



Complete Summary

GUIDELINE TITLE

NIH State-of-the-Science Conference Statement on multivitamin/mineral supplements and chronic disease prevention.

BIBLIOGRAPHIC SOURCE(S)

NIH State-of-the-Science Conference Statement on multivitamin/mineral supplements and chronic disease prevention. NIH Consens State Sci Statements 2006 May 15-17;23(2):1-30. [27 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Chronic disease, including:

- Cancer
- Cardiovascular disease
- Cataract
- Age-related macular degeneration
- Osteoporosis

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Family Practice
Geriatrics
Internal Medicine
Nutrition
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide health care providers, patients, and the general public with a responsible assessment of currently available data on multivitamin/mineral supplements and chronic disease prevention
- To assess the available scientific evidence on the benefits of multivitamin/multimineral (MVM) supplements used for chronic disease prevention, identifying the gaps in the evidence, and recommending an appropriate research agenda to meet the shortfalls

TARGET POPULATION

The general population of adults and children

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

INTERVENTIONS AND PRACTICES CONSIDERED

Vitamin and mineral supplements for prevention of chronic diseases, including:

- Single vitamin
- Single-mineral supplement
- Multivitamin/mineral supplement containing three or more vitamins and minerals but no herbs, hormones, or drugs

MAJOR OUTCOMES CONSIDERED

- Effectiveness and safety of multivitamin/mineral (MVM) supplement use
- Public assurance

- Vitamin/mineral supplementation vs. fortification
- Prevalence of MVM use in the United States
- MVM use and general health outcomes

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): A systematic review of the literature was prepared by the Johns Hopkins University Evidence-based Practice Center for the Agency for Healthcare Research and Quality for use by the National Institutes of Health (see the "Availability of Companion Documents" field).

A systematic approach was used 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.

Evidence on the efficacy and the safety of individual vitamins and minerals that are often included in multivitamin/mineral supplements was considered. 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 beta-carotene.

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

Articles published from 1966 through February 2006 using MEDLINE,[®] EMBASE,[®] and the Cochrane database were searched. 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.

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, observational studies for the Key questions about the safety of vitamin/mineral supplements were included. Differences in opinions regarding abstract inclusion or exclusion were resolved through consensus adjudication.

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.

Refer to Chapter 2 in the Evidence Report (see the "Availability of Companion Documents" field) for further information.

NUMBER OF SOURCE DOCUMENTS

Included Studies: n=63

- Key Question (KQ) 1 = 11
- KQ 2 = 10
- KQ3 = 44
- KQ4 = 24

(Articles can apply to more than one Key Question)

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): A systematic review of the literature was prepared by the Johns Hopkins University Evidence-based Practice Center for the Agency for Healthcare Research and Quality for use by the National Institutes of Health (see the "Availability of Companion Documents" field).

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.

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. A systematic approach for extracting data from the studies was used to minimize the risk of bias in how we extracted data from eligible studies. By creating standardized forms for data extraction, the aim was to maximize consistency in identifying all pertinent data available for synthesis.

At the completion of review, EPC staff graded the quantity, quality and consistency of the best available evidence addressing Key Questions 1 and 3 by adapting an evidence grading scheme recommended by the GRADE Working Group. Evidence bodies pertaining to each Key Question were classified into four basic categories: 1) "high" grade (indicating confidence that further research is very unlikely to change EPC staff's confidence in the estimated effect in the abstracted literature); 2) "moderate" grade (indicating that further research is likely to have an important impact on confidence in the estimates of effects and may change the estimates in the abstracted literature); 3) "low" grade (indicating further research is very likely to have an important impact on confidence in the estimates of effects and is likely to change the estimates in the abstracted literature); and 4) "very low" grade (indicating any estimate of effect is very uncertain).

Refer to Chapter 2 in the Evidence Report (see the "Availability of Companion Documents" field) for further information.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Office of Dietary Supplements and the Office of Medical Applications of Research of the National Institutes of Health convened a State-of-the-Science Conference on Multivitamin/Mineral (MVM) Supplements and Chronic Disease Prevention, held on May 15–17, 2006, in Bethesda, Maryland. The goal of the conference was to assess the evidence available on MVM use and outcomes for chronic disease prevention in the generally healthy population of adults and to make recommendations for future research. The conference focused on vitamins and minerals and did not deal with botanicals, hormones, or other supplements. It also did not address the treatment of vitamin or mineral deficiencies. Except for considerations of safety, the conference also did not review issues of primary relevance to pregnant women or children.

