3	200 IU		Until censoring (Mean duration 7.0 years)
Meier, 2004[147]	No treatment				
	Calcium	NS	500 mg	1 x/day	7 months
	Vitamin D	Cholecalciferol	500 IU		7 months
Hunter, 2000[148]	Placebo			1 x/day	2 years
	Vitamin D	Cholecalciferol	800 IU		2 years
Storm, 1998[149]	Placebo			2x/day	2 years
	Calcium	Calcium Carbonate	500 mg		

Evidence Table 3u. Randomized controlled trials on the efficacy of calcium and/or vitamin D in preventing chronic disease that were not included in previous systematic reviews: results

Author, year	Study supplement	Total Number in study (active/ placebo)	Main results	Total number of disease events (active/ placebo)	Hazard Ratio	Mean % change in BMD	Unadjusted estimates (95% CI)	P-value
Jackson, 2006[146]	Calcium/ Vitamin D	18,176/ 18106	Hip Fracture	175/199	0.88		0.72-1.08	
Wactawski -Wende, 2006[152]	Calcium/ Vitamin D	18,176/ 18106	Invasive Colorectal Cancer	168/154	1.08		0.86-1.34	
Meier, 2004[147]	Calcium/ Vitamin D	30/25	Change in lumbar and hip BMD (Pretreatment vs post treatment)			Lumbar spine of treatment group: +0.8%; femoral neck of treatment group: +0.1%; No significant change in controls		Lumbar spine of treatment group: 0.04; Femoral neck of treatment group: >.05
Hunter, 2000[148]	Calcium/ Vitamin D	79/79	Intrapair difference (treatment vs. control) change in Spine and Femoral neck BMD			Difference in Spine BMD: -0.001; Difference in Femur neck BMD: +0.003	SD difference in spine – 0.046; SD difference in Femur neck – 0.033	>.05
Storm 1998[149]	Calcium/ Vitamin D	NR/NR	Change in BMD over 2 years			Treatment FN BMD change +3%; Placebo FN BMD change – 0.3%; Treatment GT BMD no sig diff change; Placebo – 3%; Treatment Lumbar BMD change +3.7%; Placebo Lumbar BMD change no sig diff change		FN difference p=.1; GT difference p=.05; lumbar spine difference p<.01

Evidence Table 4a. Characteristics of the interventions in studies of the safety of vitamin A and/or beta-carotene supplements

Author, year	Control arm (duration of use)	INTERVENTION ARMS				
		Nutrient/supplement	chemical form(s)	Dose/Frequency of use	Timing of use	Duration of use
Omenn,1994[153]	Placebo (10 years or until endpoint)	Vitamin A; beta-carotene	Retinol in pilot phase (1985-1988) then retinyl palmitate in Vanguard (1988-1996)	25000 IU; 30 mg; 15 mg in asbestos pilot; 30 mg in one arm of smoker pilot; 30 mg in Vanguard cohort (1988-1996)	1x per day	8-10 years or until endpoint
Omenn,1996[93]	Placebo (10 years)	Active Treatment (vitamin A; beta-carotene)	Retinyl palmitate ; beta-carotene	25000 IU; 30 mg	1x per day	NS
Sibulesky, 1999[77]		Trace nutrients	All-rac-alpha tocopherol; Retinyl palmitate;	3 IU (2.2 tocopherol equivalent); 75 IU (23 retinol equivalent)	1x per day	4-6 years
Cartmel,1999[185]	Placebo (3.8 years)	Retinol; vitamin E; vitamin A	Retinol; all-rac-alpha tocopherol; retinol palmitate	7576 retinol equivalents; 3 IU (2.2 tocopherol equivalent); 4500 RE (15,000 IU)	NS	3.8 years
Goodman, 1993[92]	Placebo (3 years)	Retinol; beta-carotene	Retinol; beta-carotene	25000 IU; 30 mg	1x per day	NS
Xuan,1991[78]		Vitamin A; beta-carotene; vitamin E; selenium	Retinol; beta-carotene; d-alpha-tocopherol; selenium yeast	25,000 IU; 30 mg	1x per day	6 months
Ragavan, 1982[186]		Vitamin A	NS	Up to 75,000 IU	NS	NS
Stauber,1991[187]		Vitamin A	NS	0-47,000 IU	NS (supplement plus dietary intake)	5 years
Lee,1999[96]	Placebo (2.1 years)	Beta-carotene	Beta-carotene	50 mg	Every other day	2.1 years
Green,1999[84]	Placebo (4.5 years)	Beta-carotene	Beta-carotene	30 mg	1x per day (with meals)	4 years
Hennekens, 1996[95]		Beta-carotene	Beta-carotene	50 mg	Every other day	12 years
Omenn,1993[91]	Placebo (3 years)	Vitamin A/Beta-Carotene	Retinol; beta-carotene	25000 IU; 15 mg	1x per day	NS
Micozzi,1988[188]	Placebo (constant and low total carotenoid content (0.5-1.6 mg/d for 3000 kcal intake level)), (6 weeks)	Vitamin A	Retinol; beta-carotene	30 mg; 12 mg	1x per day (with meals)	6 weeks

