The Benefits of Nutritional Supplements

FOURTH EDITION

Compiled by Annette Dickinson, Ph.D.

Introduction by Steve Mister

Council for Responsible Nutrition

The Science Behind the Supplements®

ABOUT THE AUTHOR

Annette Dickinson, Ph.D., worked in Washington, D.C., for over 30 years for the Council for Responsible Nutrition (CRN). She was CRN's original staff member at its founding in 1973 and her responsibilities evolved as the organization grew over the years. She was primarily responsible for scientific and regulatory affairs and served as CRN's President prior to her retirement and move to Minnesota (her husband's home state) in 2005.

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Dr. Dickinson has authored four editions of CRN's publication *The Benefits of Nutritional Supplements*, a comprehensive review of the evidence demonstrating the health benefits of core nutritional supplements including multivitamins. The first edition appeared in 1987, and this 2012 edition is the fourth.

She was appointed in 2002 to serve a three-year term on the U.S. Food and Drug Administration's Food Advisory Committee. She was appointed by President Clinton to the Commission on Dietary Supplement Labels (1995-1997) and has been a frequent witness before the U.S. Congress and at other public forums. Her expertise includes the legal and technical aspects of marketing dietary supplements, including provisions relating to labeling, advertising, and good manufacturing practices. She earned her Ph.D. in nutritional science and her M.S. in food science from the University of Maryland.

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www.crnusa.org

Published by Council for Responsible Nutrition (CRN), Washington, D.C.

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INTRODUCTION BY STEVE MISTER

President and CEO, Council for Responsible Nutrition

The pursuit of health has never been more informed. We know more about the fields of medicine and nutrition than ever. Technological advances now allow scientists and clinicians to predict one's susceptibility to certain diseases or conditions by analyzing the DNA in cells obtained from a cheek swab. We know that the conditions a fetus is exposed to *in utero* can influence the risk of disease in adulthood. We've come so far in understanding the biology of our bodies and the biochemistry of the nutrients and other substances we ingest. The United States is recognized among the leaders of the world in technology and medicine. And yet, despite all these advances, Americans are more unhealthy, more overweight or obese, more prone to chronic disease than ever. Where did we go wrong?

Part of the answer may reside within the conflict currently being waged over healthcare reform—not the financing of healthcare, but the ways we care about health itself. The current paradigm of healthcare (or "disease care" is the better term) incentivizes physicians to treat symptoms of disease rather than preventing disease in the first place. Medical care is "siloed" by specialty area with specialists working independently of one another to treat individual symptoms rather than as a team to address the underlying causes of the symptoms. Consumers have been programmed to think there is a "magic pill" to address any and all ailments. This paradigm can no longer continue because it is ineffective, inefficient, and far too costly.

A new paradigm of healthcare is emerging: integrative healthcare, whose aim is to prevent disease in the first place and, when the need to treat the disease arises, to start treatment by addressing the underlying cause(s) or origin(s) of the disease, not the disease symptoms. At this intersection, we are discovering a new appreciation for nutrition—that what we put into our bodies (or fail to put into our bodies) on a routine basis can have lasting effects on health and wellness. Herein lies the benefit of nutritional supplements: the promise of health promotion and disease prevention. But this promise is also its greatest limitation. The "proof" required to demonstrate the promise of good health is difficult and costly to achieve; "proving" that something does not happen (i.e., demonstrating preventive

effects) is scientifically a far more difficult endeavor than demonstrating that something bad has gotten better (i.e., treatment). To study prevention is costly, sometimes impractical as it raises ethical issues, and is easily confounded by other variables that may also impact good health.

Science adds to this complexity too by constantly evolving, at times in unpredictable ways. Years of research may appear to be contradicted in a single study. Which one is right? Despite the seemingly insurmountable challenge of persuasively demonstrating the role of nutritional supplements in disease prevention, we must remain vigilant about two things: science, especially in the field of nutrition, is an ever evolving continuum of questions and answers so research must always continue because no one study is ever the "final word"; and nutritional supplements, for all their promise, are just that—supplements to, not substitutes for, a healthy diet and lifestyle. Like tools in a large toolbox, supplements are but one component of an overall approach to maintaining health and avoiding disease.

