NIH State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention

May 15–17, 2006

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsored by:

- Office of Dietary Supplements, NIH
- Office of Medical Applications of Research, NIH

Co-sponsored by:

- Centers for Disease Control and Prevention
- National Cancer Institute, NIH
- National Center for Complementary and Alternative Medicine, NIH
- National Eye Institute, NIH
- National Institute on Aging, NIH
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
- National Institute of Child Health and Human Development, NIH
- National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- U.S. Department of Agriculture
- U.S. Food and Drug Administration

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Contents

Introduction

It is estimated that more than one third of American adults take multivitamin/mineral (MVM) supplements regularly. Recommendations regarding supplement use from expert groups vary widely, as does the strength of the evidence supporting such guidelines. As more and more Americans seek strategies for maintaining good health and preventing disease, and as the marketplace offers an increasing number of products to fill that desire, it is important that consumers have the best possible information to inform their choices.

The Office of Dietary Supplements and the Office of Medical Applications of Research of the National Institutes of Health will convene a State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention, May 15–17, 2006, in Bethesda, Maryland. The goal of the conference is to assess the evidence available on MVM use and outcomes for chronic disease prevention in adults, and to make recommendations for future research. Specifically, the conference will explore the following key questions:

- What are the current patterns and prevalence of the public's use of MVM supplements?
- What is known about the dietary nutrient intake of MVM users versus non-users?
- What is the efficacy of single vitamin/mineral supplement use in chronic disease prevention?
- What is the efficacy of MVM in chronic disease prevention in the general population of adults?
- What is known about the safety of MVM for the generally healthy population?
- What are the major knowledge gaps and research opportunities regarding MVM use?

An impartial, independent panel will be charged with reviewing the available published literature in advance of the conference, including a systematic literature review commissioned through the Agency for Healthcare Research and Quality. The first day and a half of the conference will consist of presentations by expert researchers and practitioners, and open public discussions. On Wednesday, May 17, the panel will present a statement of its collective assessment of the evidence to answer each of the questions above. The panel will also hold a press conference to address questions from the media. The draft statement will be published online later that day, and the final version will be released approximately 6 weeks later.

General Information

Conference sessions will be held in the Natcher Conference Center, NIH, Bethesda, Maryland.

The conference may be viewed live via Webcast at http://videocast.nih.gov/. Webcast sessions will also be available after the conference.

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

The telephone number for the message center at the Natcher Conference Center is 301–594–7302.

Conference Sponsors

The primary sponsors of the conference are:

- Office of Dietary Supplements, NIH
- Office of Medical Applications of Research, NIH

The co-sponsors of the conference are:

- Centers for Disease Control and Prevention
- National Cancer Institute, NIH
- National Center for Complementary and Alternative Medicine, NIH
- National Eye Institute, NIH
- National Institute on Aging, NIH
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
- National Institute of Child Health and Human Development, NIH
- National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- U.S. Department of Agriculture
- U.S. Food and Drug Administration

The Agency for Healthcare Research and Quality (AHRQ) provided additional support to the conference development.

Financial Disclosure

Each speaker presenting at this conference has been asked to disclose any financial interests or other relationships pertaining to this subject area. Please refer to the material in your participant packet for details.

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

AGENDA

Monday, May 15, 2006

8:30 a.m. Opening Remarks
Paul M. Coates, Ph.D.
Director
Office of Dietary Supplements
Office of the Director
National Institutes of Health

8:40 a.m. Charge to the Panel
Barnett S. Kramer, M.D., M.P.H.
Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
J. Michael McGinnis, M.D., M.P.P.
Conference and Panel Chairperson
Senior Scholar
Institute of Medicine
The National Academies

I. What Are the Current Patterns and Prevalence of the Public's Use of Multivitamin/Mineral (MVM) Supplements?

9:00 a.m. Multivitamin/Mineral Supplements: Definition, Characterization, Bioavailability, Drug Interactions
Elizabeth Yetley, Ph.D.
Office of Dietary Supplements
National Institutes of Health

9:20 a.m. Who Uses Them—Demographics, Adults and Children, Healthy or Diseased?
Cheryl L. Rock, Ph.D., R.D.
Professor
Family and Preventive Medicine
Cancer Prevention and Control Program
University of California, San Diego

Monday, May 15, 2006 (continued)

II. What Is Known About the Dietary Nutrient Intake of MVM Users Versus Non-Users?

9:40 a.m. How and Why Do We Use Supplements?
A. Elizabeth Sloan, Ph.D.
Editor/Columnist
Food Technology
Functional Foods & Nutraceuticals and *Flavor & The Menu* Magazines

10:00 a.m. Impact of Multivitamin/Mineral Supplements at Recommended Daily Allowances Levels on Total Nutrient Intake
Suzanne Murphy, Ph.D., R.D.
Research Professor
Cancer Research Center of Hawaii
University of Hawaii

10:20 a.m. Discussion

Participants with questions or comments for the speakers should proceed to the microphones and wait to be recognized by the panel chair. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. Please be aware that all statements made at the microphone or submitted later are in the public domain.

III. What Is the Efficacy of Single Vitamin/Mineral Supplement Use in Chronic Disease Prevention?

11:00 a.m. Evidence-Based Practice Center Presentation: The Efficacy of Single Vitamin or Mineral Supplement Use in the Primary Prevention of Chronic Disease: A Systematic Review
Anthony J. Alberg, Ph.D., M.P.H.
Associate Professor
Blatt Ness Endowed Chair in Oncology
Department of Biostatistics, Bioinformatics, and Epidemiology
Hollings Cancer Center
Medical University of South Carolina

11:20 a.m. Folate and Neural Tube Defects
Roy M. Pitkin, M.D.
Professor Emeritus
University of California, Los Angeles

Monday, May 15, 2006 (continued)

III. What Is the Efficacy of Single Vitamin/Mineral Supplement Use in Chronic Disease Prevention? (continued)

11:40 a.m. Cancer
Meir J. Stampfer, M.D., Dr.P.H.
Professor of Epidemiology and Nutrition
Chair, Department of Epidemiology
Departments of Epidemiology and Nutrition
Harvard School of Public Health
Professor of Medicine
Harvard Medical School

Noon Discussion

12:30 p.m. Lunch
Panel Executive Session

1:30 p.m. Heart Disease
Maret Traber, Ph.D.
Professor
Linus Pauling Institute
Oregon State University

Combinations of Several Vitamins/Minerals

1:50 p.m. Tuning Up Metabolism With Micronutrients To Prevent Degenerative Disease
Bruce N. Ames, Ph.D.
Professor of the Graduate School
University of California, Berkeley
Senior Scientist
Nutrition and Metabolism Center
Children's Hospital Oakland Research Institute

2:10 p.m. Bone Health
Robert P. Heaney, M.D.
John A. Creighton University Professor
Professor of Medicine
Department of Medicine
Creighton University

2:30 p.m. Eye Health
Johanna M. Seddon, M.D., Sc.M.
Director, Epidemiology Unit
Department of Ophthalmology
Massachusetts Eye and Ear Infirmary

2:50 p.m. Discussion

Monday, May 15, 2006 (continued)

IV. What Is the Efficacy of MVM in Chronic Disease Prevention in the General Population of Adults?

3:30 p.m. Evidence-Based Practice Center Presentation: The Efficacy of Multivitamin/Mineral Supplement Use in the Primary Prevention of Chronic Disease: A Systematic Review
Han-Yao Huang, Ph.D., M.P.H.
Assistant Professor
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins School of Medicine

3:50 p.m. Cohort Studies and the Case for Randomized Controlled Trials
Ross L. Prentice, Ph.D.
Biostatistician
Division of Public Health Sciences
Fred Hutchinson Cancer Research Center

4:20 p.m. Discussion

5:00 p.m. Adjournment

Tuesday, May 16, 2006

8:30 a.m. Clinical Trials of Vitamin and Mineral Supplements for Cancer Prevention
Peter Greenwald, M.D., Dr.P.H.
Director, Division of Cancer Prevention
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8:50 a.m. Studies of Cost-Effectiveness of Multivitamin/Mineral Supplements for Prevention of Chronic Disease in Adults
Allen Dobson, Ph.D.
Senior Vice President
The Lewin Group

9:10 a.m. Discussion

Tuesday, May 16, 2006 (continued)

V. What Is Known About the Safety of MVM for the Generally Healthy Population?

9:40 a.m. Evidence-Based Practice Center Presentation: The Safety of Multivitamin/Mineral Supplement Use in the General Population of Adults and Children: A Systematic Review
Benjamin Caballero, M.D., Ph.D.
Professor
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10:00 a.m. Theoretical Basis for Harm
Diane Benford, Ph.D.
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Food Standards Agency

10:20 a.m. Adverse Event Reporting Systems: Current and New
Susan J. Walker, M.D.
Associate Director for Clinical Affairs
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U.S. Food and Drug Administration

VI. What Are the Major Knowledge Gaps and Research Opportunities Regarding MVM Use?

10:40 a.m. Research Challenges and Opportunities
Irwin H. Rosenberg, M.D.
Senior Scientist and University Professor
Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center
Tufts University

11:00 a.m. Discussion

Noon Adjournment

Wednesday, May 17, 2006

9:00 a.m. Presentation of the draft State-of-the-Science Statement

9:30 a.m. Public Discussion

The panel chair will call for questions and comments from the audience on the draft statement, beginning with the introduction and continuing through each subsequent section in turn. Please confine your comments to the section under discussion. The chair will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Comments cannot be accepted after 11:30 a.m.

Wednesday, May 17, 2006 (continued)

11:00 a.m. Panel Meets in Executive Session

Panel meets in executive session to review public comments. Conference participants are welcome to return to the main auditorium to attend the press conference at 2:00 p.m.; however, only members of the media are permitted to ask questions during the press conference.

2:00 p.m. Press Conference

3:00 p.m. Adjournment

The panel's draft statement will be posted to www.consensus.nih.gov as soon as possible after the close of proceedings and the final statement will be posted 6 weeks later.

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Abstracts

The following are the abstracts of the proposed speaker presentations at the NIH State-of-the-Science Conference: Multivitamin/Mineral Supplements and Chronic Disease Prevention. They are designed for use by the panelists and the participants in the conference, and as a reference document for anyone interested in conference deliberations. We are grateful to the authors.

Abstracts for the following presentations do not appear:

Cancer—Meir J. Stampfer, M.D., Dr.P.H.

Eye Health—Johanna M. Seddon, M.D., Sc.M.

Cohort Studies and the Case for Randomized Controlled Trials—Ross L. Prentice, Ph.D.

Adverse Event Reporting Systems: Current and New—Susan J. Walker, M.D.

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Multivitamin/Mineral Supplements: Definition, Characterization, Bioavailability, Drug Interactions

Elizabeth Yetley, Ph.D.

Definitions

Although the term multivitamins (MVMs) or similar terms (e.g., multis, multiples) are commonly used by scientists, regulatory bodies, and marketers, they have no standard meaning. Therefore, MVMs can refer to products with widely varying compositions and characteristics.

Among nationally representative monitoring databases, methodological differences within a survey series and across surveys as to the duration of time covered by supplement usage, the types of supplement products for which usage information was sought, and coding categories used to describe or categorize MVM and other supplement types make it impossible to track changes in prevalence of supplement use over time or to compare prevalence and intakes across surveys.[1,2] Research publications also exhibit a paucity of information as to how they define or categorize MVM supplements.