Evidence Table 4b. Results of studies with information on clinical adverse effects of vitamin A supplements in the prevention of chronic diseases

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Omenn,1994[153]	Beta carotene and/or retinol	hypertriglyceridemia	NA	NA	NA	P<0.05	Actual difference between arms were very small and negligible
Omenn,1996[93]	Beta carotene and/or retinol	NR	NR	NR	NR	NR	
Sibulesky, 1999[77]	Vitamin A	Liver enzymes	NA	NA	NR	NS	
		Symptoms (joint or bone pain, headaches, hairloss, erythema or scaly skin, unusually dry skin, desquamation, exfoliation, or eruption, red rash, unusually brittle or soft nails, lip fissures or chapping, nausea, diarrhea)	3	13			Within each randomized group, those withdrew due to side effect had similar serum concentration to those without side effect.
		Blood cell counts, chemistries, urine studies	NR	NR			Standard blood and urine chemistries were comparable between groups.
Cartmel,1999[185]	Retinol	Alopecia	7	3	NR	Not significant at 1, 13, 25, 37, 46 or 61 months	
		Conjunctivitis	2	2			
		Epistaxis	2	1			
		Cheilitis	10	10			
		Dry skin	21	9			
		Exanthema	10	9			
		Peeling palms	3	0			
		Skin infection	0	0			
		Headaches	19	31			
		Fatigue	11	12			
		Stiffness	3	5			
		Dysuria	2	0			
		Menstrual changes	0	0			
		Nausea or vomiting	2	0			
		WBC abnormality	92	122			
		Liver enzymes abnormality	134	186			
		Cholesterol	65	97			
		Hemoglobin	267	298			
		Platelet count	7	7			

Evidence Table 4b. Results of studies with information on clinical adverse effects of vitamin A and/or beta-carotene supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Goodman, 1993 [92]	Retinol; beta-carotene	Yellowing of skin	1	0	NR		
		Skin redness/dryness	14	19			
		Nosebleeds	4	0			
		Weight loss/appetite	5	6			
		Headaches	11	9			
		Anxiety/depression	21	15			
		Fatigue	13	13			
		Bone pain	14	13			
		Nausea/vomiting	1	0			
		Bowel movements	8	9			
		SGOT	0	2			
		Alkaline phosphatase	0	1			
Xuan,1991 [78]	Vitamin A	Hypercalcemia	1	NA	NA		Case study
		Muscle atrophy					
		Total body alopecia					
		Erosive dermatitis					
		Psychiatric disturbances					
Ragavan, 1982 [186]	Vitamin A	Liver function as measured by aspartate aminotransferase (AST) activity	NA	NA	NA		Retinyl esters explained only 12% of the variability in AST activity. The association of retinyl esters and AST was significant in females (r=0.47).
Stauber,1991 [187]	Vitamin A	Liver function as measured by aspartate aminotransferase (AST) activity	NA	NA	NA	0.0002	Retinyl esters explained only 12% of the variability in AST activity (Spearman's correlation coefficient, r=0.34).
Lee,1999 [96]	Beta-carotene	Yellowing of the skin	2131	1944	0.5 (0.24-1.03)		
Green,1999 [84]	Beta-carotene	Symptoms (not specified)	65	64	NR	NS	
Hennekens, 1996 [95]	Beta-carotene	Skin yellowing	1745	1535	NR		
		Minor gastrointestinal symptoms (e.g., belching)	275	124			

