The Efficacy and Safety of Multivitamin and Mineral Supplement Use To Prevent Cancer and Chronic Disease in Adults: A Systematic Review for a National Institutes of Health State-of-the-Science Conference

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Background: Multivitamin and mineral supplements are the most commonly used dietary supplements in the United States.

Purpose: To synthesize studies on the efficacy and safety of multivitamin/mineral supplement use in primary prevention of cancer and chronic disease in the general population.

Data Sources: English-language literature search of the MEDLINE, EMBASE, and Cochrane databases through February 2006 and hand-searching of pertinent journals and articles.

Study Selection: Randomized, controlled trials in adults were reviewed to assess efficacy, and randomized, controlled trials and observational studies in adults or children were reviewed to assess safety.

Data Extraction: Paired reviewers extracted data and independently assessed study quality.

Data Synthesis: 12 articles from 5 randomized, controlled trials that assessed efficacy and 8 articles from 4 randomized, controlled trials and 3 case reports on adverse effects were identified. Study quality was rated fair for the studies on cancer, cardiovascular disease, cataracts, or age-related macular degeneration and poor for the studies on hypertension. In a poorly nourished Chinese population, combined supplementation with β-carotene, α-tocopherol, and selenium reduced the incidence of and mortality rate from gastric cancer and the overall mortality rate from cancer by 13% to 21%. In a French trial, combined supplementation with vitamin C, vitamin E, β-carotene, selenium, and zinc reduced the rate of cancer by 31% in men but not in women. Multivitamin and mineral supplements had no significant effect on cardiovascular disease or cataracts, except that combined β-carotene, selenium, α-tocopherol, retinol, and zinc supplementation reduced the mortality rate from stroke by 29% in the Linxian study and that a combination of 7 vitamins and minerals stabilized visual acuity loss in a small trial. Combined zinc and antioxidants slowed the progression of advanced age-related macular degeneration in high-risk persons. No consistent adverse effects of multivitamin and mineral supplements were evident.

Limitations: Only randomized, controlled trials were considered for efficacy assessment. Special nutritional needs, such as use of folic acid by pregnant women to prevent birth defects, were not addressed. Findings may not apply to use of commercial multivitamin supplements by the general U.S. population.

Conclusions: Evidence is insufficient to prove the presence or absence of benefits from use of multivitamin and mineral supplements to prevent cancer and chronic disease.

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Multivitamin and mineral supplements are the most commonly used dietary supplements in the United States (1). According to the National Health and Nutrition Examination Survey 1999–2000, 35% of adults reported recent use of multivitamin supplements (1). Most persons use multivitamin and mineral supplements to ensure adequate intake and to prevent or mitigate diseases. The commonly used over-the-counter multivitamin and mineral supplements contain at least 10 vitamins and 10 minerals.

Many chronic diseases share common risk factors, including cigarette smoking, unhealthy diet, sedentary lifestyle, and obesity. Important underlying mechanisms for these factors to increase risk for disease include oxidative damage, inflammation, and 1-carbon metabolism (2–7). Numerous in vitro studies and animal studies have suggested favorable effects of several vitamins and minerals on these processes and on angiogenesis, immunity, cell differentiation, proliferation, and apoptosis (8–10).

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The U.S. Food and Nutrition Board has established tolerable upper intake levels for several nutrients. An upper intake level is defined as the highest level of daily nutrient intake that is likely to pose no risk for adverse effects to almost all persons in the general population (11). The strength of the evidence used to determine an upper intake level depends on data availability. Hence, an update of the data on adverse effects will help researchers to evaluate the appropriateness of upper intake levels.

We performed a systematic review to synthesize the published literature on 1) the efficacy of multivitamin and mineral supplements and certain commonly used single vitamin or mineral supplements in the primary prevention of cancer and chronic disease in the general adult population and 2) the safety of multivitamin and mineral supplements and certain commonly used single vitamin or mineral supplements in the general population of adults and children (12). The review was done for a National Institutes of Health State-of-the-Science Statement for health care providers and the general public. This report is from the systematic review and focuses on 2 questions: What is the efficacy determined in randomized, controlled trials of multivitamin and mineral supplements (each at a dose less than the upper intake level) in the general adult population for the primary prevention of cancer and chronic diseases or conditions, and what is known about the safety of multivitamin and mineral supplement use in the general population of adults and children, on the basis of data from randomized, controlled trials and observational studies?

Methods

We defined "multivitamin and mineral supplements" as any supplements that contain 3 or more vitamins or minerals without herbs, hormones, or drugs. We defined the general population as community-dwelling persons who do not have special nutritional needs. (Examples of persons with special nutritional needs are those who are institutionalized, hospitalized, pregnant, or clinically deficient in nutrients.) A disease or condition was defined as chronic if it persists over an extended period, is not easily resolved, often cannot be cured by medication (although symptoms may be controlled or ameliorated with medication), frequently worsens over time, causes disability or impairment, and often requires ongoing medical care (13). The following chronic diseases were considered: breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric cancer, or any other cancer (including colorectal polyps); myocardial infarction, stroke, hypertension, or other cardiovascular diseases; type 2 diabetes mellitus; Parkinson disease, cognitive decline, memory loss, or dementia; cataracts, macular degeneration, or hearing loss; osteoporosis, osteopenia, rheumatoid arthritis, or osteoarthritis; nonalcoholic steatohepatitis; chronic renal insufficiency or chronic nephrolithiasis; HIV infection, hepatitis C, or tuberculosis; and chronic obstructive pulmonary disease.

We focused on primary prevention trials in adults because primary prevention is the main purpose of multivitamin supplement use in the general adult population (14). Primary prevention was defined as an action taken to prevent the development of a disease in persons who are well and do not have the disease in question (15). Using this definition, we included studies for prevention of chronic disease (for example, cardiovascular disease) in persons with risk factors (for example, type 2 diabetes mellitus or hypertension) for that disease. We also included studies for prevention of malignant disorders (such as colon cancer) in persons with selected precursors of disease (such as polyps). We did not include studies in persons with carcinoma in situ or similar malignant conditions.

Literature Sources

We searched the MEDLINE, EMBASE, and Cochrane databases, including Cochrane Reviews and the Cochrane Central Register of Controlled Trials, for articles published from 1966 through February 2006. Additional articles were identified by searching references in pertinent articles, querying experts, and hand-searching the tables of content of 15 relevant journals published from January 2005 through February 2006.

Search Terms and Strategies

We developed a core strategy for searching MEDLINE, accessed through PubMed, that was based on analysis of the Medical Subject Heading terms and text words of key articles identified a priori. This strategy formed the basis for the strategies developed for the other databases (see the complete evidence report for additional details) (12).

Inclusion and Exclusion Criteria

We focused on trials that ascertained clinical end points. Biomarker data were considered if data were presented in a way that permitted ascertainment of incident cases of chronic disease. Because users of multivitamin supplements were more likely than nonusers to be women, to be older, to have higher levels of education, to have a healthier lifestyle (more physical activities, more fruit and vegetable intake, and less likely to be smokers), and to more frequently use nonsteroidal anti-inflammatory drugs (1, 16), residual confounding would limit the internal validity of observational studies. Hence, for assessment of efficacy, we focused on data from randomized, controlled trials as the strongest source of evidence. However, for assessment of safety, we included data from randomized, controlled trials and observational studies in adults and children to minimize the risk for missing any potential safety concerns.

An article was excluded if it was not written in English; presented no data in humans; included only pregnant women, infants, persons 18 years of age or younger (except if a study of persons $\leq$ 18 years of age presented data on the safety of multivitamin and mineral supplements), patients with chronic disease, patients receiving

treatment for chronic disease, or persons living in long-term care facilities; studied only nutritional deficiency; did not address the use of supplements; did not address the use of supplements separately from dietary intake; did not cover any pertinent diseases; or was an editorial, commentary, or letter. Each article underwent title review, abstract review, and assessment of inclusion or exclusion by paired reviewers. Differences in opinion were resolved through consensus adjudication. Article review, organization, and tracking were performed by using Web-based SRS, version 3.0 (TrialStat! Corp., Ottawa, Ontario, Canada).

Assessment of Study Quality

Each eligible article was reviewed by paired reviewers who independently rated its quality according to 5 domains: the description of how study participants were representative of the source population (4 items), bias and confounding (12 items), descriptions of study supplements and supplementation (1 item), adherence to treatment and follow-up (7 items), and statistical analysis (6 items). Reviewers assigned a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each item. The score for each quality domain was the proportion of the maximum score available in each domain. The overall quality score of a study was the average of the 5 scores for the 5 domains. The quality of each study in each domain was classified as good (score $\geq$ 80%), fair (score of 50% to 79%), or poor (score $<$ 50%).

For data on adverse effects, causality was evaluated with respect to temporal relationship, lack of alternative causes, dose–response relationship, evidence of increased circulating levels of the nutrient under investigation, disappearance of adverse effects after cessation of supplement use, and response to rechallenge.

Data Extraction

Paired reviewers abstracted data on study design, participant characteristics, study supplements, and results. Data abstraction forms were completed by a primary reviewer and were verified for completeness and accuracy by a second reviewer.

Evidence Grading

We graded the quantity, quality, and consistency of the evidence on efficacy by adapting an evidence grading scheme recommended by the Grading of Recommendations Assessment, Development and Evaluation Working Group (17). The strength of evidence was classified into 1 of 4 categories: high (further research is very unlikely to change our confidence in the estimates of effects), moderate (further research is likely to greatly affect our confidence in the estimates of effects and may change the estimates), low (further research is very likely to greatly affect confidence in the estimates of effects and is likely to change the estimates), or very low (any estimate of effect is very uncertain).