There are no regulatory definitions for MVMs.[3] In the United States, dietary supplements may contain a broad range of ingredients including a: (a) vitamin; (b) mineral; (c) herb or other botanical; (d) amino acid; (e) dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) concentrate, metabolite, constituent, extract, or combination of any of the ingredients described in (a) to (e) above. As a result, marketed products vary considerably in the types, numbers, and amounts of specific vitamins and minerals that they contain. They also vary as to whether they contain other ingredients that are not vitamins and minerals (e.g., dietary fiber, sugars, protein, botanicals) and other so-called bioactives (e.g., glucosamine, lycopenes).

Product Characteristics

There is little information on actual amounts of vitamins and minerals contained in MVM products; therefore, label declarations of vitamin/mineral content are often used as surrogates for actual levels. Although it is well known that nutrient overages are used by manufacturers to meet labeling regulations, there are relatively little data comparing analyzed to declared label values in marketed products. Manufacturer supplied data on levels of vitamins used in products marketed in the United Kingdom report overages of 30–100 percent of declared value for vitamin A; 50 percent for vitamin B12; 30–50 percent for vitamin D2; 30 percent for vitamin D3, folic acid, thiamin, biotin, ß-carotene, vitamin K, riboflavin, niacin, vitamin B6, and vitamin C; and 5 percent for vitamin E.[4] However, underages may also occur in some marketed products.[5]

Bioavailability

The bioavailability of vitamins and minerals in a dietary supplement product can be affected both by product and host factors. Product factors include the chemical ingredient source for a vitamin or mineral, bindings and coatings that interfere with dissolution/disintegration characteristics, or surfactants and wetting properties that enhance absorption.

Drug Interactions

Drug–nutrient interactions are the result of both host and nutrient/drug factors.[6] These interactions may either augment or interfere with the expected drug action or the bioavailability of the vitamin or mineral. If drug–nutrient interactions have been documented to occur, product labeling that identifies this potential is generally included in drug product label/labeling rather than in the dietary supplement labeling.

Conclusions

Adequate descriptions and characterization of products used in intervention trials, or reported as being used in observational studies and surveys, are essential to permit meaningful comparisons among study results or to facilitate generalization of results from a particular study product to generic effects of specific vitamins and minerals from varied food and supplement sources.

References

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Who Uses Them—Demographics, Adults and Children, Healthy or Diseased?

Cheryl L. Rock, Ph.D., R.D.

Dietary supplement use is increasingly common in the general population of the United States,[1] and usage may be even more common in some subgroups.[2] In most groups that have been surveyed, these supplements contribute a substantial proportion of the total vitamin and mineral intakes.[1,2] Thus, collecting and analyzing data on dietary supplement use is a critical component of the assessment of nutritional status, although obtaining accurate details, such as the dosage actually ingested via supplementation, can be challenging.[3,4]

The National Health and Nutrition Examination Survey (NHANES) collects data on dietary supplement usage from a nationally representative sample of the civilian, noninstitutionalized U.S. population. In NHANES 1999–2000, 52 percent of adults reported taking a dietary supplement in the past month, and 35 percent reported regular use of a multivitamin/multimineral product.[1] Prevalence of reported use of other types of vitamin and mineral supplements that were assessed ranged from 5.2 percent for B-complex vitamins to 12.7 percent for vitamin E, with 24.4 percent of the sample reporting use of calcium-containing antacids. Compared with previous NHANES survey data, these data indicate a trend of increasing use: NHANES III data indicated an overall prevalence of dietary supplement usage of 40 percent, with prevalence rates of 35 percent in NHANES II and 23 percent in NHANES I.[1,5]

As observed in other surveys and studies,[6] dietary supplement usage in NHANES 1999–2000 was associated with several demographic and lifestyle characteristics, as shown in the table below. Women (vs. men), non-Hispanic whites (vs. non-Hispanic blacks or Mexican Americans), higher level of education, lower body mass index, and higher level of physical activity were associated with greater likelihood of reporting use of dietary supplements and, specifically, multivitamin/multimineral supplements.[1]

Table 1. Demographic and Lifestyle Characteristics Associated With Multivitamin/ Multimineral Supplement Use in NHANES 1999–2000, n = 4,453*

Characteristic	Odds Ratios and 95% Confidence Intervals (OR [95% CI])
Gender	
Male	1.0
Female	1.4 (1.2, 1.7)
Age (years)**	
20–39	1.0
40–59	1.4 (1.1, 1.7)
≥60	1.7 (1.3, 2.2)
Race/ethnicity**	
Non-Hispanic white	1.0
Non-Hispanic black	0.6 (0.5, 0.7)
Mexican American	0.6 (0.5, 0.8)
Education**	
Less than high school	1.0
High school diploma	1.3 (1.0, 1.6)
More than high school	2.0 (1.5, 2.6)
Reported body mass index (kg/m^2)**	
<25.0	1.0
25.0 – <30	0.8 (0.7, 1.0)
≥30	0.7 (0.6, 0.9)
Physical activity**	
None	1.0
Moderate	1.5 (1.2, 1.9)
Vigorous	1.7 (1.3, 2.3)

* Data from Radimer et al.[1] ** *P* for trend <0.01.

In studies of children and adolescents,[7,8] patterns and predictors of dietary supplement use are similar to those observed in adult populations. For example, 54.4 percent of preschool children in the 1991 Longitudinal Follow-Up to the1988 National Maternal and Infant Health Survey used vitamin and mineral supplements, with maternal characteristics associated with adult use (non-Hispanic white, older, more educated, greater household income) associated with greater likelihood of the child taking a vitamin or mineral supplement.[7] A somewhat lower prevalence (approximately one third) of dietary supplement use has been observed in adolescents,[8] although different methodologies constrain these comparisons across surveys and studies.

In several studies and target populations, dietary supplement users have been observed to have higher micronutrient intakes from food sources and more healthful diets.[2,9,10] The prevalence of consuming excess amounts of vitamins and mineral in association with supplement use has been addressed in a few reports. For example, analysis of data from NHANES 1999–2000 suggests that 11.3 percent of adults consumed ≥400 IU of vitamin E per day.[11] In the INTERMAP Study U.S. population, supplement users had mean total intakes (from food and supplements) of vitamin E and vitamin C that were >700 percent of the average recomendation.[6]

Compared with survey data from the general population, data from target groups and populations with health concerns suggest higher prevalence rates for dietary supplement use. For example, 80.9 percent of women who had been diagnosed with early stage breast cancer surveyed in 1995–1997 reported regular use of at least one dietary supplement.[12] The use of multiple vitamin and mineral supplements was reported by 46.2 percent, but the use of single vitamin and mineral products, usually in addition to the multiple vitamin and mineral product, was considerably more prevalent than that in the general population. For example, 49.0 percent used a vitamin E supplement (compared to 12.7 percent observed in NHANES 1999–2000). As a result of this supplementation pattern, the distribution of micronutrient intakes of this population indicates that a considerably higher proportion exceed recommended levels of intakes.[13]

In conclusion, continued efforts to monitor dietary supplement behavior, and to improve methodologies that are used for assessment and monitoring of this behavior, should be encouraged. Evidence suggests that individuals with suboptimal levels of intakes from food sources are less likely to be dietary supplement users. Also, some subgroups of the population, especially persons with health concerns or chronic conditions, may be at increased risk of excess levels of intakes due to dietary supplementation.

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How and Why Do We Use Supplements?

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The reasons for taking dietary supplements are extremely complex and differ markedly by demographics, type and number of supplements taken, life stage, health status, lifestyle, etc. Motivations for vitamin and mineral (VM) users fall into four areas: health maintenance and promotion (62%), risk reduction in addition to health promotion (53%), prevention-specific medical conditions (26%), and treatment for medical conditions (21%).[1] Heavy VM users (>5 pills/day) are more motivated by prevention (51%) and treatment (32%) issues.[1]

Most adults take a supplement to improve overall health: 70% believe that taking a VM supplement is important to health—59% believe that taking a VM is extremely important to health compared with 60% who classify health professional contact and 17% who classify alternative practitioner contact as important.[2] In 2005, 84% of adults ages 18 or older took a VM—31% took a condition-specific VM and 40% took an herbal supplement—and 73% used an over-the-counter medication.[3] Multivitamins were taken by 72%, daily by 63%.[3] Of VM users, 24% do not have a specific reason for taking supplements other than they feel it is good for them.[1]

Among those motivated primarily by health maintenance and promotion, the perceived difficulty of getting adequate nutrients through their current diet (46%)[1] and a cautionary attitude of dietary insurance (31%)[1] were two prominent submotivators. In 2005, consumers thought their diet was deficient in calcium (41%), omega-3 fatty acids (32%), fiber (29%), antioxidants (26%), and vitamin C (25%).[4,5] In general, just over half of adults feel they need more vitamins (52%) and one third feel they need more minerals (34%).[4,5] After multivitamins, vitamin C is the most consumed supplement (65% of users) followed by calcium (60%), any B vitamin (47%), vitamin E (47%), vitamin D (37%), fiber (34%), garlic (33%), iron (32%), and zinc (30%).[6]

Recently, prevention has become a strong driver of VM supplement use (54%).[1] Among the general public, 69% believe VM are effective in prevention.[4] More than 70% of adults are trying to prevent heart disease, increase energy, lose weight, lessen arthritis and joint pain, alleviate vision problems, and reduce high cholesterol. More than 50% of supplement users are trying to prevent hypertension, memory and concentration issues, diabetes, osteoporosis, and frequent colds and flu; address blood sugar issues; and correct acid reflux and heartburn or intestinal regularity.[4]

Of VM users, 51% agree that condition-specific supplements (e.g., for heart, bone) are a vital part of staying healthy:[1] VMs are used by 33% for specific health or medical conditions.[1] The most-used condition-specific supplements are for joint health (24%), heart health (18%), arthritis (18%), osteoporosis or bone health (18%), immunity (17%), cholesterol (16%), prostate (15%), energy (14%), menopause (14%), and digestion (12%).[7]

One third (33%) of users use VMs to treat medical conditions. Among the general public, 62% believe VMs are effective.[1,4] Primary household shoppers report that their purchase decisions are affected by an existing medical condition (28%), the risk of future health

conditions (39%), the need to lose weight (41%), and a doctor's advice (30%).[8] Nine percent of users use supplements only when they get sick.[1]

Condition-specific supplements are the fastest growing sector of the supplement business.[9] In 2005, 44% of all U.S. supplements sold emphasized a particular health condition.[9] "Nutrition Business Journal" estimates that 14 condition-specific areas account for 84% of supplement sales—sports/energy/weight loss, general health, joints, cold/flu/immunity, cancer, heart, bone, diabetes, gastrointestinal problems, menopause, brain/mental problems, mood, sexual issues, and insomnia. The first two areas account for almost half of supplement sales, but more specific concerns are growing strongly. Sales growth of gut health, heart, and anticancer supplements was significantly more than the overall substantial sales growth of the condition-specific category.[9] Condition-specific supplement use will remain strong: 33% of women, 38% of men, and 49% of African Americans have two or more risk factors for heart disease, and heart disease is projected to jump another 24%. From 2003 to 2013, osteoporosis, cancer, and arthritis are predicted to increase by 18%, 19%, and 18% in men, respectively, and by 20%, 19%, and 17%, respectively, in women.[10,11]