Evidence Table 4b. Results of studies with information on clinical adverse effects of vitamin A and/or beta-carotene supplements in the prevention of chronic diseases (continued)

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Omenn,1993[91]	Vitamin A/Beta-carotene	Increased alkaline phosphatase	1	1	NR		
		Threshold level adverse symptoms	154	142			Text reported no difference in overall rates or rates of individual symptoms except change in bowel habits.
		Change in bowel habits	NR	NR			Text reported that rates were different between arms, but direction and magnitude were not specified.
Micozzi,1988[189]	Beta-carotene	Carotenodermia	5	1	NR		Carotenodermia was assessed by physical exam of the skin; skin yellowing was graded into 3 degrees based on subjective reading.

NR = Not reported; NS = Not significant; NA = Not applicable

Evidence Table 4c. Results of studies with information on lipid profiles associated with the use of vitamin A and/or beta-carotene supplements

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Change in active group (indicate mean (95% CI)), mean (SD), mean (SE), median or other measurements	Change in inactive group (indicate mean (95% CI)), mean (SD), mean (SE), median or other measurements	Statistical significance (p-value)	Comment
Omenn,1994[153]	Retinol; beta-carotene	Increased triglyceride levels	NA	NA	Mean: 0 mg/dL after 72 months	Mean: -25 mg/dL after 72 months	p<0.01	TG were significantly higher in the treatment group for all time-points after baseline.
Cartmel, 1999[185]	Retinol	Triacylglycerol	NA	NA	Mean (95% CI): baseline: 1.42 mmol/L (1.35-1.48); 49 months: 1.77 mmol/L (1.69-1.85)	Mean (95% CI): baseline: 1.38 mmol/L (1.32-1.45); 49 months: 1.59 mmol/L (1.52-1.66)		Significantly higher triacylglycerol levels over time in the retinol group, beginning at 1 mo and continuing throughout
		HDL			Mean (95% CI): baseline: 1.26 mmol/L (1.22-1.29); 49 months: 1.16 mmol/L (1.13-1.19)	Mean (95% CI): baseline: 1.24 mmol/L (1.21-1.28); 49 months 1.17 mmol/L (1.14-1.20)		Decreased over time in both groups, but decline was singificantly greater in the retinol group
		LDL			Mean (95% CI): baseline: 3.55 mmol/L (3.47-3.63); 49 months: 3.61 mmol/L (3.53-3.70)	Mean (95% CI): baseline: 3.55 mmol/L (3.47-3.63); 49 months: 3.49 mmol/L (3.42-3.57)		

NA = Not applicable; NR = Not Reported; LDL = low-density lipoprotein; HDL = high-density lipoprotein; SD = Standard Deviation; SE = Standard Error.