Role of the Funding Source

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Results

After title review, we identified 3710 potentially eligible articles through abstract review. After full text review, 64 articles met the inclusion and exclusion criteria. Of these, 7 articles from randomized, controlled trials contained only efficacy data, 5 articles from randomized, controlled trials contained both efficacy and safety data, and 3 articles from case reports contained only safety data. The remaining articles on the efficacy and safety of single-nutrient supplements are not included in this report.

Efficacy

Our search identified 12 articles that addressed the efficacy of multivitamin and mineral supplements in the primary prevention of cancer, cardiovascular disease, hypertension, cataracts, or age-related macular degeneration. Data for other chronic diseases and conditions were lacking. Designed vitamin and mineral combinations, but not the one-a-day type of multivitamin supplements available on the U.S. market, were used in these studies.

The 12 articles presented results from 5 randomized, controlled trials published from 1993 to 2005: the Linxian General Population Trial in China (18–22); the SUpplémentation en VItamines et Minéraux AntioXydants (SU.VI.MAX) study in France (23–25); the Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study (MONMD) in the United States (26); the Roche European American Cataract Trial (REACT) in the United States and United Kingdom (27); and the Age-Related Eye Disease Study (AREDS) in the United States (28, 29). A total of 47 289 persons were included in these trials. **Table 1** shows trial design, study supplements, participant characteristics, loss to follow-up, and self-selected supplement use.

Study Quality

Inclusion and exclusion criteria were clearly defined in most trials. The study quality was good in terms of randomization, double masking, ascertainment of trial end points, adherence, and use of an intention-to-treat

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Table 1. **Characteristics of Randomized, Controlled Trials on the Efficacy of Multivitamin and Mineral Supplement Use in Primary Prevention of Chronic Disease***

Study (Reference)	Location	Design	Exclusion Criteria	Sample, *n*	Participant Characteristics	Study Period/ Duration of Follow-up/ Loss to Follow-up or Withdrawal	Self-Selected Supplement Use before and during the Trial
Linxian General Population Trial (18, 19, 21)	Linxian County, China, where the incidence of esophageal cancer was high	RCT; fractional factorial design: placebo, AB, AC, AD, BC, BD, CD, ABCD, where A = retinyl 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; and D = β-carotene, 15 mg + selenium yeast, 50 μg + α-tocopherol, 60 mg	Age <40 or >69 y; previous use of vitamin supplements; history of stomach or esophageal cancer; debilitating disease; not living in 1 of 4 communes in Linxian	29 584	Recruited from the community; age 40–69 y; 55% women; nutritionally deprived; low intake of fresh fruits and meat and other animal products; low circulating levels of micronutrients, but overt clinical deficiencies were uncommon	1986–1991/ Total, 5.25 y/NR	NR (but previous users of any vitamins were ineligible for trial enrollment)
Linxian General Population Trial: end-of-trial endoscopy survey (20)			Age <40 or >69 y; history of cancer; did not live in 1 of 2 villages in Rencun commune; did not complete the first (1987) and end-of-trial (1991) cytologic examination	391 (in 1991)	Mean age, 53 y; 45% women; younger, more men, more smokers, and more alcohol users compared with overall trial participants	–/–/NA	
Linxian General Population Trial: end-of-trial cataract study (22)			Age <40 or >69 y; history of cancer; not living in Linxian County	5390 (in 1991)	Age 45–74 y; 55% women	–/–/NA	
SU.VI.MAX (23)	France	RCT; parallel-arm design: vitamin C, 120 mg + vitamin E, 30 mg + β-carotene, 6 mg + selenium, 100 μg + zinc, 20 mg vs. placebo	Men age <45 or >60 y; women age <35 or >60 y; disease expected to hinder participation or threaten 5-year survival; use of any supplement offered in the study; extreme beliefs or behavior regarding diet	12 741	Recruited from the community; 62% women; mean age: women, 46.6 y (SD, 6.6) (range, 35–60 y), and men, 51.3 y (SD, 4.7) (range, 45–60 y); women had higher serum levels of β-carotene and vitamin C but slightly lower levels of zinc and selenium than did men at baseline	1994–2002/ Total, 8 y; median, 7.5 y/5.8% lost to follow-up; 5.8% withdrawal	NR (but regular users of any of the vitamins or minerals provided in the study were ineligible for enrollment)

Continued on following page

Table 1—**Continued**

Study (Reference)	Location	Design	Exclusion Criteria	Sample, *n*	Participant Characteristics	Study Period/ Duration of Follow-up/ Loss to Follow-up or Withdrawal	Self-Selected Supplement Use before and during the Trial
SU.VI.MAX: prostate cancer (24)			Age <45 or >60 y; women; presence of cancer; not free of "severe health problems"; any use of study supplements; withdrawal from the trial during 4 d after randomization	5141 (men)	Recruited from the community; mean age: 51.3 y (SD, 4.6)	1994–1995/ Median, 8.9 y/NR	
SU.VI.MAX: hypertension (25)			No baseline data or no blood pressure measurements after 1 or 6.5 y of follow-up	5086	Recruited from the community; mean age, 47.8 y (SD, 6.4) in women and 52.3 y (SD, 4.7) in men	–/6.5 y/NR	
MONMD (26)	United States (8 Veterans Affairs Medical Centers)	RCT; parallel-arm design: β-carotene, 20 000 IU + vitamin E, 200 IU + vitamin C, 750 mg + citrus bioflavonoid complex, 125 mg + quercetin, 50 mg + rutin, 50 mg + bilberry extract, 5 mg + zinc picolinate, 12.5 mg + selenium, 50 μg + taurine, 100 mg + *N*-acetyl cysteine, 100 mg + L-glutathione, 5 mg + vitamin B_2, 25 mg + chromium, 100 μg vs. placebo	Did not have a 1-line decrease in 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; vitamin supplement use in the previous year	71	Recruited from clinics; veterans; mean age: multivitamin group, 72.4 y (SD, 6.8), placebo group, 71.9 y (SD, 6.8); mean smoking: multivitamin group, 0.08 packs/d (SD, 0.25), placebo group, 0.10 packs/d (SD, 0.27); mean body weight: multivitamin group, 197.3 lb (SD, 41.9), placebo group, 177.8 lb (SD, 30.6)	1992–1993/ 18 mo/ 9.8% withdrawal	NR (but persons who had vitamin use in the year before enrollment were ineligible)
REACT (27)	Boston, Massachusetts, United States; Oxford and Bradford, United Kingdom	RCT; parallel-arm design: β-carotene, 18 mg + vitamin C, 750 mg + *all-rac* α-tocopherol acetate, 600 mg, 3 divided doses daily vs. placebo	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 vitamin supplements	297	Recruited at outpatient ophthalmology clinics; mean age: U.S. sample, 64.2 y (SD, 8.49), U.K. sample, 67.8 y (SD, 8.47); smokers: U.S. sample, 15.3%, U.K. sample, 23.2%; women: U.S. sample, 62.4%, U.K. sample, 55.7%; mean body weight: U.S. sample, 74.3 kg (SD, 15.3), U.K. sample, 69.7 kg (SD, 12.6)	1990–1995/ Total, 3 y; mean, 2.8 y/46.8% dropout rate	NR (but regular users of any vitamin supplements were ineligible for enrollment)

Table 1—**Continued**

Study (Reference)	Location	Design	Exclusion Criteria	Sample, *n*	Participant Characteristics	Study Period/ Duration of Follow-up/ Loss to Follow-up or Withdrawal	Self-Selected Supplement Use before and during the Trial
AREDS: cataracts (28)	United States (11 centers)	RCT; parallel-arm design for persons in age-related macular degeneration category 1; 2 × 2 factorial design for persons in age-related macular degeneration categories 2, 3, or 4 Parallel arm: β-carotene, 15 mg + vitamin C, 500 mg + vitamin E, 400 IU vs. placebo 2 × 2 factorial design: placebo, A, B, and C, where A = β-carotene, 15 mg + vitamin C, 500 mg + vitamin E, 400 IU, B = zinc, 80 mg as zinc oxide + copper, 2 mg as cupric oxide, C = β-carotene, 15 mg + vitamin C, 500 mg + vitamin E, 400 IU + zinc, 80 mg as zinc oxide + copper, 2 mg as cupric oxide	History of cancer with a poor 7-year prognosis; major cardiovascular or cerebrovascular event within the past year; hemochromatosis; bilaterally aphakic or pseudophakic persons were ineligible for age-related macular degeneration category 1	4596	Recruited from clinics and community; participants were categorized into age-related macular degeneration categories 1, 2, 3, or 4 according to the size and extent of drusen and retinal pigment abnormality in each eye, presence of advanced age-related macular degeneration, and visual acuity; median age, 56 y; 96% white persons; 56% women; 8% smokers	1992–2001/ Total, 9 y; mean, 6.3 y/ 2.3% lost to follow-up; 15% withdrawal	55% of participants who had previous vitamin/mineral supplement use were enrolled and supplied with a brand-name multivitamin; additionally, 13% of trial participants chose to take the brand-name multivitamin in addition to study supplements; 20% of participants had self-selected use of nonstudy supplements that contained ≥1 of the study nutrients
AREDS: age-related macular degeneration (29)				3509	Recruited from clinics and community; age-related macular degeneration categories 2, 3, or 4; median age, 69 y; 97% white persons; 56% women; 8% smokers	–/–/2.4% lost to follow-up; 14.7% withdrawal	

* AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; NA = not applicable; NR = not reported; RCT = randomized, controlled trial; REACT = Roche European American Cataract Trial; SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants; U.K. = United Kingdom.

approach in statistical analyses. However, the articles generally lacked descriptions of whether the allocation sequence was concealed and whether observers independently evaluated outcomes. The articles also gave little information about previous and concomitant use of supplements and medications that could have modified the efficacy of the study supplements. No article reported on the success of blinding and the extent of unintended crossover. Overall, study quality was fair for the studies of cancer, cardiovascular disease, cataracts, and age-related macular degeneration and poor for the studies on hypertension (**Table 2**).