Cross-marketing of healthy foods and supplements with prescriptions is a fast emerging practice. People picking up condition-specific prescriptions are twice as likely to buy one- and two-letter vitamins on the same trip as are other consumers, and 78% more likely to purchase multivitamins or mineral supplements.[12] Heart-related products alone are estimated to be a $70 billion untapped market.[12] People with high cholesterol are 20% more likely than the general population to buy minerals, 17% more likely to buy multivitamins, and 13% more likely to buy one- and two-letter vitamin supplements.[13] Only 46% of users are concerned about interactions between prescribed medicines and supplements.[4]

Lifestyle issues—low energy, tiredness, and stress—are fast becoming important supplement motivators: 38% of VM users say VMs make them feel better and give them more energy.[1] During November 2005, 85% of adults reported they had at least 1 day that they did not feel healthy or energized, which kept 60% from normal activity: the reasons given were low energy (58%), a cold (49%), back or neck pain (32%), depression or anxiety (28%), joint pain (27%), and arthritis (18%).[14] Only 16% of consumers are satisfied with their energy level.[3]

Antioxidants, B vitamins, vitamins C and D, iron, zinc, protein, omega-3 fatty acids, and docosahexaenoic acid are projected to grow strongly in 2006–2007.[15] Bioavailability, which achieved mass market recognition in 2005, is a strong new motivator.[15] Scanner data project that antioxidants will be a blockbuster health trend in 2006.[16] With 75% of adults saying their nutritional needs are unique, expect more custom products.[2] Supplements specific for age and gender are preferred by 47% of users.[4]

VM users have more positive health behaviors than nonusers: fewer smoke, drink heavily, or are overweight.[2,4,17] However, no correlation exists between absence of specific chronic disease conditions and supplement use.[17]

Four key issues will continue to affect motivation for use of VM supplements: fortified foods, feeling confused or overwhelmed, taking too many pills, and word of mouth.

1. Fortified food: In 2005, 69% of adults used fortified foods and 67% used functional foods and beverages, up 56% and 51%, respectively, from 2001.[3] Fortified and functional foods sales are expected to hit $35.9 billion in 2006, up 22% over 2005.[3] Of consumers, 49% think fortified products can be used to get their daily VM requirements, up from 41% in 1999.[2] With only 10% of consumers concerned about nutrient overconsumption, monitoring the total nutrient intake from fortified, functional, and natural foods as well as supplements will be important.[2]

2. Feeling confused and overwhelmed: In 2005, 26% of adults felt overwhelmed by the nutritional aspects of supplements compared with 18% in 2003.[3] This confusion is resulting in reduced retention of information about the benefits associated with a specific nutrient. For example, the percentage of consumers who link calcium with bone health fell 12% between 2003 and 2005, to 66%; the number linking vitamin C and immunity fell 1% to 46%.[3]

3. Pill overload: Some supplement users (17%) are unhappy with the number of pills they are taking.[4] Expect the market to continue to move toward multiingredient general supplements, for example, supplements for heart health rather than single-ingredient VM products.

4. Word of mouth: Consumers are increasingly dependant on recommendations from friends and family in selecting their supplements.[4] Today's confused consumers are in need of an unbiased authoritative source of credible information and possibly a symbol such as the American Heart Association's heart symbol to help them identify reliable information.

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Impact of Multivitamin/Mineral Supplements at Recommended Daily Allowance Levels on Total Nutrient Intake

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The most common type of dietary supplement reported in the United States is a "multivitamin" supplement. Many of these products contain nutrient levels that approximate the recommended daily allowance intake levels (RDA or AI), but many contain higher levels, and may also contain nutrients or other compounds that do not have recommended intake levels. Even the name "multivitamin" is misleading, as most formulations also contain one or more minerals. Furthermore, some supplement users take more than one type of multivitamin, and may also take them more or less often than once a day, as is usually recommended on the label.

There is a paucity of data on the usual intakes of individuals who take multivitamins, both from the supplements themselves, as well as from diet plus supplements. The few reports that are available do not usually evaluate the intakes by estimating the prevalence of inadequacy or the prevalence of potentially excessive intakes. We have conducted several analyses of data from the Hawaii–Los Angeles Multiethnic Cohort (MEC), which includes 215,902 adults ages 45 years and older at baseline in 1993–1996.[1] Preliminary findings are reported in this abstract, and more complete results will be included in the full manuscript.

Data on the use of multivitamin products were collected on the MEC baseline questionnaire. Of 100,196 participants without chronic diseases, 48 percent of men and 56 percent of women reported using a multivitamin supplement at least once a week for the past year.[2] In models adjusted for several demographic covariates, persons who used any of seven supplements regularly reported a lower percent of energy from fat and higher fiber intakes than nonusers. Better dietary intakes by supplement users vs. nonusers have also been recently reported by other investigators.[3–5]

Use of supplements that contained two or more vitamins (and were considered "multivitamins" by participants) was reported on an open-ended questionnaire mailed to MEC participants in 2000–2001. Responses from 29,567 participants living in Hawaii were matched to an extensive supplement composition table maintained by the staff of the Nutrition Support Shared Resource at the Cancer Research Center of Hawaii. Nutrient profiles are based on the supplement labels. Variability in the nutrient content of the reported supplements (n=1246) was high.[6] For each of 15 nutrients examined, at least 10 percent of the products contained none of the nutrient. For 3 nutrients (thiamin, vitamin B6, and iron), the level reported in products at the 90th percentile was 10 times higher than the level in products at the median.

In conclusion, the declared nutrient composition of multivitamin supplements varies considerably, as do reported intakes from these supplements. More information is needed on the distribution of intakes using nationally representative samples, so that the prevalence of inadequate intakes, as well as the prevalence of intakes that may be excessive, can be evaluated.

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Evidence-Based Practice Center Presentation: The Efficacy of Single Vitamin or Mineral Supplement Use in the Primary Prevention of Chronic Disease: A Systematic Review

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Introduction

To improve understanding of the efficacy of multivitamin/mineral supplements in preventing chronic disease, it is necessary to consider evidence on the efficacy of individual vitamins and minerals that are included in multivitamin/mineral supplements.

Objective

We conducted a systematic review to synthesize the published data from randomized controlled trials (RCTs) on the efficacy of supplementation with single or functionally paired vitamins and minerals in the primary prevention of chronic disease in the general adult population.

Methods

We searched MEDLINE®, EMBASE®, and the Cochrane database for articles published in English from 1966 to February 2006. We also checked reference lists in pertinent articles and tables of contents in 15 peer-reviewed journals. Using duplicate review, we identified relevant articles by reviewing the titles, then abstracts, and finally full-text articles. We looked for articles that presented original data from RCTs in adults that assessed the efficacy of single vitamin/mineral supplement use in preventing selected chronic diseases. Studies were excluded if the study population was comprised of only pregnant women, patients with particular chronic diseases, patients in long-term care facilities, or individuals with a nutritional deficiency. Panel reviewers extracted data from eligible studies using a serial approach.

Results

The literature search ascertained relevant evidence for β-carotene (20 articles based on 6 RCTs), preformed vitamin A (7 articles based on 2 RCTs), vitamin E (12 articles based on 4 RCTs), folic acid/vitamin B6/vitamin B12 (2 prior systematic reviews), vitamin B2 and niacin (3 articles from 1 trial), selenium (3 articles from 1 RCT), and vitamin D/calcium (5 prior systematic reviews and a recent RCT on osteoporosis/fractures and colorectal cancer). The

evidence was available for cancer, cardiovascular disease, diabetes, eye disease, cognitive function/dementia, and bone mineral density/osteoporosis/fractures.

Daily supplementation with β-carotene of 20 mg, 30 mg, or 50 mg was not protective against malignancies, cardiovascular disease outcomes, diabetes, and age-related cataract or maculopathy.[1–19] Supplementation with β-carotene with or without vitamin A increased the incidence of lung cancer in persons with asbestos exposure or in heavy smokers[7,13,20,21] and was associated with increased mortality in some trials.[8,9,20] RCTs did not assess the efficacy of vitamin A alone in preventing chronic disease. Studies in selected populations (nutritionally inadequate, asbestos exposure, or smokers) showed no benefit of combinations of vitamin A and zinc or vitamin A and β-carotene for the prevention of stroke mortality, esophageal or gastric cancer incidence, or cardiovascular or all-cause mortality.[7,13,14,22–25]

Daily use of synthetic vitamin E supplements (50 mg or 300 IU) or natural source vitamin E (600 IU) did not reduce risk of most malignancies, cardiovascular disease, or total mortality.[1–3,20,21,26] Exceptions to this pattern were mostly confined to single studies, such as results from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) suggesting a protective effect on colorectal cancer and prostate cancer.[18,19] There was no consistent effect on cataracts or age-related maculopathy by daily use of synthetic vitamin E (50 mg) or natural vitamin E (500 IU).[16,27]

Two previous systematic reviews reported that supplementation with folic acid at daily doses ranging from 0.75 mg to 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 RCTs.[28,29] Combined vitamin B2 and niacin supplement use for approximately 5 years had no significant effects on cerebrovascular mortality, total mortality, total cancer incidence, and esophageal or gastric dysplasia/cancer incidence and esophageal or gastric cancer mortality in a poorly-nourished population in China.[22–24,30]

In a study in persons with a history of nonmelanoma skin cancer, there was no major impact supplementation with selenium (200 mcg/day) and had no effect on cardiovascular outcomes, but had protective effects on total mortality and incidence of lung, colorectal, and prostate cancers.[31–33] Another study found a significantly reduced risk of liver cancer incidence with use of selenium supplements of 200 mcg/day for 2 years.[34]

Due to the abundance of efficacy data on vitamin D/calcium and outcomes related to osteoporosis, we relied primarily on five published systematic reviews. The previous reviews reported that supplementation with calcium has short-term (particularly within 1 year) benefits in retaining bone mineral density in postmenopausal women and a possible effect on preventing vertebral fractures.[35–37] The reviews also indicate that combined vitamin D3 (700–800 IU/day) and calcium (1000 mg/day) reduces the risk of hip and other nonvertebral fractures.[38,39] Recent published data from the Women's Health Initiative (WHI) clinical trial were consistent with these systematic reviews in showing 1.06 percent higher hip bone density ($p<0.02$) and a 12 percent nonsignificant 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.[40] In the WHI trial, calcium and vitamin D supplementation had no effects on colorectal cancer incidence.[41] The trial participants' adequate

intake of calcium and vitamin D may have hindered protective effects of additional calcium/vitamin D supplement use.[41]

Conclusion

With few exceptions, the available evidence from RCTs of β-carotene, vitamin E, vitamin A (in combination with zinc or β-carotene), or combined riboflavin and niacin indicates no consistent, significant benefit of these single or paired nutrients in preventing cancer, cardiovascular disease, cataract or age-related macular degeneration. Supplementation with β-carotene increased lung cancer risk in persons with asbestos exposure or heavy smoking. Limited data suggest benefits of selenium use in cancer prevention, but no short-term benefit of folic acid (with or without vitamins B12 and B6) or vitamin B6 alone in preventing cognitive decline. Calcium supplementation had benefit for retaining bone mineral density and preventing vertebral fractures. Combined use of vitamin D and calcium may increase hip bone mineral density and reduce the risk of hip and other nonvertebral fractures, but appears to have no benefit in preventing colorectal cancer.