Evidence Table 4d. Assessment of the likelihood that reported adverse effect were caused by use of a vitamin A and or beta-carotene supplements

Author, year	Nutrient	Adverse effect	Temporal relation-ship	Dose-response relation-ship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supple-ment use	Lack of alternative cause	Recurrence after reuse of supplement
Omenn,1994 [153]	Beta carotene and/or retinol	hypertriglyceridemia	Yes	NR	NR	NR	NR	NR
Omenn,1996 [93]	Beta carotene and/or retinol	NR	NA	NA	NA	NA	NA	NA
Sibulesky, 1999 [77]	Vitamin A	Liver enzymes	Yes	NR	NR	Yes	NR	NR
Cartmel, 1999[185]	Retinol	Alopecia	Yes	NR	NR	NR	NR	NR
		Conjunctivitis						
		Epistaxis						
		Cheilitis						
		Dry skin						
		Exanthema						
		Peeling palms						
		Skin infection						
		Headaches						
		Fatigue						
		Stiffness						
		Dysuria						
		Menstrual changes						
		Nausea or vomiting						
		White blood cell count abnormality						
		Liver enzymes abnormality						
		Hemoglobin						
		Platelet count						

Evidence Table 4d. Assessment of the likelihood that reported adverse effect were caused by use of a vitamin A and or beta-carotene supplements (continued)

Author, year	Nutrient	Adverse effect	Temporal relation-ship	Dose-response relation-ship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supple-ment use	Lack of alternative cause	Recurrence after reuse of supplement
Goodman, 1993 [92]	Retinol; beta-carotene	Yellowing of skin	Yes	No	NR	Yes	No	NR
		Skin redness/dryness						
		Nosebleeds						
		Weight loss/appetite						
		Headaches						
		Anxiety/depression						
		Fatigue						
		Bone pain						
		Nausea/vomiting						
		Bowel movements						
		Serum glutamic oxaloacetic transaminase						
		Alkaline phosphotase						
Xuan,1991 [78]	Vitamin A, beta-carotene, Vitamin E, selenium	Muscle cramps	Yes	NR	NR	Yes	NR	NR
		Diarrhea						
		Poor appetite						
		Runny nose						
		Joint pain						
		Chapping of lips/face						
		Yellowing of skin						
		Broken nails						
		Hair loss						
		Tingling in limbs						
		Headache						
		Lethargy						
Ragavan, 1982 [186]	Vitamin A	Hypercalcemia			Yes		Yes	
		Muscle atrophy						
		Total body alopecia						
		Erosive dermatitis						
		Psychiatric disturbances						
		Thyroid function						
Stauber, 1991[187]	Vitamin A	Liver function as measured by aspartate aminotransferase activity	Yes	NR	Yes	No	NR	

Evidence Table 4d. Assessment of the likelihood that reported adverse effect were caused by use of a vitamin A and or beta-carotene supplements (continued)

Author, year	Nutrient	Adverse effect	Temporal relation-ship	Dose-response relation-ship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supple-ment use	Lack of alternative cause	Recurrence after reuse of supplement
Lee,1999[96]	Beta-carotene	Yellowing of the skin	Yes	NR	NR	Yes	NR	NR
Green,1999[84]	Beta-carotene	Symptoms (not specified)	NR	NR	NR	NR	NR	NR
Hennekens, 1996[95]	Beta-carotene	Skin yellowing Minor GI symptoms (e.g. belching)	NR	NR	NR	Yes	NR	NR
Omenn,1993[91]	Vitamin A/beta-carotene	Increased alkaline phosphate	Yes	NR	NR	Yes	No	NR
Micozzi,1988[188]	Beta-carotene	Carotenodermia	Yes	Yes	Yes	Yes	NR	

NR = Not reported

Evidence Table 4e. Characteristics of the interventions in studies of the safety of vitamin E supplements