Cancer

The Linxian trial examined the incidence of and mortality from all cancer, esophageal cancer, stomach (cardia and noncardia) cancer, esophageal and gastric cardia cancer, and other cancer (18). After 5.25 years of follow-up, supplementation had no significant effect on these end points (**Appendix Table 1**, available at www.annals.org). The only exceptions were reductions in the incidence of gastric cancer (relative risk, 0.84 [95% CI, 0.71–1.00]), mortality rate from cancer (relative risk, 0.87 [95% CI, 0.75–1.00]), and mortality rate from stomach cancer (relative risk, 0.79 [95% CI, 0.64–0.99]) in the groups receiv-

Table 2. **Quality of Randomized, Controlled Trials on the Efficacy of Multivitamin and Mineral Supplements in Primary Prevention of Chronic Disease***

Study (Reference)	Representativeness†	Bias and Confounding‡	Description of Supplements§	Adherence and Follow-up‖	Statistical Analysis¶	Overall
Cancer						
Linxian General Population Trial (18)	Fair	Poor	Good	Fair	Poor	Fair
Linxian General Population Trial, end-of-trial endoscopy survey (20)	Fair	Poor	Good	Fair	Fair	Fair
SU.VI.MAX (23)	Good	Fair	Good	Fair	Good	Good
SU.VI.MAX (24)	Good	Fair	Fair	Poor	Good	Fair
Overall	Fair	Poor	Good	Fair	Fair	Fair
Cardiovascular disease						
Linxian General Population Trial (21)	Poor	Poor	Fair	Poor	Fair	Poor
SU.VI.MAX (23)	Good	Fair	Good	Fair	Good	Good
Overall	Fair	Poor	Fair	Fair	Good	Fair
Hypertension						
Linxian General Population Trial (21)	Poor	Poor	Fair	Poor	Fair	Poor
SU.VI.MAX (25)	Fair	Fair	Fair	Poor	Good	Fair
Overall	Poor	Poor	Fair	Poor	Fair	Poor
Cataracts						
Linxian General Population Trial, end-of trial cataract study (22)	Fair	Poor	Good	Good	Fair	Fair
MONMD (26)	Fair	Poor	Fair	Fair	Poor	Poor
REACT (27)	Good	Fair	Good	Good	Good	Good
AREDS (28)	Good	Good	Good	Fair	Good	Good
Overall	Fair	Fair	Good	Fair	Fair	Fair
Age-related macular degeneration						
MONMD (26)	Fair	Poor	Fair	Fair	Poor	Poor
AREDS (29)	Good	Fair	Good	Good	Good	Good
Overall	Fair	Fair	Good	Fair	Fair	Fair

* AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; REACT = Roche European American Cataract Trial; SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants.
† Score was based on a maximum of 8 points. Criteria included the description of setting and population from which the study sample was drawn, inclusion and exclusion criteria, information on excluded or nonparticipating persons, and description of participants' key characteristics.
‡ Score was based on a maximum of 24 points. Criteria included random assignment; concealment of allocation sequence; description of differences in participant characteristics among randomized groups; information on previous supplement use; differences between groups in previous supplement use; description of medication use during the study; efforts made to mask study supplements; evidence on the success of blinding; confirmation of medical diagnoses; independent interpretation of clinical outcomes; blinding of clinicians, study participants, outcome assessors, and statisticians; and blinding to randomization arms.
§ Score was based on 2 points. Criterion was a description of the details of the study supplements (that is, types of supplements; chemical forms of supplements; and dosage, frequency, and duration of supplementation).
‖ Score was based on a maximum of 14 points. Criteria included description of participant flow; methods for adherence assessment; participant adherence to study supplement use; unintended crossover between randomized groups; percentage of withdrawals and loss to follow-up; and early trial cessation or other deviations from protocol.
¶ Score was based on a maximum of 12 points. Criteria included clear description of statistical analyses, reports of magnitude and uncertainties of efficacy estimates, whether unintended crossover was handled appropriately, whether loss to follow-up was handled properly, adjustment for confounders, and reporting of statistical power.

ing β-carotene, α-tocopherol, and selenium, with or without other nutrients, compared with the groups receiving vitamin and mineral combinations with no β-carotene, α-tocopherol, and selenium (**Figure 1**) (18), and a lower mortality rate from noncardia stomach cancer in those receiving retinol and zinc (relative risk, 0.59 [95% CI, 0.37–0.93]) (18). The reduction in the mortality rate from cancer was greater in women than in men (relative risk, 0.79 [95% CI, 0.64–0.98] and 0.93 [95% CI, 0.77–1.12], respectively) and in persons younger than 55 years of age than in those 55 years of age or older (relative risk, 0.71 [95% CI, 0.55–0.92] and 0.94 [95% CI, 0.80–1.11], respectively) (19). In the substudy in which participants underwent endoscopic examination at the end of the trial, supplementation with β-carotene, α-tocopherol, and selenium had no significant effect on dysplasia or early cancer of the esophagus or stomach, although the odds ratios were generally in the protective direction (20) (**Appendix Table 1**).

The SU.VI.MAX study reported no benefit of use of antioxidant supplements for cancer prevention in women (relative risk, 1.04 [95% CI, 0.85–1.29]) but a reduction in the risk for cancer in men (relative risk, 0.69 [95% CI, 0.53–0.91]) (**Appendix Table 1**, **Figure 1**) (23). In this study, women were younger than men and generally had a healthier lifestyle, as suggested by higher serum levels of β-carotene and vitamin C and fewer smokers (23). A reduction in the risk for prostate cancer by use of antioxidant supplements was observed in men with a normal baseline level of prostate-specific antigen (≤3 μg/L) (hazard ratio, 0.52 [95% CI, 0.29–0.92]) but not in those with elevated levels (24).

Cardiovascular Disease

The Linxian trial reported a lower risk for death from stroke in persons receiving β-carotene, selenium, α-tocopherol, retinol, and zinc (relative risk, 0.71 [95% CI, 0.50–1.00]) but did not find significant effects of other nutrient combinations (21) (**Appendix Table 2**, available at www.annals.org). Hemorrhagic and ischemic stroke were not distinguished, but other data sources showed that approximately two thirds of the strokes were ischemic in this sample (30). In the SU.VI.MAX study, no significant difference in the incidence of ischemic cardiovascular disease was noted between randomized groups in men and women (23) (**Appendix Table 2**).

Hypertension

At the end of the Linxian trial, participants receiving β-carotene, selenium, and α-tocopherol had a higher prevalence of isolated diastolic hypertension (relative risk, 1.23 [95% CI, 1.06–1.43]) but not isolated systolic hypertension or both types of hypertension (21) (**Appendix Table 2**). The prevalence of isolated diastolic hypertension was lower in participants receiving riboflavin, niacin, vitamin C, and molybdenum than in participants who received placebo (relative risk, 0.68 [95% CI, 0.50–0.94]), but the prevalence of hypertension in other randomized groups did not differ from that in the placebo group (21). In the SU.VI.MAX trial, the risk for hypertension did not differ between the antioxidant group and the placebo group (25) (**Appendix Table 2**).

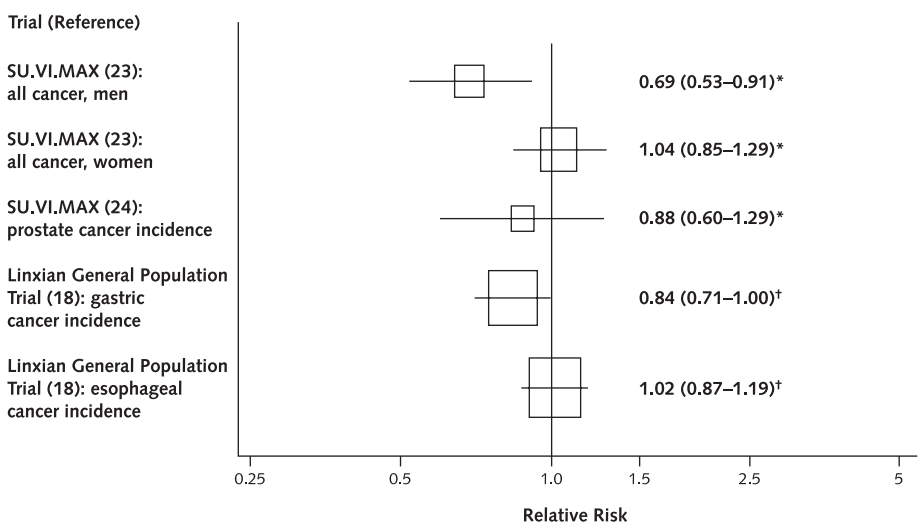
Total Mortality Rate

Overall, data on total mortality pointed to either no increased risk or lower risk in the groups that used multivitamin and mineral supplements (**Figure 2**). In the Linxian trial, the total mortality rate was lower among persons who received β-carotene, selenium, and α-tocopherol (relative risk, 0.91 [95% CI, 0.84–0.99]) but not other nutrient combinations (18, 21). In AREDS, a statistically nonsignificant increase in total mortality rate was seen among participants receiving antioxidants compared with those not receiving antioxidants (relative risk, 1.06 [99% CI, 0.84–1.33]) (28). However, when analysis was limited to participants with age-related macular degeneration categories 2, 3, and 4, the total mortality rate was lower in the groups receiving zinc combined with antioxidants (relative risk, 0.87 [99% CI, 0.60–1.25]) (29). The SU.VI.MAX study showed a lower total mortality rate among men receiving antioxidants and zinc compared with men receiving placebo (relative risk, 0.63 [95% CI, 0.42–0.93]), but no risk reduction in women (relative risk, 1.03 [95% CI, 0.64–1.63]), whereas the Linxian trial reported no differences by sex or age (19). In REACT, 9 deaths occurred in the antioxidant group (among 81 participants) and 3 deaths occurred in the placebo group (among 77 participants) (27). The causes of death in the antioxidant group were esophagitis, sudden death, aneurysm, pulmonary fibrosis, cancer, and coronary thrombosis, whereas the causes of death in the placebo group were cancer and coronary thrombosis (27).