The Agency for Healthcare Research and Quality Evidence-based Practice Center established a team and a work plan to develop an 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.

Evidence-based Practice Center (EPC) staff worked with the technical experts and representatives of the Office of Medical Applications of Research and the Agency for Healthcare Research and Quality (AHRQ) to develop the following 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?

Evidence was presented by experts and a systematic review of the literature prepared by The Johns Hopkins University EPC, through the AHRQ. Scientific evidence was given precedence over anecdotal experience.

An impartial, independent panel was charged with reviewing the available published literature in advance of the conference, including a systematic literature review commissioned through the AHRQ. The non-Department of Health and Human Services, non-advocate 13-member panel drafted its statement based on scientific evidence presented in open forum and on published scientific literature. The draft statement was presented on the final day of the conference and circulated to the audience for comment. The panel released a revised statement later that day at <http://consensus.nih.gov>.

Refer to the original guideline document and Chapter 2 in the Evidence Report (see the "Availability of Companion Documents" field) for further information.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note: For the purpose of this statement, the term *MVM* refers to any supplement containing three or more vitamins and minerals but no herbs, hormones, or drugs, with each component at a dose less than the tolerable upper level determined by the Food and Nutrition Board—the maximum daily intake likely to pose no risk for adverse health effects.

Use of multivitamin/mineral supplements (MVMs) has grown rapidly over the past several decades, and dietary supplements are now used by more than half of the adult population in the United States. In general, MVMs are used by individuals who practice healthier lifestyles, thus making observational studies of the overall relationship between MVM use and general health outcomes difficult to interpret. Despite the widespread use of MVMs, there is still insufficient knowledge about the actual amount of total nutrients that Americans consume from diet and supplements. This is at least in part due to the fortification of foods with these nutrients, which adds to the effects of MVMs or single-vitamin or single-mineral supplements. Historically, fortification of foods has led to the remediation of vitamin and mineral deficits, but the cumulative effects of supplementation and fortification have also raised safety concerns about exceeding upper levels. Thus, there is a national need to improve the methods of obtaining accurate and current data on the public's total intake of these nutrients in foods and dietary supplements.

In systematically evaluating the effectiveness and safety of MVMs in relation to chronic disease prevention, few rigorous studies were found on which to base clear conclusions and recommendations. Most of the studies examined do not provide strong evidence for beneficial health-related effects of supplements taken singly, in pairs, or in combinations of three or more. Within some studies or

subgroups of the study populations, there is encouraging evidence of health benefits, such as increased bone mineral density and decreased fractures in postmenopausal women who use calcium and vitamin D supplements. However, several other studies also provide disturbing evidence of risk, such as increased lung cancer risk with beta-carotene use among smokers.

The current level of public assurance of the safety and quality of MVMs is inadequate, given the fact that manufacturers of these products are not required to report adverse events and the United States Food and Drug Administration (FDA) has no regulatory authority to require labeling changes or to help inform the public of these issues and concerns. It is important that the FDA's purview over these products be authorized and implemented.

Finally, the present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease. The resolution of this important issue will require advances in research and improved communication and collaboration among scientists, health care providers, patients, the pharmaceutical and supplement industries, and the public.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved knowledge of currently available data on the effectiveness and safety of multivitamin/mineral supplements for chronic disease prevention in the generally healthy population of adults

POTENTIAL HARMS

- There is evidence that certain ingredients in mineral/multivitamin (MVM) supplements can produce adverse effects, including reports from randomized controlled trials (RCTs) that noted excess lung cancer occurring in asbestos workers and smokers consuming beta-carotene. In addition, esophageal cancer excess was found with long-term follow-up of older Chinese patients treated with selenium, beta-carotene, and vitamin E supplements. There was also evidence for gender difference in patterns of lung cancer and cardiovascular disease risk related to beta-carotene. In another study, patients with elevated prostate-specific antigen levels at baseline who were receiving an MVM intervention had higher incidence of prostate cancer.