That's what makes this latest edition of *The Benefits of Nutritional Supplements* (Fourth Edition) so valuable and so salient. Even in the past ten years, there has been so much research that further explains the role of nutrients for good health and the prevention of disease. Sometimes the research has validated what we already thought we knew, and other times it has sent our understanding of nutrition in a different direction. Is it possible that antioxidants can have a protective effect for some and be a catalyst for disease in others? Do variations in other behaviors impact how well we absorb and make use of certain nutrients? With so much of the knowledge base being updated, CRN wants to be sure we are providing our audiences with the most current information possible. *The Benefits of Nutritional Supplements* provides readers with objective information about the benefits of these products. It tracks the research suggesting previously unknown effects of a healthy diet and concedes areas where the prior thinking just hasn't held up in studies. We hope that by creating a more informed, health-conscious consumer, we are doing our part for real healthcare reform—the kind of reform that helps people live longer, more robust, and more fulfilling lives.

A WORD ABOUT DEFINITIONS

Dietary supplements are defined in the Food, Drug and Cosmetic Act, in Section 201(ff), as products "intended to supplement the diet." They may contain a variety of ingredients including vitamins, minerals, amino acids, herbs or other botanicals, or other dietary substances "for use by man to supplement the diet by increasing the total dietary intake."

This paper will focus on a subset of dietary supplements which we shall designate as "nutritional supplements," by which we mean primarily supplements of essential nutrients such as vitamins and minerals, plus related compounds such as omega-3 fatty acids and fiber. The author of this paper is a nutritionist whose area of expertise includes these dietary components and does not extend to the category of herbs and botanicals. Readers are referred to other sources of information regarding the botanical category, including information on CRN's website and the numerous publications of the American Botanical Council.

A WORD ABOUT METRIC MEASURES

Several vitamins and minerals are required and recommended in very small quantities, measured in micrograms. These include folic acid, vitamin B-12, selenium, chromium, and iodine, among others. For purposes of nutrition labeling of dietary supplements and other foods, the official abbreviation of the term "microgram" is "mcg." The scientific notation for a microgram is "µg." In this paper, we will use the labeling abbreviation rather than the scientific notation for microgram quantities.

UNITS OF MEASURE

g	Gram (1 g = 1000 mg)
mg	Milligram (1000 mg = 1 g)
mcg, µg	Microgram (1000 mcg = 1 mg)
IU	International Units (used for vitamins A, D, and E)
nmol/L	Measure of blood concentration of some nutrients (nanomoles per liter)

ABBREVIATIONS USED IN THIS DOCUMENT

AHA	American Heart Association
AI	Adequate Intake (DRI value)
AMD	Age-related macular degeneration
ATBC	Alpha-Tocopherol Beta-Carotene clinical trial
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CDC	Centers for Disease Control and Prevention
CRN	Council for Responsible Nutrition
DRIs	Dietary Reference Intakes (RDA, AI, EAR, UL)
DNA	Building block of genes (deoxyribonucleic acid)
EAR	Estimated Average Requirement (DRI value)
FDA	Food and Drug Administration
GISSI	Multicenter study on omega-3s, vitamin E and heart disease
HHS	Department of Health and Human Services
HOPE	Multicenter trial on vitamin E and heart disease
HOPE-2	Multicenter trial on B vitamins and cardiovascular disease
HOPE-TOO	Extension of multicenter trial on vitamin E and heart disease
IOM	Institute of Medicine
MI	Myocardial infarction (heart attack)
MVM	Multivitamin/multimineral dietary supplements
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NOF	National Osteoporosis Foundation
NTDs	Neural tube birth defects
RDAs	Recommended Dietary Allowances (DRI value)
RR	Relative Risk
SELECT	Multicenter trial on selenium, vitamin E, and prostate cancer risk
UL	Upper Level of Tolerable Intake (DRI value)

The Benefits of Nutritional Supplements

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Executive Summary

Nutrient shortfalls have health consequences that could impact daily life and overall wellbeing. National nutrition surveys show shortfalls in intakes of many nutrients. About one-third of American adults fail to get their average daily requirement for vitamin C, even though vitamin C is relatively easy to obtain from foods; low intakes can lead to poor energy levels and weakness. More than 90 percent of adults fail to get their average daily requirement of vitamin E, and many fall short in other vitamins and minerals, which can impact immune function. More than two-thirds of women of childbearing age have low intakes of iron, which can impair cognitive function, physical capability, and endurance.

Even the most conscientious consumers find it difficult to get all the nutrients they need from food alone. While dietary improvement is a desirable goal, changing dietary patterns is extremely difficult. On the assumption that it is better for people to obtain recommended amounts of vitamins and minerals than to limp along with low intakes, a multivitamin with minerals which can be purchased for less than a dime a day is an inexpensive and effective way to fill a number of known nutrient gaps.