Cataracts and Age-Related Macular Degeneration

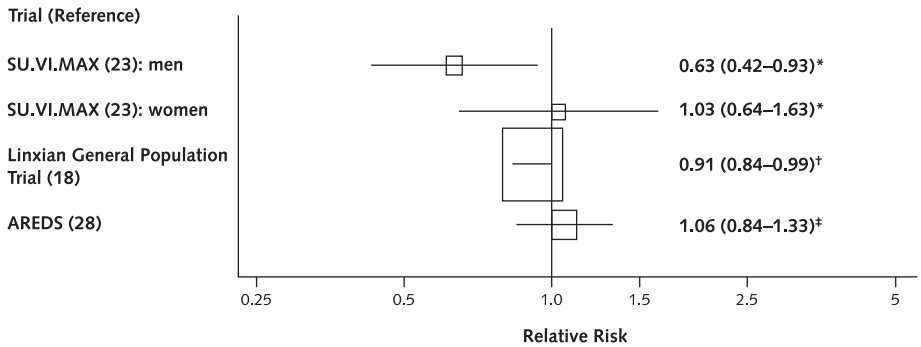
In the Linxian trial, supplementation with combined α-tocopherol, selenium, and β-carotene had no effect on nuclear cataract, cortical cataract, or posterior subcapsular cataract (22) (**Appendix Table 3**, available at www.annals

Figure 1. **Relative risk for cancer with use of multivitamin and mineral supplements.**



The lines represent 95% CIs, the midpoints of the lines represent the relative risk estimates, and the size of the boxes represents the relative size of the study sample. SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants. *Vitamin E + selenium + β-carotene + zinc + vitamin C. † Vitamin E + selenium + β-carotene.

Figure 2. **Relative risk for all-cause mortality with use of multivitamin and mineral supplements.**



The lines represent 95% CIs, the midpoints of the lines represent the relative risk estimates, and the size of the boxes represents the relative size of the study sample. AREDS = Age-Related Eye Disease Study; SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants. *Vitamin E + selenium + β-carotene + zinc + vitamin C. † Vitamin E + selenium + β-carotene. ‡ Vitamin E + vitamin C + β-carotene.

.org). In the MONMD study, distance visual acuity decreased in the placebo group but was unchanged in the multivitamin group ($P = 0.03$). The multivitamin group also had slightly better M-print visual acuity and fewer scotoma in left eyes ($P = 0.07$) after 12 months of supplementation but did not differ from the placebo group in several other cataract measurements (26) (**Appendix Table 3**).

In REACT, the primary measure for estimating the effect on cataract formation was the change from baseline in the percentage pixel opaque in the anteriorly focused retroillumination image. At the end of the second year, there was a small positive effect on the percentage pixel opaque in both the U.S. and United Kingdom groups. After the third year, the positive effects were greater in the U.S. group but not the United Kingdom group. Unfavorable changes in secondary outcomes (posterior subcapsular cataract, nuclear cataract, cortical cataract, and nuclear color) were smaller in the active supplement group, but none differed significantly from the placebo group (27) (**Appendix Table 3**).

In AREDS, no appreciable effects of antioxidant supplementation were found on development or progression of cataract or visual acuity loss after 6 years of follow-up (28) (**Appendix Table 3**). The odds ratio for developing advanced macular degeneration was 0.75 (95% CI, 0.55–1.03) in participants who received zinc alone, 0.80 (95% CI, 0.59–1.09) in those who received antioxidants alone, and 0.72 (95% CI, 0.52–0.98) in those who received combined zinc and antioxidants, compared with placebo (29). When participants with extensive small drusen, nonextensive intermediate-sized drusen, or pigment abnormalities were excluded, the odds ratio for progression to advanced age-related macular degeneration was 0.76 (95% CI, 0.55–1.05) in those who received antioxidants alone and 0.66 (95% CI, 0.47–0.91) in those who received combined zinc and antioxidants (29). The odds ratio of having at least moderate visual acuity loss was 0.73 (95% CI, 0.54–0.99) among participants who received antioxidants plus zinc, but this finding was not statistically significant for other groups (29) (**Appendix Table 3**).

Strength of Evidence

Taking into consideration the quantity, quality, and consistency of evidence, we concluded that the strength of evidence on the efficacy of multivitamin/mineral supplementation in the general adult U.S. population was very low for primary prevention of cancer, cardiovascular disease, and hypertension and low for cataract and age-related macular degeneration (**Table 3**).

Safety

Eight articles reported on the adverse effects of multivitamin and mineral supplements from 4 randomized, controlled trials and 3 case reports (26–29, 31–34) (**Appendix Table 4**). The randomized, controlled trials met only 2 of the 6 causality criteria: temporal relationship and evidence of supplement use. Overall, no consistent pattern of increased adverse events was evident. In the MONMD study, "a few cases of diarrhea" were reported that the authors attributed to use of ascorbic acid (750 mg/d) (26). In REACT, the frequency of reported side effects did not differ between the antioxidants and placebo groups (27). In AREDS, skin yellowing was more frequently reported by the antioxidant group than the placebo group (8.3% compared with 6.1% [$P = 0.001$] in the cataract study and 8.3% compared with 6.0% [$P = 0.008$] in the age-related macular degeneration study) (28, 29). In a feasibility trial in China, participants received combinations of retinol, 25 000 IU; β-carotene, 50 mg; α-tocopherol, 800 IU; and selenium, 400 μg. Such symptoms as broken nails and skin yellowing were reported to be generally improved in the groups receiving multivitamin and mineral supplements (31).

One case report documented the occurrences of rash with an excessive dose of niacin (240 mg, of which 40 mg was from multivitamin supplements) (32). This report

showed a dose–response relationship, recurrence after rechallenge, and symptom disappearance after discontinuation of challenge; provided evidence on supplement use; and discussed a lack of alternative cause (32). The other 2 reports did not address any of the causality criteria (33, 34) (**Appendix Table 4**).

Discussion

In the Linxian and SU.VI.MAX studies, the types of vitamin and mineral supplements overlapped and the doses were similar (1 to 2 times the U.S. Recommended Daily Allowance). The efficacy for cancer prevention differed somewhat but had similar implications (18, 20, 23, 24). Whereas the multivitamin and mineral supplements used in the Linxian trial reduced the mortality rate from cancer by 21% in women and 7% in men, the efficacy of the supplement use in the SU.VI.MAX study in reducing cancer incidence was evident only in men. This sex-dependent efficacy may be attributed to the different nutritional status of the study samples: The Linxian sample had generally poor nutritional status, and men in the SU.VI.MAX study

Table 3. **Grade of the Evidence on the Efficacy of Multivitamin and Mineral Supplements in Primary Prevention of Chronic Disease***

Criteria	Evidence Grade on the Efficacy of Multivitamin and Mineral Supplements				
	Cancer: Linxian General Population Trial (18, 20), SU.VI.MAX (23, 24)	Cardiovascular Disease: Linxian General Population Trial (21), SU.VI.MAX (23)	Hypertension: Linxian General Population Trial (21), SU.VI.MAX (25)	Cataract: REACT (27), Linxian General Population Study (22), AREDS (28), MONMD (26)	Age-Related Macular Degeneration: AREDS (29), MONMD (26)
Total patients studied, *n*	42 325	42 325	34 670	10 354	3580
Types of study	RCTs	RCTs	RCTs	RCTs	RCTs
Grade for quality, consistency, and directness of evidence					
Were study designs randomized trials (high quality), nonrandomized controlled trials (medium quality), or observational studies (low quality)?	4	4	4	4	4
Did the studies have serious (–1), very serious (–2), or no (0) limitations in quality?	–1	–1	–2	0	0
Did the studies have important inconsistency? (–1)	0	0	0	0	0
Was there some (–1) or major (–2) uncertainty about the directness or extent to which the participants, interventions, and outcomes are similar to those of interest?	–2	–2	–2	–1	–1
Were data imprecise or sparse? (–1)	–1	–1	–1	–1	–1
Did the studies have a high (–1) or low (0) probability of reporting bias?	0	0	0	0	0
Did the studies show minimal (0), strong (1), or very strong (2) evidence of an association between the intervention and recruitment outcomes?†	0	0	0	0	0
Did the studies have evidence (1) or no evidence (0) of a dose–response gradient?	0	0	0	0	0
Did the studies have unadjusted plausible confounders that would have reduced the magnitude of the observed association (1), or were no such confounders present (0)?	1	1	1	0	0
Overall evidence grade	1	1	0	2	2
Overall evidence grade (high, medium, low, or very low)	Very low	Very low	Very low	Low	Low

* AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; REACT = Roche European American Cataract Trial; RCT = randomized, controlled trial; SU.VI.MAX= SUpplémentation en VItamines et Minéraux AntioXydants.
† "Strong" was defined as a significant relative risk or odds ratio > 2 on the basis of consistent evidence from ≥2 studies with no plausible confounders; "very strong" was defined as a significant relative risk or odds ratio > 5 on the basis of direct evidence, with no major threats to validity.

had suboptimal antioxidant status compared with women (23). Findings from these trials corroborated those of some observational studies that suggest benefits of fruits and vegetables on cancer prevention (35). However, these trials were not designed to test whether supplementation with multivitamins and minerals can replace a balanced, healthful diet in prevention of chronic disease.