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Folate and Neural Tube Defects

Roy M. Pitkin, M.D.

Neural tube defects (NTDs), the second most common type of congenital malformation in the United States, result from failure of the neural tube to close early in embryonic life. There are two main types of NTDs: anencephaly, in which the cerebral cortex fails to develop, and spina bifida, where the defect involves the lumbar portion of the spinal cord; the former invariably causes death either before or shortly after birth, whereas spina bifida leads to paraplegia with its attendant disability, but affected individuals can have an otherwise normal life.

Considerable evidence over the past several decades has pointed to an association between folate status during pregnancy and NTDs. Initially, case-control investigations comparing NTD cases with normals suggested that various indices of folate insufficiency were more common in women who gave birth to NTD-affected offspring. Later, observational studies seemed to confirm that folate-sufficient women (especially those taking supplemental folic acid) are probably protected against the congenital defect in their infants. Finally, two large, well-designed, randomized controlled trials (RCTs) in the early 1990s settled the matter by demonstrating that folic acid supplements taken periconceptionally reduce the frequency of NTDs significantly. The first of these trials[1] tested the ability of a daily supplement of 4 mg of folic acid, begun at least 1 month before conception and continued through the first trimester, to prevent NTDs in offspring of women who had previously borne infants with NTDs (i.e., a recurrence study). Involving multiple collaborating institutions in different countries, it demonstrated a 72 percent reduction in risk with the intervention. The second study,[2] one assessing reduction in primary occurrence of the defect in a Hungarian population, involved folic acid supplements of 0.8 mg plus multivitamins begun at least 1 month before conception and continued until the second missed menses. It found no NTDs among 2,104 supplemented pregnancies, compared with six cases among 2,052 unsupplemented women, a statistically significant difference.

As a result of these RCTs demonstrating the efficacy of supplemental folic acid in preventing NTDs, in 1992 the U.S. Public Health Service recommended women of childbearing age increase their folic acid intake, and shortly thereafter the major nutritional and medical organizations involved concurred. Because the window of effectiveness is only about 4 weeks after conception, a time when many women may not even be aware they are pregnant, most authorities advised that all women of childbearing age and at risk for conception take folic acid supplements continuously. In spite of a public education campaign, however, surveys after several years indicated that less than a third of women at risk were taking folic acid supplements, leading the Food and Drug Administration to mandate folic acid fortification of cereal grain products in 1996. Although some have argued that the fortification level of 140 mg per 100 g is too low, a number of studies have demonstrated that mandatory fortification has been accompanied by improvement in folate status of pregnant women and, more importantly, decline in NTD births.

Interpretation of the literature on folate and birth defects is confounded by uncertainty as to the mechanism of action, specifically whether NTDs are actually caused by folate deficiency

or if the protection observed reflects a drug effect of folic acid supplements independent of vitamin deficiency (or, as some have suggested, that folic acid supplements might act by promoting spontaneous loss of affected fetuses). Additionally, there has been some confusion arising from terminologic imprecision and differing bioavailability of different folate sources (e.g., the bioavailability of food folate is only about half that of chemical folic acid consumed on an empty stomach). In addition to mechanism of action, a major research need is clarification of dose–response effects of folic acid in preventing NTDs. Such data will likely inform the debate about proper fortification levels; moreover, they are also needed to clarify the issue of recurrence prevention, since the currently recommended level for this purpose, 4 mg daily, is double the tolerable upper limit.

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Heart Disease

Maret Traber, Ph.D.

Heart disease is the number one cause of death in the United States.[1] It is also the leading cause of death of women, according to the American Heart Association. For this presentation, heart diseases include coronary artery disease, hypertensive heart disease, congestive heart failure, peripheral vascular disease, and atherosclerosis, including cerebral artery disease and strokes.[2]

Healthy Diet

Heart disease has long been recognized to be multifactorial in nature, its onset takes decades in most individuals, and diet is well recognized as an important risk factor. Hu and Willett[3] have estimated that "among non-smokers, 74% of coronary events might have been prevented by eating a healthy diet (using non-hydrogenated unsaturated fats, whole grains, an abundance of fruits and vegetables and adequate omega-3 fatty acids), maintaining a healthy body weight, exercising regularly for half an hour or more daily, and consuming a moderate amount of alcohol ($\geq$5 g/d)." Nonetheless, such a diet is apparently extremely difficult to achieve for most Americans. The Women's Health Initiative Randomized Controlled Dietary Modification Trial[4] aggressively attempted to change women's diets (reduce total fat intake to 20 percent of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d), yet the women in the intervention arm only increased fruit and vegetable intake to 1.1 servings per day and had some success in decreasing fat intake. The diet had no significant effect on coronary heart disease, but "trends toward greater reductions in coronary heart disease risk were observed in those with lower intakes of saturated fat or trans fat or higher intakes of vegetables/fruits."[4] Given the poor record of dietary changes, the possibility of individual nutrient supplements to stave off the disorder has been a long-standing quest.

Cholesterol

Reduction of endogenous cholesterol by diet as a means to reduce heart disease risk was unsuccessfully attempted for decades. With the advent of cholesterol synthesis inhibitor drugs (HMGCoA reductase inhibitors, "statins"), it was possible to demonstrate that serum cholesterol reduction decreased mortality from coronary heart disease and even to suggest the over-the-counter use of statins![5] The data from the statin studies have demonstrated that serum cholesterol is an appropriate biomarker for heart disease risk. Therefore, the Food and Drug Administration has determined that phytosterols can have a health claim for lowering heart disease risk given that they lower serum cholesterol (http://www.cfsan.fda.gov/~dms/ds-ltr30.html#ftnote2).

Cholesterol as a biomarker gives some guidance as to what might be useful in linking a dietary component, a biomarker, and a disease. Thus, cholesterol as a component of the atherosclerotic lesion is not measurable, but cholesterol in the serum or specific lipoproteins can readily be measured. The drug studies demonstrated that lowering serum cholesterol resulted in

decreased mortality from heart disease. Thereafter, it has only been necessary to show that a dietary component reduces serum cholesterol.

Antioxidants

The question as to why cholesterol would cause atherosclerosis led Steinberg and colleagues[6] to posit that modification of low density lipoproteins (LDLs) made these cholesterol carriers more susceptible to uptake by scavenger cells (e.g., macrophages). The proposed modification was by lipid peroxidation. This hypothesis became known as the oxidative modification theory, leading to the corollary that antioxidants would be beneficial in stopping lipoprotein oxidation. Since vitamin E is the most potent antioxidant that stops lipid peroxidation,[7] clinical trials to show its benefit in heart disease were undertaken. The first of these trials was in an English population and was successful at showing that vitamin E prevented second heart attacks,[8] but subsequent larger trials were unsuccessful in showing vitamin E benefit.[9,10] Now, 10 years later, nearly 200 trials using vitamin E supplements have been carried out, and a recent review and meta-analysis claims that vitamin E neither has benefit or harm.[2] It is noteworthy that in most trials biomarkers were not used, nor were oxidative stress markers, lipid peroxidation markers, or even plasma vitamin E concentrations measured.

Given the extensive basic science demonstrating that vitamin E is an antioxidant, inhibits smooth muscle cell proliferation, platelet adhesion, and aggregation and monocyte endothelial adhesion; it has benefit in animal atherosclerosis models; and it has benefit in humans with respect to LDL oxidation, platelet effect,s and anti-inflammatory effects (as reviewed[11]), it is difficult to argue that the mechanistic aspects of vitamin E's actions are unknown and need further study. Nonetheless, the actual processes that generate the requirement for vitamin E are unknown, leading to confusion as to why humans require vitamin E.

Our studies have demonstrated in humans that during oxidative stress, vitamin E is depleted. Specifically cigarette smokers, as a result of their increased oxidative stress (assessed by plasma F2-isoprostane concentrations), have a faster plasma vitamin E disappearance than nonsmokers.[12] Importantly, smokers with the lowest plasma vitamin C concentrations had the fastest vitamin E disappearance, presumably because vitamin C regenerates vitamin E.[13] When smokers were supplemented with vitamin C, their vitamin E disappearance rates were normalized.[14] Additionally, in endurance runners during a 50 kilometer race compared with a rest day, both F2-isoprostane concentrations and vitamin E disappearance were elevated.[15] Daily supplementation with vitamin E (400 IU) and vitamin C (1000 mg) for 6 weeks prior to the race prevented the increase in F2-isoprostanes, but not markers of inflammation.[16] Taken together, these data strongly support the concept that vitamin E is required for its antioxidant properties, specifically as a lipid soluble antioxidant preventing the propagation of lipid peroxidation, and that inadequate levels would lead to greater oxidative stress and its sequelae, such as heart disease. Conversely, supplementation with vitamin E would then be predicted to be beneficial, not in the treatment of heart disease, but in its prevention.

The only trial to test whether vitamin E supplements would prevent heart disease was the Women's Health Study.[17] Here 40,000 women ages at least 45 years were randomly assigned to receive vitamin E (600 IU every other day), placebo and aspirin, or placebo; the study lasted 10 years. There was a significant 24 percent reduction in cardiovascular death that was largely

attributable to fewer sudden deaths in the vitamin E group (38 vs. 51 in the placebo group). In women ages at least 65 years (10 percent of study participants) assigned to vitamin E, there was a significant 26 percent reduction in major cardiovascular events. There was a 34 percent reduction in myocardial infarction and a 49 percent reduction in cardiovascular deaths; no reduction in stroke rate was observed. There was no significant effect of vitamin E on total mortality. The only significant adverse effect was an increase in the risk of epistaxis (nosebleeds),[17] likely as vitamin E decreases platelet aggregation.[18] It is noteworthy that vitamin E efficacy was not evaluated with biomarkers, but with mortality or heart attacks, etc. And the authors of the study reported that vitamin E provided no overall benefit and do not support recommending vitamin E supplementation for cardiovascular disease prevention among healthy women.[17]

Unfortunately, the current recommended dietary allowance (RDA) of 15 mg α-tocopherol per day for women or men[19] is not met by more than 90 percent of the population because vitamin E is found in foods not commonly consumed such as almonds, sunflower seeds, and olive oil.[20,21] Based on vitamin E kinetic studies done with deuterium labeled vitamin E, the RDA values appear correct.[22] And with respect to dietary vitamin E intakes, cardiovascular disease risk is lower with higher intakes.[23] Thus, we are left with increased risk of heart disease with low vitamin E intakes, a population that consumes insufficient amounts of vitamin E to meet its needs, and conflicting data concerning the use of multivitamins.[24,25]

Other Dietary Components

Fish oil is one of the possible foods that could be used as a dietary supplement in decreasing the risk of heart disease. A recent meta-analysis suggests a role for fish oil (eicosapentaenoic acid, docosahexaenoic acid) or fish in secondary prevention because a significant reduction in total mortality, coronary heart disease death, and sudden death were reported.[26] However, as noted for the vitamin E studies, there are no biomarkers or intermediate clinical endpoints that could be used for evaluating other nutrients. Additionally, since fish oils are highly polyunsaturated, they require adequate protection from oxidation, reinforcing the concept that adequate vitamin E amounts be consumed.