Author, year	Control arm (duration of use)	INTERVENTION ARMS				
		Nutrient/supplement	chemical form(s)	Dose/Frequency of use	Timing of use	Duration of use
Lee,2005 [87]	Placebo (10.1 years)	Vitamin E	Alpha-tocopherol	600 IU	every other day	10.1 years
McNeil,2004 [113]		Vitamin E	D-alpha-tocopherol	335 mg	1x per day	4 years
de Gaetano, 2001 [117]	No vitamin E (3.6 months)	Vitamin E	Synthetic alpha tocopherol	300 mg	1x per day	3.6 months (mean)
Sibulesky, 1999 [77]		Trace nutrients	All-rac-alpha tocopherol; Retinyl palmitate;	3 IU (2.2 tocopherol equivalent); 75 IU (23 retinol equivalent)	1x per day	4-6 years
		Treatment 2; treatment 3	D-alpha-tocopherol	1000 IU; 1500IU		
Xuan,1991 [78]		Vitamin A; beta-carotene; vitamin E; selenium	Retinol; beta-carotene; d-alpha-tocopherol; selenium yeast	25000 IU; 30 mg; 50 mg; 800 IU; 400 mcg	1x per day	6 months
Simons,1996 [189]	Placebo (soybean oil), (6 weeks)	Treatment 1 (500IU/d)	D-alpha-tocopherol	500 IU	NS	6 weeks
Tsai,1978 [190]	Placebo (4 weeks)	Intervention - megavitamin E	Dl-alpha-tocopherol acetate	200 IU	3x per day (with meals)	4 weeks

NS – Not specified

Evidence Table 4f. Results of studies with information on clinical adverse effects of vitamin E supplements in the prevention of chronic diseases

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group, indicate what type	Statistical significance (p-value)	Comment
Lee,2005 [87]	Vitamin E	Epistaxis	NR	NR	1.06 (1.01-1.11)	0.02	
McNeil,2004 [113]	Vitamin E	Adverse events	351	327	NR	0.56	
		Major adverse event (death, disability, hospitalization)	127	128			
de Gaetano, 2001 [117]	Vitamin E	Bleeding: gastrointestinal bleed; intracranial bleed; ocular bleed; epistaxis; other	16; 11; 2; 1; 1;	14; 11; 0; 1; 1; 1	NA		
		Gastrointestinal disease other than bleed	6	5			
		Other events	30	27	NR	0.003	
Sibulesky, 1999 [77]	Vitamin E; vitamin A	Liver enzymes	NA	NA			
		Symptoms (joint or bone pain, headaches, hairloss, erythema or scaly skin, unusually dry skin, desquamation, exfoliation, or eruption, red rash, unusually brittle or soft nails, lip fissures or chapping, nausea, diarrhea)	3	13			
		Blood cell counts, chemistries, urine studies	NR	NR			
Xuan,1991 [78]	Vitamin E, selenium	Stroke	1 (vitamin E + selenium)	1 (placebo)	NR		
Simons,1996 [189]	Vitamin E	Nausea	1	0	NR		In the 1500 IU/d arm
		Increased bowel frequency					
		Recurrent tenosynovitis in ankle					
Tsai,1978 [190]	Vitamin E	Muscular weakness	13/17 (male/female)	12/14 (male/female)	NR		No significant effect on serum cholesterol level in both gender; level of tryglyceride increased but not statistically significant in females.
		Gastrointestinal disorder	0/6 (male/female)	0/0 (male/female)			
		Worse work performance	4/6 (male/female)	4/4 (male/female)			
		Worse sexuality	1/0 (male/female)	0/1 (male/female)			
		Worse general well-being	5/10 (male/female)	5/6 (male/female)			
		Serum cholesterol level	NA	NA			
		Serum triglyceride level	NA	NA			

NR = Not reported; NS = Not significant; NA = Not applicable

Evidence Table 4g. Assessment of the likelihood that reported adverse effect were caused by use of a vitamin E supplement