The lack of benefits from supplementation in women in the SU.VI.MAX study might have been due to a threshold effect for those who had adequate dietary intake. However, women in the SU.VI.MAX study were on average 5 years younger than men, and the cardiovascular events in women were only 22.6% of the events in men (23). Hence, the study may have had insufficient statistical power to test for sex-specific efficacy. Furthermore, an important limitation of the SU.VI.MAX study (as well as several other studies in our review) was that participants often were permitted to use vitamin or mineral supplements other than the assigned study supplements, and data on self-selected supplement use were not reported. Most studies also did not provide information on such factors as medication use, which could have modified the effects of the nutrients. These limitations were rarely discussed in the literature. 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 from the Women's Health Study that 40% of the participants used multivitamin and mineral supplements in addition to the study supplements (vitamin E or placebo), and the relative risk for major cardiovascular disease in those receiving vitamin E compared with those receiving placebo was 0.88 (95% CI, 0.75–1.03) in women who did not use multivitamin supplements and 1.02 (95% CI, 0.84–1.25) among women who used supplements (36). Because multivitamin and mineral supplements are widely used by the general public in the United States, particularly among middle-aged or older persons, it would be difficult now to recruit persons representative of the general population into large-scale randomized, controlled trials of multivitamin and mineral supplementation.

For cataract prevention, AREDS was the largest study, and the findings were internally consistent in showing no benefit of use of multivitamin and mineral supplements (28). Whereas REACT found a deceleration in cataract progression in the U.S. study site, similar benefits were not seen in the United Kingdom study site. With respect to prevention of age-related macular degeneration, a high dose of vitamin E (400 IU) and zinc (2 times the upper intake level) was used in AREDS, and the benefit on preventing the progression to advanced age-related macular degeneration was limited to persons at high risk for advanced disease (29).

The implications of data on total mortality are uncertain. Total mortality is relevant to chronic disease prevention because it may provide a clue to potential harms. However, the risk for death should be considered on the basis of plausible biological mechanisms and the evidence on the effects of the nutrients on specific disorders. Because of the great heterogeneity across studies, we did not calculate an aggregate estimate for total mortality rate for the trials that reported such data. The 9% reduction in risk for total mortality by multivitamin and mineral supplements in the Linxian trial probably resulted from reductions in the rates of death from stomach cancer and stroke (18, 21). Similarly, the reduced total mortality rate among men in the SU.VI.MAX study may have reflected the 31% reduction in the incidence of cancer (23).

During our review process, we identified 2 studies that addressed changes in cognitive performance by daily use of a mixture of vitamins and minerals for 6 months or daily use of combined folic acid (800 μg), vitamin B_6 (3 mg), and vitamin B_{12} (500 μg) for 4 months (37, 38). No improvement in cognition was found. These studies, however, were subject to several limitations, such as uncertain clinical significance, short-term supplementation, the lack of a gold standard test, and training and learning of the cognitive tests.

Marked heterogeneity is found in the literature on the questions addressed in this review, in terms of differences in study design (for example, factorial design), targeted study sample (differing cultural, lifestyle, and genetic backgrounds), chemical forms and doses of supplements, and specific outcome measures. This heterogeneity made it difficult to synthesize results across studies and inappropriate to perform quantitative synthesis (such as meta-analysis). The differences in study samples were particularly problematic because no study has examined the efficacy of multivitamin and mineral supplements in prevention of cancer or cardiovascular disease in the general U.S. population. It is therefore difficult to determine whether the results of studies in China and France can be applied to the United States.

We did not include observational studies on the associations between multivitamin/mineral supplement use and risk for chronic diseases. Extensive confounding variables that a linear combination of the variables in regression models may not fully take into account can seriously compromise the internal validity of observational studies. In addition, in previous observational studies, validated tools were not developed for collecting accurate information on the various compositions and doses of commercially available multivitamin and mineral supplements. Furthermore, survey questionnaires used in observational studies often were not updated in a timely manner to capture the changes in compositions and doses within a product, and participants may have had errors and recall bias in reporting supplement use. Although previous observational studies did not show consistent evidence for or against a benefit of multivitamin and mineral supplements in prevention of cardiovascular disease (39), the inconsistency might have been primarily due to measurement errors and

confounding variables. We therefore considered it important to focus primarily on the strongest source of evidence: randomized, controlled trials.

The potential adverse effects of multivitamin and mineral supplements have not been systematically determined in well-designed randomized, controlled trials. Because of uncertainties regarding design (for example, doses and outcome monitoring) and ethical constraints, such studies may never be performed. A few adverse effects of nutrients in multivitamin preparations may be interpreted as common responses in the general population because they occurred with certain consistency in different primary prevention trials. Examples include skin yellowing with sustained consumption of β-carotene (40, 41); increases in serum triglyceride levels with vitamin A supplementation (42); and minor bleeding, particularly epistaxis, with vitamin E supplementation. However, there was no consistent evidence to suggest that vitamin E supplementation results in more serious bleeding events, such as hemorrhagic stroke (36, 43). With the caveat that available data are limited, a general conclusion is that consumption of multivitamin supplements for prolonged periods appears to be safe. In addition, some studies confirmed the adverse effects used to define the tolerable upper intake level, such gastrointestinal symptoms or diarrhea with vitamin C use. Although the tolerable upper intake level for this nutrient was set at 2 g/d, these symptoms could have occurred with a daily dose of 750 mg (26). A tolerable upper intake level represents a probability of a nutrient at a threshold level causing an adverse event in the general population, and the probability may vary with subgroups and different circumstances.

Case reports are subject to serious methodologic limitations. As a result, the overall strength of the evidence from case reports is weak. To date, data from case reports have been rarely used. In a previous systematic review of case reports of drug adverse effects, 83% of suspected adverse reactions were not further evaluated in confirmatory studies, and adverse effect alerts were not systematically incorporated into published drug reference information (44). In view of the rapidly increasing number of persons who choose to use dietary supplements, and given that many food products are fortified with several nutrients, the dietary intake of certain nutrients in the United States may well be greater than the Recommended Daily Allowances. Hence, it is important to study the level of intake among consumers. A systematic reporting and tracking system for adverse events would facilitate such studies.

It remains unproven that a balanced, healthful diet is superior to multivitamin and mineral supplement use. Because of feasibility and availability of resources, most randomized, controlled trials had approximately 5 years of follow-up, and some followed participants for only 2 to 3 years; however, chronic disease may take 10 to 20 years or longer to develop. It is unknown whether persons should take multivitamin and mineral supplements for a lifetime or during certain life stages to obtain benefits. To date, no published randomized, controlled trials have examined the efficacy of the commonly used over-the-counter multivitamin supplements, and the optimal compositions and doses of multivitamin and mineral supplements have not been systematically tested. Future research should be directed toward developing valid in vivo biomarkers that predict disease risk and measuring those biomarkers in randomized, controlled trials to guide the search for optimal composition and doses of multivitamin and mineral supplements. Additional research is also needed to examine how efficacy may vary by age, sex, duration of supplementation, adherence to intervention regimens, dietary patterns, and genetic polymorphisms. More attention should be given to nutrient–nutrient interactions and to controlling for cointerventions and use of medications and other dietary supplements.

In summary, data are scarce on the efficacy and safety of multivitamin and mineral supplement use in primary prevention of chronic disease in the general adult population. Evidence accumulated to date suggests potential benefits of multivitamin and mineral supplements in the primary prevention of cancer in persons with poor nutritional status or suboptimal antioxidant intake. However, the applicability of the findings to use of commercially available supplements by the general U.S. population is limited by differences in study sample and in the compositions and doses of the supplements. The evidence also indicates that multivitamin and mineral supplementation has no significant effect in the primary prevention of hypertension, cardiovascular disease, and cataracts but may slow progression of age-related macular degeneration among persons at high risk for advanced stages of the disease.

Our findings have important implications for clinical practice and public health policy. When people ask about the need for multivitamin and mineral supplements, clinical practitioners should be aware that although supplements are unlikely to have serious adverse effects, it remains unclear whether supplementation is efficacious in preventing cancer, cardiovascular disease, or other major chronic diseases and conditions in the general U.S. adult population. Clinical practitioners may need to consider other factors, such as pregnancy, for which folic acid supplementation is beneficial in preventing birth defects, and other special nutritional needs when making recommendations about use of multivitamin and mineral supplements. For public health policymakers, our conclusion is that the strength of evidence is insufficient to support the presence or the absence of a benefit from routine use of multivitamin and mineral supplements by adults in the United States for primary prevention of cancer, cardiovascular disease, hypertension, cataracts, or age-related macular degeneration, and that there are no data from randomized, controlled trials on the efficacy of multivitamin and mineral supplement use for preventing type 2 diabetes mellitus, Parkinson disease, dementia, hearing loss, osteoporosis, os-

teopenia, rheumatoid arthritis, osteoarthritis, nonalcoholic steatohepatitis, chronic renal insufficiency, chronic nephrolithiasis, HIV infection, hepatitis C, tuberculosis, or chronic obstructive pulmonary disease.