Hyperhomocysteinemia is associated with increased risk of heart disease. It is unclear as to whether supplementation with folic acid not only will decrease homocysteine levels, but also decrease heart disease risk. The B-Vitamin Treatment Trialists' Collaboration has just reviewed the design and statistical power of 12 randomized trials assessing the effects of lowering homocysteine with B-vitamin supplements on risk of cardiovascular disease.[27] They concluded that the individual trials may not involve sufficient number of vascular events or last long enough to have a good chance on their own to detect reliably plausible effects of homocysteine lowering on cardiovascular risk, but the combined analysis of these trials should have adequate power to determine whether lowering homocysteine reduces the risk of cardiovascular events within a few years.

Conclusion

Heart disease is such a complex disorder that it is not surprising that an easy remedy has not been found. Dietary and lifestyle changes must be dramatic to achieve heart healthy goals.

Research as to how to achieve and maintain these changes are urgently needed. Biomarkers to assess progress toward these goals are also needed. Although it appears overly optimistic to assume that one or two nutrients might have benefit, if such nutrients were discovered, then it is also important to have a clear idea of adverse effects and the level of intake where these become problematic.

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Tuning Up Metabolism With Micronutrients To Prevent Degenerative Disease

Bruce N. Ames, Ph.D.

I propose that a triage system optimized through evolution deals with micronutrient shortages. When micronutrients are in short supply, metabolism required for long-term health (e.g., DNA protection or antioxidant defense), is dispensed with in order to maintain metabolism required for short-term survival (e.g., energy production). Thus, a plentiful supply of micronutrients throughout life would optimize development, minimize DNA damage leading to diseases such as cancer, and maximize longevity. Suggestions for tuning up metabolism to prevent chronic degenerative diseases, some of which affect cognition, are provided.

Poor nutrition has long been linked to increased risk of many diseases, including major public health problems such as cancer, heart disease, and diabetes. It is becoming clear that unbalanced diets are a major contributor to ill health in the population, with smoking following close behind. The human diet requires both macronutrients (fat, carbohydrates) and micronutrients (about 40 essential minerals, vitamins, fatty acids, and amino acids). Historically, most discussion and research involving diet and disease has been directed at macronutrients. Based on our research and that of others, I have come to believe that far too little attention has been given to the importance of optimal micronutrients in the diet, which are required for virtually all metabolic and developmental processes. Today, processed carbohydrate and fat calories come with few micronutrients, are remarkably inexpensive, and there are widespread marginal vitamin and mineral deficiencies even in developed countries such as the United States.[1–3] Micronutrient malnutrition[3] appears to be the norm in the obese.[4]

Significant chronic metabolic damage may occur if micronutrient deficiencies are at levels between those which cause acute clinical symptoms and the recommended daily allowance (RDA).[1,2,5] When one input to the metabolic network is inadequate, there are repercussions for a large number of systems that may lead to degenerative diseases. The optimum intake of any micronutrient is that which is required to maximize a healthy lifespan, which is higher than the amount needed to prevent acute symptoms, and may be higher than the RDA.[1]

Micronutrient shortage during development may be particularly harmful. During the brain growth spurt, from the third trimester of pregnancy through the first 2 years of life, nerves are myelinated and trillions of neural connections are made. These highly energetic processes require a plentiful supply of micronutrients. We are writing a series of comprehensive overviews of the evidence suggesting that an inadequate intake of micronutrients such as iron, omega-3 fatty acids, or choline during this period can result in lasting cognitive dysfunction.[6–8]

The Mitochondrial Connection

Mitochondrial decay appears to be a major contributor to aging and associated degenerative diseases.[9] Aging mitochondria exhibit a decrease in membrane potential, respiratory control ratio, and cellular oxygen consumption, and an increase in oxidant byproducts.[10] Oxidative damage to DNA, RNA, proteins, and lipids in mitochondrial membranes

is a major consequence of this decay,[5,10–13] resulting in functional decline of mitochondria, cells, and organs such as the brain.[5,12] Feeding the mitochondrial metabolites acetyl carnitine and lipoic acid to old rats rejuvenates the mitochondria and improves brain and other function.[*5,10–13]

Micronutrient deficiencies cause DNA damage and accelerate mitochondrial senescence. The production of mutagenic oxidants through mitochondrial decay with age in primary human cells in culture is accelerated by micronutrient deficiencies.[1,2] Deficiency at <50 percent of the RDA is widespread in the United States, e.g., iron (25 percent of menstruating women),[3] zinc (10 percent of the population),[3] or biotin (40 percent of pregnant women).[14] The mechanism has been clarified: these, and several other micronutrients, are required for heme synthesis in mitochondria, and their deficiencies cause a deficit of heme-*a* and therefore of complex IV (an excess of IV minimizes oxidants), of which heme-*a* is an essential component.[1,2,15,16] Complex IV deficits result in oxidant leakage, DNA damage, accelerated mitochondrial decay, and cellular aging.[2,15] By a different mechanism, magnesium deficiency in human cells in culture leads to DNA damage and premature senescence (Killilea & Ames in preparation). Magnesium intakes are very low in about half of the U.S. population, particularly among the poor, obese, and elderly.[3,17,18] The need to set micronutrient requirements to minimize DNA damage has been discussed.[19] We are investigating what level of each micronutrient causes DNA damage in humans.

Common micronutrient deficiencies are likely to result in damage to DNA by the same mechanism as radiation (an oxidative mutagen)[20] and many synthetic chemicals.[21] However, DNA damage resulting from micronutrient deficiencies is likely to be orders of magnitude greater than that caused by normal environmental exposure to radiation,[1,20] as we found in a comparison of chromosome breaks by folate deficiency and radiation.[20] Public health is not served when large amounts of tax dollars are used to address minor hypothetical risks[21] instead of major risks.

Take a Multivitamin for Insurance

More than 20 years of efforts to improve the American diet have not been very successful, particularly for the poor. A parallel approach that focuses on micronutrient malnutrition, in addition to continuing efforts to improve diet, might be more successful. It may be easier to convince people to take an inexpensive and safe multivitamin/mineral pill as insurance against ill health than to markedly change their eating habits. Another useful and inexpensive supplement may be docosahexaenoic acid (DHA) from fish oil; inadequate intakes of omega-3 fatty acids are widespread and appear to be important for brain function.[6,22] Fiber supplementation is also inexpensive; inadequate fiber intakes, both soluble and insoluble, are widespread and important.[23] Fortification of food, such as folate fortification, is another approach that has made a difference. However, fortification does not allow for differences among individuals. Menstruating women need more iron than men or older women, who may be getting too much. Also, the requirements of the elderly for vitamins and metabolites are known to be different from the young, but this issue has not been seriously examined.[24,25] An optimal intake of micronutrients and metabolites can also vary with genetic constitution.[24,25] With more knowledge, it seems likely that a variety of multivitamin pills will be developed that reflects different needs depending on age, sex, genetics, etc. Evidence is accumulating that a multivitamin/mineral supplement is good insurance, and would markedly improve health, e.g.,

heart disease, cancer, immune function, and cataracts, particularly for those with inadequate diets.[1,2,26–37] The caveat is, of course, that too much of many of the minerals (e.g., iron, zinc, copper, and selenium) and some of the vitamins (e.g., vitamin A) are toxic, though taking amounts contained in a typical multivitamin/mineral pill as insurance is not of concern. Advice to take a multivitamin should always be coupled with advice to eat a good diet, as we also need other nutrients like fiber and omega-3 fatty acids not typically found in standard supplements but still essential to a balanced diet.[38] Tuning up metabolism with an optimum intake of micronutrients and metabolites, which vary with age and genetic constitution, may result in a marked increase in health, particularly for the poor, at little cost.

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[*]Conflict of interest. Dr. Ames is one of the founders of Juvenon (www.juvenon.com), a company that has licensed the University of California patent on acetyl carnitine + lipoic acid for rejuvenating old mitochondria (Ames and T. Hagen, inventors), sells acetyl carnitine + lipoic acid supplements, and does clinical trials on them. Ames founder's stock was put in a nonprofit foundation at the founding in 1999. He is director of Juvenon's Scientific Advisory Board, but has no stock in the company and has not taken, and will not take, any reimbursement from them.

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Bone Health

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The principal bone health issue related to vitamins and minerals is osteoporosis, its primary prevention and the support of its pharmacotherapy. The nutrients concerned are calcium and vitamin D. Reports from three recent clinical trials have cast doubt upon the efficacy of both,[1–3] but design flaws in each trial explain their findings, and for both nutrients there is a large antecedent body of evidence conclusively showing both that prevailing intakes are inadequate and that raising those intakes, even late in life, confers a bone health benefit. This evidence is marshaled in three NIH Consensus Conference reports,[4–6] in the DRI monograph,[7] in the Current Dietary Guidelines for Americans,[8] and in the Surgeon General's Report on Bone Health.[9]

Calcium operates in two ways, by protecting and sustaining bone mass and by regulating bone remodeling. Low bone mass and high remodeling activity independently render bone fragile. Calcium's protection of bone mass is achieved by offsetting obligatory calcium losses from the body, which in typical adults are on the order of 200 mg/d, mainly through kidneys and skin. If absorbed calcium is not at least that much, then bone resorption is increased and small volumes of bone are torn down to scavenge their calcium. Resorption is under direct control of PTH, and PTH secretion is an inverse function of absorbed calcium intake. Since net intestinal calcium absorption averages only about 10 percent, ingested intake needs to be high if bone mass is not to be sacrificed to sustain ECF [Ca^{2+}].

Closely connected with this mechanism is the role calcium plays in regulating bone remodeling. The high PTH secretion of low calcium intakes increases bone remodeling activity. Remodeling loci on bony trabeculae produce focal weakness and lead to trabecular fractures. Partly because of prevailing low calcium and vitamin D status and partly because of estrogen withdrawal, remodeling in the cancellous bone of women triples from just before menopause to age 65.[10] Remodeling activity is now recognized to be a predictor of fracture,[11] and the reduction of fracture risk with various interventions is better explained by the reduction in remodeling than by their small effect on bone mass.[12] This is seen graphically in the divergence of fracture risk curves between treated and control individuals in published trials—a divergence that begins within days or weeks of starting treatment, consistent with the immediate suppression of PTH-mediated bony resorption when calcium intake is raised.[13]

Like calcium, vitamin D operates in multiple ways. Most straightforward is its classical role in facilitating calcium absorption. The efficiency of calcium absorption is a direct function of vitamin D status. Low status effectively raises the calcium requirement. Calculations easily demonstrate that, in the absence of vitamin D-mediated active calcium absorption, ingested calcium intake would have to be 3,000 mg/d or higher to ensure absorption of enough calcium to offset obligatory losses.[14] Low vitamin D status, like low calcium intake, leads to increased PTH secretion and increased bony remodeling, and hence aggravates the effects of prevailing low calcium intakes. Absorption is not optimal at serum vitamin D levels below 80 nmol/L (32 ng/mL).[15] Vitamin D also improves neuromuscular function and thereby reduces falls, a major contributor to osteoporotic fractures.[16,17]

Existing recommendations for calcium intake (1,000–1,500 mg/d)[5,7] remain approximately correct, but vitamin D recommendations[7] are low by nearly an order of magnitude. A large and still growing body of evidence shows conclusively that 400 IU/d (the AI for adults ages 50–70) will raise serum 25(OH)D by less than 10 nmol/L (2.5 ng/mL).[18] A postmenopausal woman with a typical value of 50 nmol/L would require at least 1,200 IU/d to reach what is now widely considered to be the low end of the normal range (80 nmol/L).