Nutrition experts at the Harvard School of Public Health have created an online version of a food pyramid with a notation recommending a "daily multivitamin plus extra vitamin D (for most people)." Recognizing the special nutritional needs of senior citizens, researchers at Tufts University designed a food guide pyramid for the elderly, which features a flag at the top as a reminder that supplements of calcium, vitamin D, and vitamin B-12 may be needed for optimal health. The American Academy of Nutrition and Dietetics (formerly the American Dietetic Association) has a policy statement emphasizing the importance of good food choices but also recognizing that supplements can help some people meet their nutritional needs.

Dietary supplements are used by the majority of adults in the United States. More women than men use them; use also increases with age and education. Health professionals are just as likely as members of the general public to use supplements regularly. Supplement use should be seen as one component of the search for a healthier lifestyle, including improvements in overall food habits and engaging in physical exercise. While much of the current research on nutrition and health focuses on the prevention of chronic disease, the primary reason most people use multivitamins and other nutritional supplements is to support overall wellness.

A generous intake of calcium plus vitamin D demonstrably helps build optimum bone mass during childhood and adolescence and also slows the rate of bone loss that naturally occurs with aging. National surveys show that U.S. calcium and vitamin D intakes are below recommended levels, especially for women—despite the fact that substantial research has shown supplements of calcium and vitamin D to be effective in maintaining or increasing bone density, and potentially in protecting health in other ways as well.

Nutritional supplements are similarly helpful in addressing a woman's increased nutrient needs during pregnancy. Prenatal multivitamins with minerals are commonly prescribed to ensure that both the baby's and the mother's needs are met. In addition to meeting normal nutritional needs during pregnancy, a multivitamin can also play a critical role in protecting against some birth defects. An abundance of data shows that women who get 400 mcg of supplemental folic acid per day for one to three months prior to conception and one to three months after conception can substantially lower the risk of having a baby with a neural tube defect such as spina bifida. In most studies demonstrating these results, the protective amount of folic acid was consumed in the form of a multivitamin supplement.

While adequate nutrient intake is critical for all age groups, it may have particular significance for the elderly. Antioxidant supplements have been shown to have a positive impact on eye health and cognitive function. Adequate nutritional status also affects the condition of the skin and supports lung and muscle function. Calcium and vitamin D supplements, as previously noted, can have a powerful impact on bone health, and the Surgeon General says it is never

...a multivitamin with minerals which can be purchased for less than a dime a day is an inexpensive and effective way to fill a number of known nutrient gaps.

too late to benefit from improved intakes of these nutrients. Vitamin D may also reduce the incidence of falls in older people. Vitamin and mineral supplements have been shown in some studies to improve immune function in the elderly. Low zinc intakes are associated with an increased risk of infections, including pneumonia. Supplemental intakes of vitamin E have had a positive effect in decreasing upper respiratory infections in some studies. For these reasons, it makes sense to encourage the elderly to use multivitamin and mineral supplements. Some experts have also advocated providing a basic multivitamin and mineral supplement to the elderly in nursing homes, as a matter of policy, to avoid risking the consequences of inadequate intakes.

...a healthy lifestyle must include a focus on dietary improvement...

Traditional models of health and nutrition were focused on dietary improvement and nutritional adequacy. Good dietary patterns and adequate nutrient intakes based on the Recommended Dietary Allowances were considered the best guides to health, but chronic disease prevention through dietary modification was not a common topic of discussion. This focus changed dramatically in the 1980s following the publication of numerous reports suggesting a direct relationship between dietary factors and the incidence of numerous "killer diseases." The reports asserted that improved dietary patterns, including increased intakes of fruits, vegetables, and whole grains, could reduce the risk of chronic disease. They also discussed which components of these foods were likely to be most protective, including fiber and a number of antioxidant nutrients. The reports emphasized the importance of improved food habits and downplayed the importance of increasing the intake of specific nutrients, but at the same time numerous clinical trials were undertaken specifically to evaluate the possibility that supplementation with some of the individual nutrients (especially antioxidants) might reduce the risk of cancer and heart disease.