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Appendix Table 1. **Efficacy of Multivitamin and Mineral Supplement Use in Primary Prevention of Cancer***

Study (Reference)	Disease End Point	Study Supplement†	Participants, n‡			Disease Events, n‡			Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)	Comments
			Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients	Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients			
Linxian General Population Trial (18)	Total cancer incidence	Retinol + zinc	29 584	–	–	1298	–	–	1.00 (0.89–1.11)	–	
		Riboflavin + niacin							0.95 (0.85–1.06)	–	
		Vitamin C + molybdenum							1.06 (0.95–1.18)	–	
		β-Carotene + selenium + α-tocopherol							0.93 (0.83–1.03)	–	
	Gastric cancer incidence	Retinol + zinc	29 584	–	–	539	–	–	0.96 (0.81–1.14)	–	
		Riboflavin + niacin							1.04 (0.88–1.23)	–	
		Vitamin C + molybdenum							1.10 (0.92–1.30)	–	
		β-Carotene + selenium + α-tocopherol							0.84 (0.71–1.00)	–	
	Esophageal cancer incidence	Retinol + zinc	29 584	–	–	640	–	–	1.07 (0.92–1.25)	–	
		Riboflavin + niacin					–	–	0.86 (0.74–1.01)	–	
		Vitamin C + molybdenum					–	–	1.06 (0.91–1.24)	–	
		β-Carotene + selenium + α-tocopherol					–	–	1.02 (0.87–1.19)	–	
	Esophageal/cardia cancer incidence	Retinol + zinc	29 584	–	–	1075	–	–	1.05 (0.93–1.19)	–	
		Riboflavin + niacin							0.94 (0.83–1.06)	–	
		Vitamin C + molybdenum							1.06 (0.94–1.20)	–	
		β-Carotene + selenium + α-tocopherol							0.94 (0.84–1.06)	–	
	Total cancer death	Retinol + zinc	29 584	–	–	792	–	–	0.97 (0.85–1.12)	–	
		Riboflavin + niacin							0.98 (0.85–1.13)	–	
		Vitamin C + molybdenum							1.06 (0.92–1.21)	–	
		β-Carotene + selenium + α-tocopherol							0.87 (0.75–1.00)	–	
	Stomach cancer death	Retinol + zinc	29 584	–	–	331	–	–	1.03 (0.83–1.28)	–	
		Riboflavin + niacin							1.00 (0.81–1.24)	–	
		Vitamin C + molybdenum							1.09 (0.88–1.36)	–	

Appendix Table 1—**Continued**

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)	Comments
			Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients	Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients			
		β-Carotene + selenium + α-tocopherol							0.79 (0.64–0.99)	–	
	Esophageal cancer death	Retinol + zinc	29 584	–	–	360	–	–	0.93 (0.76–1.15)	–	
		Riboflavin + niacin							0.90 (0.73–1.11)	–	
		Vitamin C + molybdenum							1.05 (0.85–1.29)	–	
		β-Carotene + selenium + α-tocopherol							0.96 (0.78–1.18)	–	
	Esophageal/gastric cardia cancer death	Retinol + zinc	29 584	–	–	613	–	–	1.04 (0.89–1.22)	–	
		Riboflavin + niacin							0.95 (0.81–1.11)	–	
		Vitamin C + molybdenum							1.06 (0.90–1.24)	–	
		β-Carotene + selenium + α-tocopherol							0.90 (0.77–1.05)	–	
Linxian General Population Trial: end-of-trial endoscopy survey (20)	Esophageal and gastric cancer and dysplasia	Retinol + zinc	391	197	194	60	28	32	–	0.83 (0.47–1.46)	Adjusted for age, sex, smoking, and alcohol use
		Riboflavin + niacin		194	197		34	26	–	1.39 (0.79–2.44)	Adjusted for age, sex, smoking, and alcohol use
		Vitamin C + molybdenum		206	185		37	23	–	1.61 (0.91–2.86)	Adjusted for age, sex, smoking, and alcohol use
		β-Carotene + selenium + α-tocopherol		177	214		25	35	–	0.83 (0.47–1.46)	Adjusted for age, sex, smoking, and alcohol use
	Esophageal and gastric cancer	Retinol + zinc	391	197	194	31	13	18	–	0.61 (0.29–1.31)	
		Riboflavin + niacin		194	197		18	13	–	1.46 (0.68–3.11)	
		Vitamin C + molybdenum		206	185		21	10	–	1.99 (0.90–4.41)	
		β-Carotene + selenium + α-tocopherol		177	214		12	19	–	0.79 (0.36–1.69)	

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Appendix Table 1—**Continued**

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)	Comments
			Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients	Total	Supplements with Specified Nutrients	Supplements without Specified Nutrients			
SU.VI.MAX (23)	Cancer incidence	Vitamin C + vitamin E + β-carotene + selenium + zinc	12 741	6364	6377	562	267	295	0.90 (0.76–1.06)		$P = 0.02$ for the interaction between sex and randomized group
	Women only		7713	3844	3869	350	179	171	1.04 (0.85–1.29)	–	
	Men only		5028	2520	2508	212	88	124	0.69 (0.53–0.91)§	–	
SU.VI.MAX (24)	Prostate cancer incidence	Vitamin C + vitamin E + β-carotene + selenium + zinc	5034	2522	2512	103	49	54	0.88 (0.60–1.29)	–	Men only
			4563	2293	2270	51	18	33	0.52 (0.29–0.92)§	–	In men with initial PSA level < 3.0 μg/L
			292	149	143	50	31	19	1.54 (0.87–2.72)	–	In men with initial PSA level ≥ 3.0 μg/L

* – = not reported; PSA = prostate-specific antigen; SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants.
† Unless otherwise specified, comparisons were made between groups receiving the combination of the listed nutrients and the groups receiving combinations of placebo or nutrients other than the nutrients listed.
‡ The total number is presented (when available) if the number in each comparison group was not reported.
§ $P < 0.01$.

Appendix Table 2. Efficacy of Multivitamin and Mineral Supplement Use in Primary Prevention of Cardiovascular Disease and Hypertension*

Study (Reference)	Disease End Point	Study Supplement	Participants, *n*			Disease Events, *n*		Incidence of Disease End Point, *n per 1000 persons*		Prevalence of Disease End Point, %		Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		
Linxian General Population Trial (21)	Death from stroke	Retinol + zinc + riboflavin + niacin vs. placebo	29 584†	–	–	66	77	3.5	4.1	–	–	0.85 (0.61–1.18)	–
		Retinol + zinc + vitamin C + molybdenum vs. placebo				71	77	3.8	4.1	–	–	0.91 (0.66–1.27)	–
		Retinol + zinc + β-carotene + selenium + α-tocopherol vs. placebo				55	77	2.9	4.1	–	–	0.71 (0.50–1.00)	–
		Riboflavin + niacin + vitamin C + molybdenum vs. placebo				60	77	3.2	4.1	–	–	0.78 (0.55–1.09)	–
		Riboflavin + niacin + β-carotene + selenium + α-tocopherol vs. placebo				58	77	3.1	4.1	–	–	0.75 (0.53–1.05)	–
		Vitamin C + molybdenum + β-carotene + selenium + α-tocopherol vs. placebo				67	77	3.6	4.1	–	–	0.86 (0.62–1.20)	–
		Retinol + zinc + riboflavin + niacin + vitamin C + molybdenum + β-carotene + selenium + α-tocopherol vs. placebo				69	77	3.7	4.1	–	–	0.88 (0.64–1.22)	–
		Retinol + zinc				–	–	–	–	–	–	0.99 (0.84–1.18)	–
		Riboflavin + niacin										0.94 (0.79–1.11)	–

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Appendix Table 2—**Continued**

Study (Reference)	Disease End Point	Study Supplement	Participants, *n*			Disease Events, *n*		Incidence of Disease End Point, *n per 1000 persons*		Prevalence of Disease End Point, %		Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		
		Vitamin C + molybdenum†										1.04 (0.88–1.24)	–
		β-Carotene + selenium + α-tocopherol										0.91 (0.76–1.07)	–
	Hypertension	Retinol + zinc + riboflavin + niacin vs. placebo	29 584†	–	–	–	–	–	–	–	–	Isolated systolic: 1.08 (0.85–1.38)	–
												Isolated diastolic: 0.94 (0.70–1.26)	–
												Both systolic and diastolic: 1.08 (0.87–1.35)	–
		Retinol + zinc + vitamin C + molybdenum vs. placebo				–	–	–	–	–	–	Isolated systolic: 1.11 (0.88–1.41)	–
												Isolated diastolic: 0.94 (0.70–1.26)	–
												Both systolic and diastolic: 0.93 (0.74–1.16)	
		Retinol + zinc + β-carotene + selenium + α-tocopherol vs. placebo				–	–	–	–	–	–	Isolated systolic: 1.07 (0.85–1.36)	–
												Isolated diastolic: 1.23 (0.93–1.62)	–
												Both systolic and diastolic: 1.01 (0.81–1.26)	–
		Riboflavin + niacin + vitamin C + molybdenum vs. placebo				–	–	–	–	–	–	Isolated systolic: 0.96 (0.76–1.22)	–
												Isolated diastolic: 0.68 (0.50–0.94)	–
												Both systolic and diastolic: 0.92 (0.74–1.15)	–

