Multivitamin/Mineral Supplements and Prevention of Chronic Disease: Executive Summary

Han-Yao Huang, Benjamin Caballero, Stephanie Chang, Anthony J Alber, Richard D Semba, Christine Schneyer, Renee F Wilson, Ting-Yuan Cheng, Gregory Prokopowicz, George J Barnes II, Jason Vassy, and Eric B Bass

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

2 Address correspondence to H-Y Huang, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E-6144, Baltimore, MD 21205-2223. E-mail: hyhuang@jhsph.edu.
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 steatohepatitis, non-alcoholic fatty-liver disease; (h) chronic renal insufficiency, chronic nephropathiasis; 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 multitamins 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 group 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 D₃ (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 D₃ (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 supple-
ments as well as calcium and vitamin D supplements up to 1000
mg and 600 IU per day, respectively, and thus the WHI partici-
pants 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 multivita-
min/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 supplemen-
tation 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 chil-
dren in a small randomized controlled trial. More recent trials
have not clarified this issue because they targeted deficient pop-
ulations and/or included other micronutrients in the intervention
formulation.

**FUTURE RESEARCH**

In vitro studies and animal models have helped us to under-
stand 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 knowl-
dge 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 func-
tion 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 ran-
domized controlled trials on antioxidants was derived from ep-
idemiological 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 micronu-
trients. 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 partic-
ipants’ 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 supple-
ments. Furthermore, collective study findings also may not apply
to every individual. Additional research should be done, partic-
ularly in existing randomized controlled trials, to examine how
efficacy may vary by age, time since trial enrollment to diagno-
sis, self-selected supplement use, dietary patterns, disease his-
tory, medication use, and/or genetic polymorphisms.

With many food products being fortified with several nutri-
ents, 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/min-
eral supplement use or more generally, dietary supplement use,
in the general population. Such research should also consider subpop-
ulations for which these parameters may differ.