Author, year	Nutrient	Adverse effect	Temporal relationship	Dose-response relationship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supple-ment use	Lack of alter-native cause	Recurrence after reuse of supplement
Lee,2005 [87]	Vitamin E	Epistaxis	Yes	NR	NR	NR	NR	NR
McNeil,2004 [113]	Vitamin E	Adverse events	Yes	NR	NR	Yes	NR	NR
		Major adverse event (death, disability, hospitalization)						
de Gaetano, 2001[117]	Vitamin E	Bleeding: gi bleed; intracranial bleed; ocular bleed; epistaxis; other	Yes	NR	NR	NR	NR	NR
		GI disease other than bleed						
		Other events						
Sibulesky, 1999 [77]	Vitamin A	Liver enzymes	Yes	NR	NR	Yes	NR	NR
		Symptoms (joint or bone pain, headaches, hairloss, erythema or scaly skin, unusually dry skin, desquamation, exfoliation, or eruption, red rash, unusually brittle or soft nails, lip fissures or chapping, nausea, diarrhea)						
		Blood cell counts, chemistries, urine studies						
Xuan,1991 [78]	Vitamin E, selenium	Stroke	Yes	NR	NR	Yes	NR	NR
Simons,1996 [189]	Vitamin E	Nausea	Yes	NR	NR	Yes	NR	NR
		Increased bowel frequency						
		Recurrent tenosynovitis in ankle						
Tsai,1978 [190]	Vitamin E	Muscular weakness, gastrointestinal disorder, worse work performance, worse sexuality, worse general well-being, serum cholesterol level, serum triglyceride level	Yes	NR	NR	Yes	NR	NR

NR = Not reported

Evidence Table 4h. Characteristics of the interventions in studies of the safety of other supplements

Author, year	Control arm (duration of use)	INTERVENTION ARMS				
		Nutrient/supplement	Chemical form(s)	Dose/Frequency of use	Timing of use	Duration of use
Clark,1996 [133]	Placebo (10 years)	Selenium	Selenium yeast	200 mcg	NS	10 years
Xuan,1991 [78]		Vitamin A	Retinol	25000 IU; 30 mg	1x per day	6 months
		Beta carotene	Beta-carotene	50 mg		
		Vitamin E	D-alpha-tocopherol	800 Iu		
		Selenium	Selenium yeast	400 mcg		
Coplin,1991 [191]		Chelated iron (bis-glycino iron II)	Bis-glycino iron chelate	50 mg	1x per day (before breakfast)	NS
		Ferrous sulfate				
Idjradinata, 1994 [159]	Placebo (syrup), (4 month)	Iron	Ferrous sulfate	3 mg/kg	NS	4 months
MMWR,1993 [192]		Iron	Ferrous sulfate	30-40 tablets of 325 mg/tablet	Accidental poisoning	NS

NS = Not specified

Evidence Table 4i. Results of studies with information on clinical adverse effects of other supplements in the prevention of chronic diseases

Author, year	Nutrient	Adverse effect	Adverse effects in supplement group, n (%)	Adverse effects in inactive group, n (%)	Point estimate in active group	Statistical significance (p-value)	Comment
Clark,1996 [133]	Selenium	Gastrointestinal upset	21	14	NR		
Xuan,1991 [78]	Vitamin E, selenium	See comments	See comments	See comments	NR		See comments in the same study above
		Stroke	1 (vitamin E + selenium)	1 (placebo)			
Coplin,1991 [191]	Iron	Moderate-to-severe adverse symptoms (abdominal pain, bloating, constipation, diarrhea, nausea, vomiting, headache, fatigue)	14 (ferrous sulfate)	8 (chelate form)	NR		The remaining 16 women had same symptom profile with both preparations.
		Abdominal pain	7 (ferrous)	9 (chelated)			
		Bloating	10 (ferrous)	9 (chelated)			
		Constipation	13 (ferrous)	13 (chelated)			
		Diarrhea	9 (ferrous)	7 (chelated)			
		Nausea	12 (ferrous)	9 (chelated)			
		Vomiting	0 (ferrous)	0 (chelated)			
		Gastrointestine	25 (ferrous)	23 (chelated)			
		Headache	5 (ferrous)	7 (chelated)			
		Fatigue	6 (ferrous)	6 (chelated)			
		Overall total	26 (ferrous)	25 (chelated)			
Idjradinata, 1994 [159]	Iron	Growth retardation (in wt gain, measured by kg every 2 weeks)	NR	NA	NA		Mean (SE) change (kg) every two weeks in active group 0.070 (0.011), in placebo group 0.106 (0.010)
MMWR,1993 [192]	Iron	Deaths	5	NR	NR		Poisoning
Strause,1994 [193]	Calcium; trace minerals; calcium and minerals; placebo	Adverse symptoms causing drop-out, most commonly gastrointestinal upset (nausea, gas, indigestion)	Ca 6, minerals 3, Ca and minerals 4	Placebo 3	NR		
		Drop-outs due to surgery, major illness, or death	Ca 2, minerals 1, Ca and minerals 2	Placebo 1			