Appendix Table 2—**Continued**

Study (Reference)	Disease End Point	Study Supplement	Participants, *n*			Disease Events, *n*		Incidence of Disease End Point, *n per 1000 persons*		Prevalence of Disease End Point, %		Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		
		Riboflavin + niacin + β-carotene + selenium + α-tocopherol vs. placebo				–	–	–	–	–	–	Isolated systolic: 0.98 (0.77–1.25)	–
												Isolated diastolic: 0.90 (0.67–1.22)	–
												Both systolic and diastolic: 1.03 (0.82–1.28)	–
		Vitamin C + molybdenum + β-carotene + selenium + α-tocopherol vs. placebo				–	–	–	–	–	–	Isolated systolic: 0.93 (0.73–1.19)	–
												Isolated diastolic: 1.13 (0.86–1.50)	–
												Both systolic and diastolic: 0.85 (0.67–1.06)	–
		Retinol + zinc + riboflavin + niacin + vitamin C + molybdenum + β-carotene + selenium + α-tocopherol vs. placebo				–	–	–	–	–	–	Isolated systolic: 0.91 (0.71–1.16)	–
												Isolated diastolic: 1.10 (0.84–1.47)	–
												Both systolic and diastolic: 0.97 (0.77–1.20)	–
		Retinol + zinc				–	–	–	–	–	–	Isolated systolic: 1.07 (0.96–1.21)	–
												Isolated diastolic: 1.13 (0.98–1.31)	–
												Both systolic and diastolic: 1.05 (0.94–1.18)	–

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Appendix Table 2—Continued

Study (Reference)	Disease End Point	Study Supplement	Participants, *n*			Disease Events, *n*		Incidence of Disease End Point, *n per 1000 persons*		Prevalence of Disease End Point, %		Unadjusted Relative Risk (95% CI)	Unadjusted Odds Ratio (95% CI)
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		
		Riboflavin + niacin				–	–	–	–	–	–	Isolated systolic: 0.95 (0.85–1.08)	–
												Isolated diastolic: 0.84 (0.73–0.98)	–
												Both systolic and diastolic: 1.05 (0.94–1.18)	–
		Vitamin C + molybdenum				–	–	–	–	–	–	Isolated systolic: 0.94 (0.84–1.07)	–
												Isolated diastolic: 0.95 (0.82–1.10)	–
												Both systolic and diastolic: 0.89 (0.79–0.99)	–
		β-Carotene + selenium + α-tocopherol				–	–	–	–	–	–	Isolated systolic: 0.93 (0.83–1.05)	–
												Isolated diastolic: 1.23 (1.06–1.42)	–
												Both systolic and diastolic: 0.98 (0.87–1.09)	–
SU.VI.MAX (23)	Ischemic cardiovascular disease incidence	Vitamin C + vitamin E + β-carotene + selenium + zinc vs. placebo		6364	6377	134	137	–	–	–	–	0.97 (0.77–1.20)	–
SU.VI.MAX (25)	Hypertension‡	Vitamin C + vitamin E + β-carotene + selenium + zinc vs. placebo	Women	1502	1431	–	–	–	–	Year 1: 19.4	Year 1: 20.8	–	1.10 (0.95–1.29)
							–	–	–	Year 6: 34.6	Year 6: 32.4	–	
			Men	1117	1431	–	–	–	–	Year 1: 44.7	Year 1: 42.0	–	1.04 (0.87–1.23)
										Year 6: 54.6	Year 6: 53.8		

* Comparisons were made between the groups receiving the combination of the listed nutrients and groups receiving combinations of placebo or nutrients other than the nutrients listed. –= not reported; SU.VI.MAX = SUpplémentation en VItamines et Minéraux AntioXydants.
† The number of participants in each randomized group was not reported.
‡ Defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive drug use at the end of the study.

Appendix Table 3. Efficacy of Multivitamin and Mineral Supplement Use in Primary Prevention of Cataracts and Age-Related Macular Degeneration*

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Prevalence of Disease End Point		Unadjusted Odds Ratio (95% or 99% CI)§	Change in Outcome Measure		Comment
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	All Participants	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		Treatment Group	Placebo Group	
Linxian General Population Trial: cataracts (22)	Prevalence of nuclear cataracts	Retinol + zinc	3249	1628	1621	–	–	–	0.120	0.151	0.77 (0.58–1.02)	–	–	
		Riboflavin + niacin		1623	1626	–	–	–	0.107	0.169	Overall, 0.59 (0.45–0.79); 0.99 (0.62–1.59) in persons age 55–64 y; 0.45 (0.31–0.64) in persons age 65–74 y	–	–	
		Vitamin C + molybdenum		1654	1595	–	–	–	0.121	0.150	0.78 (0.59–1.04)	–	–	
		β-Carotene + selenium + α-tocopherol		1617	1632				0.146	0.125	1.19 (0.90–1.59)	–	–	
	Prevalence of cortical cataracts	Retinol + zinc		1628	1621	–	–	–	0.342	0.325	1.08 (0.92–1.27)	–	–	
		Riboflavin + niacin		1623	1626	–	–	–	0.342	0.325	1.08 (0.92–1.27)	–	–	
		Vitamin C + molybdenum		1654	1595	–	–	–	0.325	0.342	0.92 (0.79–1.09)	–	–	
		β-Carotene + selenium + α-tocopherol		1617	1632	–	–	–	0.330	0.338	0.96 (0.82–1.13)	–	–	
	Prevalence of posterior subcapsular cataracts	Retinol + zinc		1628	1621	–	–	–	0.008	0.013	0.59 (0.31–1.14)	–	–	
		Riboflavin + niacin		1623	1626	–	–	–	0.016	0.006	2.64 (1.31–5.35)	–	–	
		Vitamin C + molybdenum		1654	1595	–	–	–	0.011	0.009	1.25 (0.65–2.38)	–	–	
		β-Carotene + selenium + α-tocopherol		1617	1632	–	–	–	0.013	0.008	1.56 (0.81–3.00)	–	–	

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Appendix Table 3—Continued

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Prevalence of Disease End Point		Unadjusted Odds Ratio (95% or 99% CI)§	Change in Outcome Measure		Comment
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	All Participants	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		Treatment Group	Placebo Group	
MONMD (26)	Acuity of left eyes, distance visual acuity [logMAR]	β-Carotene + vitamin E + vitamin C + zinc picolinate + selenium + vitamin B_2 + chromium + nonvitamin/ mineral nutrients vs. placebo	71	39	32	–	–	–	–	–	–	From 0.17 to 0.19 logMAR‖	From 0.26 to 0.35 logMAR	No difference between randomized groups in refraction, metamorphosia, and Lens Opacities Classification System II readings on nuclear color, nuclear opalescence, and posterior subcapsular opacities; unexpected cortical cataractogenic effect for right eyes in the multivitamin group
	Acuity of left eyes, near visual acuity [M print]		71	39	32	–	–	–	–	–	–	From 0.77 M to 0.89 M¶	From 1.29 M to 2.03 M	
REACT (27)	Anterior percentage pixel opaque (primary end point)	β-Carotene + vitamin C + *all-rac* α-tocopherol vs. placebo	158	81	77	–	–	–	–	–	–	Baseline, 5.7 ± 1.6, last, 7.3 ± 2.0; mean change from baseline, 1.7 ± 1.0**	Baseline, 5.0 ± 1.4; last, 8.3 ± 2.2; mean change from baseline, 3.3 ± 1.4	Unfavorable changes in secondary outcomes were smaller in the active supplement group, but none was significantly different from placebo group.
AREDS: cataract (28)	Total lens events	Vitamin C + vitamin E + β-carotene	4596	2286	2310	1541	756	785	–	–	0.97 (0.84–1.11)	–	–	Adjustments for several potential confounders did not materially alter results
	Cataract surgery		4596	2286	2310	675	–	–	–	–	0.94 (0.77–1.14)	–	–	
	Severe lens event		4596	2286	2310	991	–	–	–	–	0.92 (0.76–1.12)	–	–	
	Nuclear event	Vitamin C + vitamin E + β-carotene	4331	–	–	1674	–	–	–	–	0.98 (0.84–1.14)	–	–	

Appendix Table 3—Continued

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Prevalence of Disease End Point		Unadjusted Odds Ratio (95% or 99% CI)§	Change in Outcome Measure		Comment
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	All Participants	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		Treatment Group	Placebo Group	
		Vitamin C + vitamin E + β-carotene vs. placebo	2715	–	–	1027	–	–	–	–	1.00 (0.82–1.22)	–	–	
	Cortical event	Vitamin C + vitamin E + β-carotene	4329	–	–	1058	–	–	–	–	0.99 (0.82–1.19)	–	–	
		Vitamin C + vitamin E + β-carotene vs. placebo	2715	–	–	625	–	–	–	–	0.91 (0.71–1.15)	–	–	
	Posterior subcapsular event	Vitamin C + vitamin E + β-carotene	4329	–	–	888	–	–	–	–	0.94 (0.78–1.14)	–	–	
		Vitamin C + vitamin E + β-carotene vs. placebo	2715	–	–	535	–	–	–	–	0.91 (0.70–1.17)	–	–	
	Lens event in eyes without opacities	Vitamin C + vitamin E + β-carotene (comparison group not specified)	823	–	–	—	–	–	–	–	0.85 (0.55–1.33)	–	–	Among those with no or minimal opacity in at least 1 eye at enrollment
	Loss of visual acuity score of 15 letters or more	Vitamin C + vitamin E + β-carotene vs. placebo	–	537	580	172	–	–	–	–	1.03 (0.63–1.66)	–	–	Among those without age-related macular degeneration at enrollment
AREDS: age-related macular degeneration (29)	Progression to advanced age-related macular degeneration (among those in age-related macular degeneration categories 2, 3, or 4)	Vitamin C + vitamin E + β-carotene	3609	–	–	803	–	–	–	–	0.87 (0.70–1.09)	–	–	

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Appendix Table 3—**Continued**