Because of widespread confusion and misinterpretation of the results of the Women's Health Initiative (WHI) trial of calcium and vitamin D, and the resulting potential for damage, some explanation of what happened seems indicated. Calcium is a threshold nutrient, i.e., bony protection occurs only up to a certain intake (the "threshold"), above which no further effect is seen. The threshold is, in fact, the basis for the current AI.[7] The women entering WHI all had calcium intakes averaging between 1,100 and 1,200 mg/d, i.e., many were already at or above the calcium intake threshold. Hence, these women were predicted to show little or no effect of supplemental calcium.[19] To muddy the waters still further, women in WHI were allowed to continue taking their personal calcium supplements in addition to the study tablets. Also, roughly half were receiving estrogen and half were obese. Finally, those with low bone mass were continued in trial even if they were taking bisphosphonates. Any of these factors, by itself, might have been enough to obscure any effect of the study intervention. Together, they all but guaranteed failure. It is actually somewhat surprising, therefore, that there was a 12 percent nonsignificant reduction in hip fracture in the cohort as a whole, and a 30 percent significant reduction in treatment-adherent subjects.

For vitamin D, the dose employed in WHI (400 IU/d) has been shown to be insufficient to reduce fractures detectably,[20] and hence in retrospect would not have been predicted to have an effect.

For both interventions, treatment adherence was a major problem. By study's end, only about 60 percent were taking the prescribed number of pills. That was a particular problem also in two recent failed trials from the United Kingdom employing 800 IU vitamin D per day, and requiring adherence to a daily pill-taking regimen.[2,3] In both, documentable compliance was no higher than 40–50 percent, and in neither was an effect found. By contrast, a roughly comparable trial, requiring only three doses of vitamin D per year (averaging at 800 IU/d),[21] found a statistically significant reduction in osteoporotic fractures and also produced a rise in serum 25(OH)D near the optimal range. Adherence problems such as these raise important questions about the optimal mode of delivery of these important nutrients, and suggest that fortification may be preferred over supplementation.

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Evidence-Based Practice Center Presentation: The Efficacy of Multivitamin/Mineral Supplement Use in the Primary Prevention of Chronic Disease: A Systematic Review

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Introduction

Multivitamin/mineral supplements are the most commonly used nutritional supplements in the United States. Whether their use prevents chronic disease warrants rigorous evaluation.

Objective

We conducted a systematic review to synthesize published data from randomized controlled trials (RCTs) on the efficacy of multivitamin/mineral supplement use in the primary prevention of chronic disease in the general adult population.

Methods

We defined multivitamin/mineral supplements as any supplements containing three or more vitamins and/or minerals without herbs, hormones, or drugs, each at a dose less than the upper limit (UL) determined by the Food and Nutrition Board. The following chronic diseases were considered: (1) breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric cancer, or any other malignancy; (2) myocardial infarction, stroke; (3) type 2 diabetes mellitus; (4) Parkinson's disease, dementia; (5) cataracts, macular degeneration, hearing loss; (6) osteoporosis, osteopenia, rheumatoid arthritis, osteoarthritis; (7) nonalcoholic steatorrheic hepatitis, nonalcoholic fatty-liver disease; (8) chronic renal insufficiency, chronic nephrolithiasis; and (9) HIV infection, hepatitis C, tuberculosis.

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 RCTs 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) no human data; (3) only pregnant women; (4) only infants; (5) only subjects of age ≤18 years; (6) only patients with chronic diseases; (7) only patients receiving treatment for chronic disease or living in long-term care facilities; (8) only studied nutritional deficiency; (9) did not address use of supplements separately from dietary intake; (10) did not cover defined disease endpoints; or (11) was an editorial, commentary, or letter.

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 (criterion fully met) to each item. The score for each quality category was the percentage of the total points 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, eligibility of participants, 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.

Results

Our search identified 10 articles published from 1993 to 2006 that addressed the efficacy of multivitamin/mineral supplements in the primary prevention of cancer, cardiovascular disease, cataract and age-related macular degeneration (AMD).[1–10] Data on other diseases were lacking. The 10 articles documented results from 5 RCTs, including (1) the Linxian General Population Trial in China, (2) the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study in France, (3) the Multi-Center Ophthalmic and Nutritional Eye-Related Macular Degeneration Study in the United States, (4) the Roche European American Cataract Trial (REACT) in the United States and the United Kingdom, and (5) the Age-Related Eye Disease Study (ARED) in the United States.

Quality of these studies was good in terms of randomization, double-masking, ascertainment of trial endpoints, adherence, and an intention-to-treat approach in statistical analyses. There was a paucity of data on self-selected supplement use and medication use that

might have effects on the efficacy of study supplements. None of the studies reported success of blinding and the extent of unintended crossover.

Data on cancer and cardiovascular outcomes came from the Linxian General Population Trial and the SU.VI.MAX trial. In the Linxian General Population Trial, there were borderline significant reductions in gastric cancer incidence (relative risk [RR] 0.84, 95 percent confidence interval [CI] 0.71–1.00), gastric cancer mortality (RR 0.79, 95 percent CI 0.64–0.99), and cancer mortality (RR 0.87, 95 percent CI 0.75–1.00) in persons with daily supplementation with combined β-carotene, vitamin E and selenium supplements at doses 1 to 2 times the U.S. Recommended Daily Allowances (RDAs) for 5 years, but there were no significant effects on total cancer incidence and cerebrovascular mortality.[1] The SU.VI.MAX study documented a reduced cancer risk by daily supplementation with vitamin C (120 mg), vitamin E (30 mg), β-carotene (6 mg), selenium (100 μg), and zinc (20 mg) for 7.5 years as compared to placebo in men but not in women (RR 0.69, 95 percent CI 0.53–0.91 and RR 1.04, 95 percent CI 0.85–1.29, respectively),[3] and a reduced prostate cancer risk in men with normal prostate-specific antigen levels at baseline (hazard ratio 0.52, 95 percent CI 0.29–0.92),[9] but no significant effect on ischemic cardiovascular disease incidence.[3] In this trial, men had lower serum levels of vitamin C and β-carotene than women at baseline.

Multivitamin/mineral supplement use for 3–6 years had no significant benefits in preventing cataract.[2,4–6] Combined zinc (80 mg zinc oxide and 2 mg cupric oxide) and antioxidants (vitamin C 500 mg, vitamin E 400 IU, and β-carotene 15 mg), at doses 5–15 times the RDAs, had beneficial effects on AMD only in those with intermediate AMD in one or both eyes, or those with advanced AMD in one eye.[7]

Total mortality was lower among those who received β-carotene, selenium, and vitamin E in the Linxian General Population Trial (RR 0.91, 95 percent CI 0.84–0.99).[1,8,9] In the ARED study, total mortality was not significantly higher or lower among those receiving antioxidants, alone or in combination with zinc, as compared to those receiving placebo.[6,7] 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 (RR 0.63, 95 percent CI 0.42–0.93 in men and RR 1.03, 95 percent CI 0.64–1.63 in women).[3]

Conclusion

Limited evidence suggests some benefits of multivitamin/mineral supplements in cancer prevention among individuals with poor nutritional status or a diet with less fruits and vegetables. The heterogeneity in the study populations upon which this evidence is based limits generalization to the U.S. population. Multivitamin/mineral supplements confer no significant benefit in preventing cardiovascular disease and cataract. Persons at high risk of advanced AMD may benefit from supplementation with a combination of antioxidants and zinc. The overall strength of evidence on the efficacy of multivitamins/minerals for the prevention of chronic disease is rated as very low.

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Clinical Trials of Vitamin and Mineral Supplements for Cancer Prevention

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For the past three decades, cancer prevention clinical trials have been based on rationales developed from laboratory and epidemiological research that has identified numerous natural and synthetic agents for further testing in people. The premise is that medical interventions that aim to prevent, arrest, or reverse either the initiation phase of carcinogenesis or the progression of premalignant cells have become an important research aim for cancer prevention. A large part of this effort has focused on the identification of bioactive food components (BFCs) in the diet that appear to decrease or increase the risk of cancer. Among the BFCs of interest, investigations of vitamins and minerals have produced intriguing results, especially in observational epidemiologic studies.[1] Based on the results from these studies, clinical trials of vitamin and mineral supplements have been designed and conducted to establish their benefit, or lack of benefit, for cancer prevention. Public interest appears high for cancer prevention clinical trials of multivitamins—defined as preparations with two or more vitamins and/or minerals, regardless of the form of consumption—because approximately 20–30 percent of the population consumes multivitamin supplements daily.[2] However, there are few large, randomized, placebo-controlled clinical trials of multivitamins with specific cancer sites as the primary endpoint. Selected larger trials are reviewed below; results from these trials form the basis for clinical trials now underway, which should report results within the next few years.

The Nutrition Intervention Trials (i.e., the Linxian Trials) were conducted by the National Cancer Institute (NCI) in collaboration with the Chinese Institute of the Chinese Academy of Medical Sciences. The Linxian Trials were based on epidemiological evidence that the people of Linxian, China, had low intakes of various nutrients and one of the world's highest rates of esophageal cancer and dysplasia, and gastric cardia cancer.[3] The results of the two Linxian Trials, which were randomized, double-blind chemoprevention trials, were the first human experimental studies to show that multivitamin supplementation in a population that was borderline nutritionally deficient could lower the risk of stomach cancer and a possible modest benefit against esophageal cancer. The Linxian General Population Trial began in 1986 and randomized 29,594 adults ages 40–69 who received 1 of 4 combinations of multivitamin supplements containing retinal and zinc; riboflavin and niacin; vitamin C and molybdenum; and β-carotene, vitamin E, and selenium each day for 5 years. Doses were equivalent to 1–2 times the U.S. recommended daily allowances (RDAs).[4] A second trial, the Linxian Dysplasia Trial, enrolled 3,318 adults ages 40–69 with evidence of severe esophageal dysplasia, a precursor for esophageal cancer. Trial participants were randomized to receive either a placebo or a daily supplement of 14 vitamins and 12 minerals, at 2–3 times the U.S. RDA, for 6 years.[5]

Results of the general population trial indicated a significant benefit for those receiving the β-carotene/vitamin E/selenium combination, including a 13 percent reduction in cancer mortality, which included a 21 percent decrease in stomach cancer mortality and a 4 percent decrease in deaths from esophageal cancer.[4] Results from the dysplasia trial showed that supplementation had a significant effect, conferring a 1.2 times chance of having no esophageal

dysplasia after 30 and 72 months of intervention with a multivitamin, multimineral combination compared to those participants who were given the placebo.[3] To add to these important findings, postintervention followup indicates that the beneficial effects of the β-carotene/vitamin E/selenium combination in the general population trial is still evident up to 10 years after completion of the intervention. These benefits were consistently greater in participants who were younger at the beginning of the intervention.