- Vitamin D and calcium may increase the risk for kidney stones for certain people. These data raise safety questions both in general and in special populations. Although these studies are not definitive, they do suggest possible safety concerns that should be monitored for primary components of multivitamins.
- There is potential for adverse effects in individuals consuming dietary supplements that are above the upper level. This can occur not only in individuals consuming high-potency single-nutrient supplements but also in individuals who consume a healthy diet rich in fortified foods in combination with MVM supplements. Furthermore, by law, the listing of ingredient amounts on nutrient supplement labels is the minimum content; thus, higher intakes are probable. Data from prospective studies have shown that individuals taking MVM dietary supplements improved their nutritional adequacy with respect to several nutrients but also increased the proportion of their intakes above the upper level for several of the supplemented nutrients. With the strong trends of increasing MVM and other dietary supplement consumption, and the increasing fortification of the U.S. diet, the guideline developers are concerned that a growing proportion of the population may be consuming levels considerably above the upper level, thus increasing the possibility of adverse effects.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research and that the information provided is not a substitute for professional medical care or advice.
- This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health (NIH) or the federal government.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 May 15-17

GUIDELINE DEVELOPER(S)

National Institutes of Health (NIH) State-of-the-Science Panel - Independent Expert Panel

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

National Institutes of Health State-of-the-Science Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: J. Michael McGinnis, M.D., M.P.P., (*Panel and Conference, Chairperson*), Senior Scholar, Institute of Medicine, The National Academies, Washington, DC; Diane F. Birt, Ph.D., Distinguished Professor, Department of Food Science and Human Nutrition, Director, Center for Research on Botanical, Dietary Supplements, College of Agriculture and College of Human Sciences, Iowa State University, Ames, Iowa; Patsy M. Brannon, Ph.D., R.D., Professor, Division of Nutritional Sciences, Cornell University, Ithaca, New York; Raymond J. Carroll, Ph.D., Distinguished Professor of Statistics, Professor of Nutrition and Toxicology, Department of Statistics, Texas A&M University, College Station, Texas; Robert D. Gibbons, Ph.D., Director, Center for Health Statistics, Professor of Biostatistics and Psychiatry, University of Illinois at Chicago, Chicago, Illinois; William R. Hazzard, M.D., Professor, Department of Medicine, Division of Gerontology and Geriatric Medicine, University of Washington, Chief, Geriatrics and Extended Care, VA Puget Sound Health Care System, Seattle, Washington; Douglas B. Kamerow, M.D., M.P.H., U.S. Editor, BMJ, Professor of Clinical Family Medicine, Georgetown University, Chief Scientist, Health, Social, and Economics Research, RTI

International, Washington, DC; Bernard Levin, M.D., Professor of Medicine, Vice President for Cancer Prevention and Population Sciences, University of Texas M.D., Anderson Cancer Center, Houston, Texas; James M. Ntambi, Ph.D., Steenbock Professor, Departments of Biochemistry and Nutritional Sciences, University of Wisconsin–Madison, Madison, Wisconsin; Nigel Paneth, M.D., M.P.H., Professor of Epidemiology, Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing, Michigan; Douglas Rogers, M.D., Head, Section of Pediatric and Adolescent Endocrinology, The Cleveland Clinic Cleveland, Ohio; Audrey F. Saftlas, Ph.D., M.P.H., Professor, Department of Epidemiology, The University of Iowa, College of Public Health, Iowa City, Iowa; William Vaughan, Senior Policy Analyst Consumer's Union, Washington, DC

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on National Institutes of Health (NIH) Consensus and State-of-the-Science panels are reviewed prior to selection to assure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [National Institutes of Health \(NIH\) Consensus Development Conference Program Web site](#).

Print copies: Available from the NIH Consensus Development Program Information Center, PO Box 2577, Kensington, MD 20891; Toll free phone (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); autofax (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); e-mail: consensus_statements@mail.nih.gov.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- NIH State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention. 2006 May. 79 p. Available in Portable Document Format (PDF) from the [National Institutes of Health \(NIH\) Consensus Development Conference Program Web site](#).
- Multivitamin/mineral supplements and prevention of chronic disease. 2006 May. Available from the [AHRQ Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

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