NR = Not reported; NS = Not significant; NA = Not applicable

Evidence Table 4j. Assessment of the likelihood that reported adverse effects were caused by use of any other supplement

Author, year	Nutrient	Adverse effect	Temporal relationship	Dose-response relationship	Adverse effects disappeared after discontinuation of supplementation	Evidence of supple-ment use	Lack of alternative cause	Recurrence after reuse of supplement
Clark,1996 [133]	Selenium	Gastrointestinal upset	Yes	NR	NR	Yes	NR	NR
Xuan,1991 [78]	Vitamin E, selenium	Stroke	Yes	NR	NR	Yes	NR	NR
Coplin,1991 [191]	Iron	Moderate-to-severe adverse symptoms (abdominal pain, bloating, constipation, diarrhea, nausea, vomiting, headache, fatigue)	NR	NR	NR	NR	NR	
Idjradinata, 1994 [159]	Iron	Growth retardation (in wt gain, measured by kg every 2 weeks)	NR	NR	NR	Yes	NR	
Strause, 1994 [193]	Calcium; trace minerals; calcium and minerals; placebo	Adverse symptoms, most commonly GI upset (nausea, gas, indigestion)	NR	No	NR	No	No	NR

NR = Not reported

List of Acronyms

AERS	Adverse Event Reporting System
AHRQ	Agency for Healthcare Research and Quality
AMD	Age-related macular degeneration
AREDS	Age-Related Eye Disease Study
ATBC	Alpha-Tocopherol Beta-Carotene Cancer Prevention
BCC	Basal cell carcinomas
BMD	Bone mineral density
BMI	Body mass index
CARET	Beta-Carotene and Retinol Efficacy Trial
CENTRAL	The Cochrane Central Register of Controlled Trials
CFSAN	Center for Food Safety and Applied Nutrition
CI	Confidence interval
DRI	Dietary reference intake
DSHEA	Dietary Supplement Health and Education Act
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GRAS	Generally Recognized As Safe
HR	Hazard ratio
IPO	Percentage pixel opaque
LOAEL	Lowest-observed-adverse- effect level
LOCS II	Lens Opacities Classification System
MeSH	Medical Subject Heading
MONMD	Multi-center Ophthalmic and Nutritional Eye-Related Macular Degeneration Study
NCSP	Nambour Skin Cancer Prevention Trial
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
NPC	Nutritional Prevention of Cancer
OMAR	Office of Medical Applications of Research
OR	Odds ratio
PDF	Portable document format
PHS	Physician's Health Study
PPP	Primary Prevention Project
RDA	Recommended daily allowance
RE	Retinol equivalent
REACT	Roche European American Cataract Trial
RR	Relative risk
SAM	S-adenosylmethionine
SCC	Squamous cell carcinoma
SCP	Skin Cancer Prevention Study
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SU.VI.MAX	Supplementation en Vitamines et Mineraux Antioxydants
UF	Uncertainty factor
UL	Tolerable upper level intake
VECAT	Vitamin E, Cataract, and Age-Related Maculopathy Trial
VLDL	Very low density lipoprotiens
WHI	Women's Health Initiative study
WHS	Women's Health Study