The Physicians' Health Study (PHS), a population trial enrolling approximately 22,000 U.S. physicians, was a 12-year randomized, double-blind, placebo-controlled trial with a 2 x 2 factorial design that tested aspirin and β-carotene (50 mg on alternate days) for the prevention of cardiovascular disease (CVD) and cancer.[5] The PHS was begun in 1982 and ended in 1995. The β-carotene component showed no significant evidence of benefit or harm from β-carotene on either cardiovascular disease or cancer in this predominately non-smoking population; the aspirin component was stopped in 1987 after data indicated a 44 percent reduction on the risk of a first heart attack with aspirin use. PHS II, a follow-on, randomized, double-blind, placebo-controlled trial to the PHS, is in progress and will be completed in 2008.[6] The PHS II includes approximately 15,000 U.S. physicians, with at least one-half having participated in PHS I. PHS II investigates effect of vitamin E, vitamin C, and multivitamin supplementation alone or in combination on cancer, CVD, and eye disease. PHS II is the first randomized multivitamin trial to test hypotheses that vitamin E reduces the risk of prostate cancer and vitamin C may potentially be of benefit in the primary prevention of cancer.

Other clinical trials of multivitamin supplement use and cancer prevention have produced negative or possibly harmful results for the primary end points regarding supplement use. The Finnish–NCI collaborative Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) of 29,133 male smokers ages 50–69 reported negative results.[7] Participants were randomly assigned to 1 of 4 supplementation regimens, including α-tocopherol (50 mg) and β-carotene (20 mg) together, individually, or placebo. Results of the trial indicated that among those men taking β-carotene, there was a 16 percent increase in lung cancer incidence; results for α-tocopherol indicated a statistically insignificant 2 percent decrease in lung cancer incidence. Interestingly, prostate cancer, a secondary endpoint, was reduced one third during the intervention, but the benefit was reduced after supplementation concluded.[8] The Beta-Carotene and Retinol Efficacy Trial (CARET) reported an increase (39 percent) in lung cancer incidence among male smokers who received a combination of β-carotene and retinyl palmitate.[9] These were surprising results because observational and epidemiologic studies had suggested that individuals, who consume high dietary levels of β-carotene, generally from a high level of consumption of vegetables and fruits, have a lower risk of cancer and CVD. Since the results of ATBC and CARET were reported, there has been much discussion of the causes for these negative results; this has been reviewed elsewhere.[10]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), sponsored by NCI, and based in part on results from the ATBC trial, is a randomized, double-blind, placebo-controlled, population-based trial. SELECT began in 2001 and studies 35,534 healthy men and the efficacy of selenium (200 μg L-selenomethionine) and vitamin E (400 IU dl α-tocopherol acetate), alone and in combination, for the prevention of prostate cancer.[11] Study participants include White, Hispanic, Hispanic African American, and Asian men ages 55 and older, and African American men ages 50 and older. The trial is being conducted at 435 SELECT sites in the United States,

Puerto Rico, and Canada. The trial will last 12 years, including 7 years of intervention plus follow-up, with a primary endpoint of biopsy-proven prostate cancer. Secondary goals of SELECT are to assess the effect of selenium and vitamin E on the incidence of lung and colon cancer and on overall survival rates. In addition, SELECT will examine the molecular genetics of cancer risk, explore possible associations between diet and cancer, assess age-related memory loss, and assess participants' quality of life. An important feature of SELECT is the collection/preservation of blood sample components that will permit the evaluation of a wide variety of biochemical and molecular hypotheses, particularly those that are prominent in prostate carcinogenesis (i.e., polymorphisms in hormone-related genes such as the androgen receptor, CYP17, SRD5A2, and HSD3β2).[12] This investigation is being conducted to provide a better understanding of variations in response to multivitamins.

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI. MAX) study is a large, population-based, double-blind, placebo-controlled, randomized trial assessing the impact of daily supplementation with antioxidant vitamins and minerals on risk of cancer and heart disease in men and women.[13] An adjunct trial to the main SU.VI.MAX trial enrolled 13,017 men and women who were given either placebo or a single capsule containing a combination of 120 mg vitamin C, 30 mg α-tocopherol, 6 mg β-carotene, 100 μg selenium, and 20 mg zinc, taken daily for 8 years. These dosages are 40–80 percent lower than those used in other trials, such as ATBC, CARET, and PHS, examining the effects of multivitamin supplementation on cancer risk. Duration of supplementation in SU.VI.MAX is the second longest among antioxidant supplementation trials after PHS I. In the adjunct study, supplementation was associated with a moderate, nonsignificant reduction in prostate cancer rate.[13] However, there was a statistically significant reduction in men with normal baseline PSA who received the supplements; in men with elevated PSA at baseline, supplementation was associated with a borderline significant increase in risk of prostate cancer. Supplementation did not affect the levels of several biomarkers of prostate cancer risk, including PSA and IGF.

Clinical trials of multivitamin supplements for cancer prevention have provided clues to their potential benefit. A systematic approach for discerning combinations that prevent specific cancers is being conducted through basic experimental science that will lead to additional human trials. The NCI is currently investigating multivitamin supplements in more than 20 trials, many of them small phase 1 and phase 2 trials to determine safety and efficacy. Results from these small trials and ongoing large-scale clinical trials will help direct future research to answer the many unanswered questions about the potential use of multivitamin supplements for cancer prevention.

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Studies of Cost-Effectiveness of Multivitamin/Mineral Supplements for Prevention of Chronic Disease in Adults

Joan DaVanzo, Ph.D. and Allen Dobson, Ph.D.

Vitamins are essential components of a normal diet, and sufficient amounts are thought to be needed to ensure optimum health. Vitamin supplementation, along with a healthy diet, is recommended as being key to maintaining good health. Surveys of dietary intake and physical and laboratory data reveal that the usual American diet does not always provide a sufficient level of vitamins and minerals. A 2002 article in "The Journal of the American Medical Association" maintained that "Pending strong evidence of effectiveness from randomized trials, it appears prudent for all adults to take vitamin supplements."[1]

The purpose of this research, commissioned by Wyeth Consumer Healthcare, is to estimate both the health effects and expected cost savings in healthcare for the average American who takes a daily multivitamin. We sought to determine if multivitamin use has an independent effect on self-reported health status, controlling for demographics, healthy behaviors, and other factors known to influence health. Other areas examined in the analysis included chronic health conditions and health risk behaviors among users and nonusers of multivitamins.[1,2]

The two primary questions guiding the study scope and analytic approach are:

1. What are the effects of multivitamin use on self-reported health status?

2. What are the potential medical cost savings associated with the health effects of multivitamin use?

Data Sources

The study used two complementary data sources, the National Health and Nutrition Examination Survey (NHANES), administered through the Centers for Disease Control and Prevention's National Center for Health Statistics; and the Medical Expenditure Panel Survey (MEPS), administered through the Agency for Health Care Research and Quality.

Analytic Framework

The key study issues were to determine (1) if multivitamin use has an independent effect on self-reported health status, after taking into account the known predictors of good health, and (2) whether this effect is associated with lower healthcare expenditures. In order to demonstrate cost savings, multivitamin use must first be shown to be a significant predictor of health status, controlling for other known covariates, such as age, gender, race, healthy or protective behaviors, body mass index, usual source of healthcare, etc. Healthcare costs included all medical care expenditures with prescription drugs and chiropractic care, but excluded alternative medicine (e.g. acupuncture) and over-the-counter drugs.

Analysis

The analytic approach to addressing the research question was comprised of two distinct phases. The first phase examined the role of multivitamin use in health status. The second phase incorporated the models used in phase one to calculate savings in medical care expenditures among people who took multivitamins vs. nonusers. We linked cost savings associated with self-reported good health to changes in good health associated with long-term multivitamin use.

Key Study Findings

In building our models, the first step was to determine the extent to which self-reported good health is related to different lengths of multivitamin use, controlling for age. The second step was to add sex, race, ethnicity, and source of medical care to the model along with multivitamin use. To determine cost savings, we made three different comparisons:

- The unadjusted difference in average annual healthcare costs for multivitamin users vs. nonusers

- The savings in health care costs due to increased good health for long-term (>11 years) multivitamin users

- The difference in costs for long-term users (>11 years) vs. short-term users (<11 years)

Key findings from the study are:

- Multivitamin use is positively associated with the odds of self-reported good health across all length of use categories, controlling for age, sex, race, ethnicity, and source of medical care. As a group, multivitamin users tend to engage in health enhancing behaviors more frequently than their nonuser counterparts and incur approximately $100 less per year in health care expenditures. This translates to an annual savings of $8.0 billion from reduced healthcare costs for those who use a multivitamin and engage in health enhancing behaviors.

- After age, socioeconomic factors (e.g., education and income) are the primary explanatory variables underlying the multivitamin–health relationship. When education and/or income are added to this study's models, they are highly significant predictors of health status.

- Multivitamin use is positively associated with other healthy behaviors, such as not smoking, moderate use of alcohol, physical activity, and healthy eating.

- Even when education and/or income are added to our most comprehensive models, long-term multivitamin use (>11 years) remains a statistically significant predictor of good health.

- The estimated average probability of being in good health for long-term multivitamin users was 89 percent. The estimated average probability of being in good health had users not taken multivitamins was 76 percent.

- Given their characteristics, we estimated the average annual health expenditures for all long-term multivitamin users if they were in good health were found to be $4,835. Average annual health expenditures for all long-term multivitamin users if they were in poor health were found to be $11,580. Approximately 13 percent of long-term multivitamin users went from poor health to good health in this analysis (89 per cent vs. 76 percent). The value of "good health" for the long-term multivitamin user is $6,745, with aggregate cost savings of $3.9 billion.

- If current multivitamin users who have taken multivitamins for less than 11 years had actually taken multivitamins for at least 11 years in 2001, the total health care savings would be $58.1 billion, or an average savings of $813 per multivitamin user.

Table 1 summarizes the findings of the cost analyses.

Table 1. Summary of Cost Analyses

	Aggregate Annual Healthcare Cost Savings	Expected Average Healthcare Cost Savings	Per Capita Annual Healthcare Cost Savings
Comparison of multivitamin users vs. nonusers	$8.0 billion		$104
Value of "good health" for the long-term multivitamin user	$3.9 billion	$6,745	$749
Savings if shorter-term users were long-term users	$58.1 billion	$6,224	$813

Source: Lewin Group estimates based on analyses of the National Health and Nutrition Examination Survey (NHANES) 1999–2000 and the 2001 Medical Expenditures Panel Survey (MEPS).

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Evidence-Based Practice Center Presentation: The Safety of Multivitamin/Mineral Supplement Use in the General Population of Adults and Children: A Systematic Review

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Introduction

In the absence of standardized methods to assess risk associated with vitamin/mineral supplement use, adverse effects have been reported in a variety of ways; in some cases reflecting a subjective self-assessment of "safety," and in others a specific assessment of risk based on objective indicators, such as laboratory tests.

Objective

To weigh the potential risk and benefits of vitamin/mineral supplement use, we conducted a systematic review of published data on the safety of multivitamin/mineral supplements (MVS) and commonly used single vitamin or mineral supplements in the general population of adults and children.