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Prevalence of Disease End Point		Unadjusted Odds Ratio (95% or 99% CI)§	Change in Outcome Measure		Comment
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	All Participants	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		Treatment Group	Placebo Group	
		Vitamin C + vitamin E + β-carotene vs. placebo									0.80 (0.59–1.09)	–	–	Analysis adjusted for sex, age, race, and category, and smoking status at enrollment, did not materially alter the size or direction of estimates
		Vitamin C + vitamin E + β-carotene + zinc vs. placebo									0.72 (0.52–0.98)††	–	–	
	Loss of visual acuity score of ≥ 15 letters from baseline (among those in age-related macular degeneration categories 2, 3, or 4)	Vitamin C + vitamin E + β-carotene	3597	–	–	1197	–	–	–	–	0.90 (0.74–1.09)	–	–	
		Vitamin C + vitamin E + β-carotene vs. placebo									0.88 (0.67–1.15)	–	–	
		Vitamin C + vitamin E + β-carotene + zinc vs. placebo									0.79 (0.60–1.04)‡‡	–	–	
	Progression to advanced age-related macular degeneration (among those in age-related macular degeneration categories 3 or 4)	Vitamin C + vitamin E + β-carotene	2556	–	–	775	–	–	–	–	0.83 (0.66–1.06)§§	–	–	

Appendix Table 3—Continued

Study (Reference)	Disease End Point	Study Supplement†	Participants, *n*‡			Disease Events, *n*‡			Prevalence of Disease End Point		Unadjusted Odds Ratio (95% or 99% CI)§	Change in Outcome Measure		Comment
			Total	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	All Participants	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients	Received Supplements with Specified Nutrients	Received Supplements without Specified Nutrients		Treatment Group	Placebo Group	
		Vitamin C + vitamin E + β-carotene vs. placebo	2549	–	–	1022	–	–	–	–	0.76 (0.55–1.05)‡‡	–	–	
		Vitamin C + vitamin E + β-carotene + zinc vs. placebo									0.66 (0.47–0.91)‖‖	–	–	
	Loss of visual acuity score of ≥ 15 letters from baseline (among those in age-related macular degeneration categories 3 or 4)	Vitamin C + vitamin E + β-carotene									0.86 (0.70–1.07)	–	–	
		Vitamin C + vitamin E + β-carotene vs. placebo									0.85 (0.63–1.14)	–	–	
		Vitamin C + vitamin E + β-carotene + zinc vs. placebo									0.73 (0.54–0.99)¶¶	–	–	

* –= not reported; AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; REACT= Roche European American Cataract Trial.
† Unless otherwise specified, comparisons were made between groups receiving the combination of the listed nutrients and groups receiving combinations of placebo or nutrients other than the nutrients listed.
‡ Total number was presented (when available) if the number in each comparison group was not reported.
§ 95% CIs are reported for the Linxian General Population Trial, and 99% CIs are reported for AREDS.
‖ Difference from placebo, −0.7 logMAR ($P = 0.03$).
¶ Difference from placebo, −0.62 ($P = 0.07$).
** Difference between groups, −1.6 ($P = 0.05$).
†† $P = 0.007$.
‡‡ $P = 0.03$.
§§ $P = 0.05$.
‖‖ $P = 0.001$.
¶¶ $P = 0.008$.

Appendix Table 4. **Adverse Effects of Multivitamin and Mineral Supplement Use***

Study, Year (Reference)	Study Design	Type of Supplementation	Frequency and Duration of Use	Adverse Effect	Occurrence of Adverse Effects, *n* (%)		Relative Risk (99% CI)	*P* Value	Comment
					Treatment Group	Placebo Group			
REACT, 2002 (27)	RCT	β-Carotene, 18 mg + vitamin C, 750 mg + *all-rac* α-tocopherol acetate, 600 mg vs. placebo (corn oil)	3 divided doses daily (with meals) for 3 y	Intercurrent illness	107	84	–	NS	Persons who completed the study and those who dropped out did not differ; proportions of early dropouts and late dropouts were very similar; frequency of side effects (defined by the World Health Organization) did not differ between randomized groups
				Death	9 (coronary thrombosis, renal-cell cancer, throat cancer, carcinomatosis, esophagitis, sudden death, aneurysm, pulmonary fibrosis)	3 (coronary thrombosis, bile duct cancer, lung cancer)	–	0.07	
				Skin yellowing	–	–	–	–	6 persons overall were reported to have skin yellowing, but the number in each randomized group was not specified
AREDS: cataract study, 2001 (28)	RCT	Vitamin C, 500 mg + vitamin E, 400 IU + β-carotene, 15 mg vs. placebo	2 divided doses (with meals) for 6.3 y	Hospitalization (due to mild to moderate symptoms)	173 (7.3)	221 (9.3)	–	0.01	No clinically or statistically significant difference in changes in cholesterol level or hematocrit
				Primary adverse effect (caused by skin and subcutaneous tissue problems)	56 (2.4)	21 (0.9)	–	<0.001	
				Change in skin color	203 (8.6)	146 (6.1)		<0.01	
				Chest pain	467 (19.8)	541 (22.8)		0.01	
				Death	251	240	1.06 (0.84–1.33)	0.53	Similar results for analysis of antioxidants only vs. placebo
AREDS: age-related macular degeneration study, 2001 (29)	RCT	Antioxidants (vitamin C, 500 mg + vitamin E, 400 IU + β-carotene, 15 mg) vs. no antioxidants	2 divided doses (with meals) for 6.3 y	Yellow skin	151 (8.3)	106 (6.0)	–	0.008	No clinically or statistically significant difference in changes in cholesterol level or hematocrit

Appendix Table 4—**Continued**

Study, Year (Reference)	Study Design	Type of Supplementation	Frequency and Duration of Use	Adverse Effect	Occurrence of Adverse Effects, *n* (%)		Relative Risk (99% CI)	*P* Value	Comment
					Treatment Group	Placebo Group			
				Hospitalization due to mild to moderate symptoms (e.g., chest pain or discomfort, vasovagal episode, fever)	135 (7.4)	181 (10.1)	–	0.005	
				Hospitalization due to infections	29 (1.6)	15 (0.8)	–	0.04	
				Skin and subcutaneous tissue conditions	41 (2.2)	18 (1.0)	–	0.003	
				Circulatory adverse experience	6 (0.3)	15 (0.8)	–	0.04	
				Mortality	216	194	1.10 (0.85–1.42) for antioxidants vs. no antioxidants	0.35	Similar results when comparing antioxidants and placebo
MONMD, 1996 (26)	RCT	β-Carotene, 20 000 IU + vitamin E, 200 IU + vitamin C, 750 mg + zinc picolinate, 12.5 mg + selenium, 50 μg + vitamin B_2, 25 mg + chromium, 100 μg + non-vitamin/mineral nutrients vs. placebo (starch)	2 divided doses for 18 mo	Diffuse whole-body maculopapular rash	1	–	–	–	Possible adverse reaction or cross-reaction with hypertensive medication (hydrochlorothiazide and atenolol)
				Transient diarrhea	–	–	–	–	No significant difference between randomized groups in changes in diarrhea, constipation, nausea, vomiting, and dyspeptic symptoms
Xuan et al., 1991 (31)	RCT	Placebo, A, B, AB, C, AC, BC, ABC, D, AD, BD, ABD, CD, ACD, BCD, and ABCD, where A = retinol, 25 000 IU/d; B = β-carotene, 50 mg/d; C = α-tocopherol, 800 IU/d; D = selenium, 400 μg/d	Once daily for 6 mo	See comments	See comments	See comments	–	–	83% ever smoked; median age, 54 y; symptoms (muscle cramps, diarrhea, decreased appetite, runny nose, joint pain, lip chapping, yellowing of skin, broken nails, hair loss, tingling in limbs, headache, lethargy) were generally improved in the intervention group

Continued on following page

Appendix Table 4—**Continued**

Study, Year (Reference)	Study Design	Type of Supplementation	Frequency and Duration of Use	Adverse Effect	Occurrence of Adverse Effects, *n* (%)		Relative Risk (99% CI)	*P* Value	Comment
					Treatment Group	Placebo Group			
				Allergic dermatitis	1	–	–	–	These dropout cases (1 with allergic dermatitis and 2 with continued gastric pain) may have occurred for reasons related to supplement use, but the types of supplements used were not reported
				Gastric pain	2				
Grouhi and Sussman 2000 (32)	Case report	Niacin, 240 mg (from multivitamin, B-complex, and antinausea tablets)	NS	Pseudoallergic toxic reaction	1 (nonsmoker, age 40 y)	–	–	–	Multivitamin contained calcium, 100 mg; vitamin E, 800 IU; vitamin C, 300 mg; niacin, 40 mg; and selenium, 200 μg; the case-patient also took echinacea, barley green, licorice root, and Chinese herbs
Gulati et al., 1999 (33)	Case report	Vitamin A acetate + vitamin E acetate + vitamin C + vitamin B_2 + copper sulfate + zinc sulfate + selenium dioxide monohydrate	NS	Fixed drug eruption (a pattern of cutaneous drug reaction which occurs at the same site or sites each time the particular drug is administered)	1 (Indian, age 58 y)	–	–	–	
Ohtake et al., 2005 (34)	Case report	Vitamin C, 6000 mg + calcium lactate, 1000 mg + vitamin D, 250 IU + laxatives	Once daily for 10 y	Severe proximal tubular dysfunction, calcified lesion, hypokalemic nephropathy	1 (Japanese, age 48 y)	–	–	–	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

* AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; NS = not significant; RCT = randomized, controlled trial; REACT = Roche European American Cataract Trial.