Methods

Literature Sources

We searched for relevant articles published from 1966 to February 6, 2006 using MEDLINE®, EMBASE®, and the Cochrane database. We also reviewed the tables of contents of 15 relevant journals from January 2005 through February 2006. Additional articles were identified by searching references in pertinent articles or by querying experts.

Eligibility Criteria

An article was included if it reported on adverse effects of multivitamin/mineral supplement use and did not meet any of the following exclusion criteria: (1) not written in English; (2) no human data; (3) only pregnant women; (4) only infants; (5) only patients with particular chronic diseases; (6) only patients receiving treatment for chronic disease or in long-term care facilities; (7) did not address use of supplements separately from dietary intake; or (8) was an editorial, commentary, or letter.

Article Inclusion/Exclusion

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

Extraction of Data

Reviewers abstracted data on study design, study participants' characteristics, supplement use (type, dose, and chemical forms of study supplements, and duration, frequency, and timing of study supplement use), and study results. Each data abstraction form was verified by a second reviewer for completeness and accuracy.

Assessment of Causality

We assessed the likelihood that reported adverse effects were caused by supplement use by considering temporal relationship, lack of alternative causes, dose–response relationship, evidence of increased circulating levels of the nutrient under investigation, and response to rechallenge.

Results

Few studies reported adverse effects in an objective, systematic fashion. In most cases, adverse effects were reported with a subjective assessment of safety defined by investigators' or by participants' self-perception.

We identified 11 studies using MVS preparations for prevention of chronic disease in which the following criteria were met to assess adverse effects: (1) randomized allocation of treatment, (2) adequate sample size, (3) well-defined population, (4) defined dose and total intake of the nutrient(s), and (5) adequate duration of exposure. Doses were usually 2 to 10 times the recommended daily allowance. Overall, we found no consistent pattern of increased adverse effects in the active group compared with the placebo group, with the exception of changes in skin color, which was common in studies in which beta-carotene was part of the MVS.[1,2] In the few studies using multivitamin supplements where mortality was compared between active and control groups, no significant effects of supplementation on this outcome was found.[1–4]

Calcium

A recent Cochrane review,[5] found that studies were too different (exposure time, doses, etc.) to draw a general conclusion regarding the safety of calcium supplements. One recent randomized controlled trial (RCT) reported incidence of kidney stones in postmenopausal women consuming a 1g/d calcium carbonate supplement for 8 years (with 400 IU of vitamin D).[6] Kidney calcifications were also described in a case report of a patient consuming 1g/d of calcium lactate, but in this case chronic hypokalemia may have played a major role.[7]

Vitamin A

Two RCTs found that long-term use of retinol supplements increased serum triglyceride levels. In the Carotene and Retinol Efficacy Trial (CARET),[8] the active group (25,000 IU/day of retinol) exhibited a modest but statistically significant rise in serum triglycerides after 8 years of follow-up. This increase occurred within the first year. Another study in healthy adults aged 18–54 years[9] compared the effects of 15,000 IU of vitamin A (4500 RE) versus 75 IU for 5 years and found an increase in serum triglycerides in the high-dose group, from 1.0 umol/L at baseline to 1.30 umol/L at year 3 and 1.18 umol/L at year 5. There was no effect on liver enzymes, and no increase above defined maximal plasma retinol levels (3.49 umol/L).

The possibility that high intakes of retinol increase the risk of hip fractures, particularly in postmenopausal women, was raised by one observational study that tracked 35–77-year-old women for 18 years.[10] This study reported an increased risk of hip fractures in persons at the higher quartile of total retinol intake, but found no significant difference in fracture risk between users and nonusers of MVS or vitamin A. Another observational study in 34,000 postmenopausal women found no significant correlation between retinol intake and hip or all-type fractures.[11] Cross-sectional studies of the Women's Health Initiative cohort[12] found no correlation between diet-only or total retinol intake and bone mineral density. A cross-sectional analysis of national survey data found no correlation between serum retinyl ester concentrations and bone mineral density.[13]

Vitamin E

At a dosage of 50 IU per day, synthetic vitamin E supplementation increased subarachnoid hemorrhage (relative risk 1.50, CI 0.97–2.32) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) in heavy smokers.[14,15] In the Women's Health Study,[16] participants received 600 IU of natural source vitamin E every other day. No excess adverse effects were identified in the active group, except for a marginally significant increase in epistaxis. Authors attributed this to a chance finding, since there was no other evidence of an effect on bleeding (coagulation time, hemorrhage, hemorrhagic stroke, etc). The Primary Prevention Project (PPP) study[17] administered synthetic α-tocopherol of 300 mg/d for 3.6 years to people >65 years of age. Only bleeding and mortality were monitored, with no significant differences between active and control groups when the trial was prematurely stopped. In the ATBC trial, the overall relative risk of total mortality during the 8 years of posttrial follow-up was 1.01 (CI 0.96 to 1.05).[18] Other trials documented a slight excess of deaths among persons receiving vitamin E supplements, but based on the causes of death, the investigators concluded that excessive deaths were unlikely to be attributed to vitamin E.[19]

Selenium

One RCT administered 200 µg/day of selenium for 4.5 years to 1,300 patients and reported that of the active group had more gastrointestinal symptoms than in the placebo group (21 vs. 14 participants). There were no differences in plasma selenium levels between those who did not have symptoms and those who did.

Iron

A small RCT in 40 iron-sufficient, nonanemic children showed a significant reduction in weight gain over 4 months in supplemented (3mg/kg/day) vs. nonsupplemented children.[20] More recent trials have not fully clarified this issue, because they targeted deficient populations and/or included other micronutrients in the intervention formulation

Conclusion

Limited data suggest MVS use for 1–8 years is safe. Among the adverse effects reported in RCTs, a prominent one is yellowing of the skin when beta-carotene is administered. Two RCTs found modest increases in serum triglyceride levels after vitamin A supplementation. One observational study suggested that calcium supplementation may increase the risk of kidney stones. Vitamin E supplementation was associated with an increase in incidence of epistaxis but not associated with an increased risk of more serious bleeding events.

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Theoretical Basis for Harm

Diane Benford, Ph.D.

This presentation will draw largely from a recent report on a technical workshop on nutrient risk assessment, convened by the Food and Agriculture Organization (FAO) and World Health Organization (WHO),[1] and the reports of the European Union, United Kingdom, and United States authoritative bodies used as major sources at that workshop.[2–4]

It is widely accepted that risks for nutrient substances form separate dose–response relationships. At lower doses, risk of ill health due to nutritional deficiency increases with decreasing dose. At higher doses, risk of ill health due to toxicity increases with increasing dose. These two dose–response curves overlie to produce an apparent "U" shape, with the base of the "U" representing the intake range not associated with adverse effects. The width of this range varies for different nutrients. For example, the range for vitamin C is broad. Different authorities recommend adult reference intakes in the region of 45–90 mg/d and note possibility of harmful effects at doses above 1000 mg/d, a difference in excess of 10 fold.[2,5,6] At the other extreme, recommended intakes of vitamin A are 600–900 µg retinol equivalents per day and there is evidence of harm at intakes above 1500 µg retinol equivalents per day.[2,3] The width of the range may also vary for the same nutrient at different stages of life. However, even this may be an oversimplification, since there may be a number of dose–benefit relationships and dose–toxicity relationships for the same nutrient, such that a dose that is beneficial for some subgroups may be harmful to others within the same population.

The WHO/FAO workshop defined an upper level of intake as the maximum level of habitual intake from all sources of a nutrient or related substance judged to be unlikely to lead to adverse health effects in humans.[1] The upper level is not a threshold for adverse effects, and some individuals will be less susceptible to toxicity than others. Marginally exceeding an upper level occasionally by a small amount is unlikely to be harmful, but as the amount above the upper level increases, it becomes more likely that some people will suffer harm.

The nature of possible adverse effects varies with different nutrients and whether they are consumed in food or in concentrated form as supplements. Large single doses of some nutrients are known to cause gastrointestinal effects such as nausea, diarrhea, or constipation (e.g., vitamin C, iron), which are reversible on lowering the dose. Others may have more serious and irreversible effects. For example there is evidence that vitamin A can cause malformations of the unborn child and also liver damage. In other instances there are plausible links, based on a combination of epidemiological data, case reports, and results of animal experiments, between nutrient intake and some major public health problems, such as cancer, bone health, and neurological conditions. Manganese is clearly neurotoxic and is known to cause a syndrome resembling Parkinson's disease as a result of occupational exposure by inhalation, but there are very few data of relevance to possible effects of intakes from diet and supplements. Two trials intended to investigate the hypothesis that β-carotene could reduce cancer risk were halted when supplementation at 20–30 mg/d showed an association with increased incidence of lung cancer in smokers and asbestos-exposed individuals. However, an explanation for this observation has still not been determined.

For some vitamins and minerals, such as vitamin B12, harmful levels have not been reported, but this may be related to a lack of evidence rather than any fundamental difference that renders them nontoxic regardless of intake.

Whether there is a possibility of harm from multivitiamin (MVM) supplements at the U.S. recommended daily allowances (RDAs) levels will depend on the total amount taken in from the diet as well as the width of the range of safe intake. Thus people who regularly consume liver and liver products have a high intake of vitamin A, and taking MVM supplements could result in exceeding the upper levels, which could be harmful to some individuals. Similarly, concomitant use of a number of different supplement products, individually at RDA levels, could lead to a total intake above upper levels. A further complication is that different sources of a single nutrient may be chemically different, which could lead to different biological properties with respect to both function and toxicity (e.g., cholecalciferol and ergosterol as sources of vitamin D). Some nutrient sources present in supplements are poorly defined chemically (e.g., components of mineral yeasts). There may also be concern about harmful effects of contaminants and other nonnutrient components of some supplements.

The available data on harmful levels of nutrients are generally limited. Most studies, whether in humans, experimental animals, or in vitro systems, are conducted not for characterizing adverse effects but for other purposes such as investigating possible benefits.[1] Animal studies may be useful for investigating mechanisms of effect and determining biological plausibility of observations from epidemiological studies, but comprehensive packages of studies, such as those used to assess toxicity of other types of chemicals, are rarely available. Furthermore, studies conducted at high doses in animals may result in nutrient imbalance not relevant to lower doses.

Controlled human studies have been conducted to investigate beneficial effects, and generally have not included adequate measures for reporting adverse effects. Also, they often involved only one supplemental dose level and so are not informative on dose–response relationships. The value of such studies could be improved in the future if they incorporate relevant markers of potential adverse effects, selected on the basis of biological plausibility or animal studies. Biomarkers of total nutrient status might help to provide data on dose–response relationships.

Opportunities for using postmarket surveillance to establish safety of MVM supplements are very limited, because it would be important to consider total nutrient intake and specific sources of nutrients in such investigations. If an acute effect (e.g., gastrointestinal effects) occurs within a few hours of taking a supplement, then it might be possible for the consumer to make the link and report an adverse effect. But longer-term effects would be extremely difficult to link to a particular supplement. There would also be limitations related to diverse regulatory contexts in different countries.

While the general principles of nutrient risk assessment have been established, there are enormous gaps in the information required to conduct a robust risk assessment. A systematic approach to filling these research gaps may not be feasible in terms of the costs and ethics of conducting appropriate studies, and there is a need to prioritize on nutrients of concern. At the

very least, it would be important for controlled trials of purported beneficial effects to include appropriate measures of harm.

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