While countless epidemiological trials support the hypothesis that dietary improvement can reduce the risk of chronic disease, the design of clinical trials to test that hypothesis is a challenge. Nevertheless, many clinical trials have in fact demonstrated benefits against disease for specific nutrients—for example, calcium to protect against osteoporosis, folic acid to help prevent some birth defects, and omega-3 fatty acids to reduce the risk of heart disease. On the other hand, clinical trials of beta-carotene for cancer prevention, vitamin E for lowering heart disease risk, B vitamins for protecting against cardiovascular disease, and selenium and vitamin E for prevention of prostate cancer so far have largely failed to confirm the benefits suggested by earlier studies.

There is vigorous debate regarding the appropriate design of clinical trials to test the hypothesis that specific nutrients or combinations of nutrients may help protect against chronic disease. Most trials are done with one or a few nutrients, even though vitamins and minerals generally work as a team in normal metabolism and never operate alone. Clinical trials are often undertaken in people who have already suffered the disease of interest—for example, in people who have recently suffered a stroke or heart attack. Testing the effects of vitamin or mineral supplements in such populations cannot be considered a true test of the prevention hypothesis.

Should the disappointing results of many of these clinical trials lead to a reconsideration of the appropriate study design for evaluating the preventive effects of nutritional interventions? Many experts believe a robust reconsideration is necessary.

The bottom line is that a healthy lifestyle must include a focus on dietary improvement. Generous intakes of the essential nutrients will support the normal functioning of the body and enhance health in a myriad of ways. The rational use of nutritional supplements, combined with a healthy diet, will contribute substantially to health promotion and disease prevention.

The rational use of nutritional supplements, combined with a healthy diet, will contribute substantially to health promotion and disease prevention.

Who Needs Dietary Supplements? Almost Everyone.

Even the most conscientious consumers find it difficult to get all the nutrients they need from food alone, and dietary supplements can help fill nutrient gaps. A sensible program of nutritional supplementation for most adults definitely would include a multivitamin, preferably with minerals. Other nutritional supplements could be added on the basis of a person's age, gender, and dietary pattern.

Much of the current research on nutrition and health focuses on the prevention of chronic disease. While this is obviously important, most people say the primary reason they use multivitamins and other nutritional supplements is to support overall wellness. For example, in one survey conducted for the Natural Marketing Institute, more than 60 percent of respondents said vitamin and mineral supplements were important to them for overall health and wellness, compared to about 20 percent who mentioned prevention of disease. (Dwyer, 2005)

OFFICIAL RECOMMENDATIONS

Scientists have put substantial effort into developing and revising nutritional recommendations over the years. The Food and Nutrition Board was established within the National Research Council of the National Academy of Sciences in 1940, and the first Recommended Dietary Allowances (RDAs) were presented in May 1941 in Washington, D.C., at a National Nutrition Conference called by President Franklin D. Roosevelt. The recognized purpose was "to recommend the amounts of the various nutrients that should be provided for the armed forces and also for the general population." (Roberts, 1958) The first published edition of the RDAs was in 1943, and it covered only calories, protein, two minerals (calcium and iron), and five vitamins (A, C, thiamin, riboflavin, and niacin). The RDAs were revised periodically through the Tenth Edition in 1989, by which time the coverage had expanded to include 13 vitamins, 12 minerals, and three electrolytes. Each edition was a small, single volume of text.

The RDAs have been the accepted reference value for desirable nutrient intake for almost 70 years. Beginning in 1994, the Food and Nutrition Board (now housed in the Institute of Medicine of the National Academies) undertook a broader approach to nutritional recommendations and for the first time proposed to consider reduction in the risk of chronic disease as a potential criterion for establishing recommendations for nutrient intake, in addition to consideration of nutrient requirements for maintenance of normal function. (Institute of Medicine, 1994) In the new recommendations, the RDA remains the key reference, but it is joined by three other values. Together, these four values are now called Dietary Reference Intakes (DRIs). The DRIs were published in a series of large volumes, beginning in 1997 and concluding in 2004, with each volume prepared by a different expert committee covering a limited set of nutrients: bone-related nutrients, B vitamins, antioxidant nutrients, trace nutrients (vitamins A and K plus 12 trace minerals), macronutrients, and electrolytes. The four volumes on vitamins and minerals are each 400 to 800 pages in length. (Institute of Medicine, 1997, 1998, 2000, 2001) A 500-page volume summarizing all of the DRI reports was published in 2006. (Institute of Medicine, 2006)

The DRIs will not be revised periodically in their entirety, as were the RDA books, but instead will be

revisited only when new scientific evidence requires a reappraisal of specific nutrients. The first major revision, relating to calcium and vitamin D, was published in 2010. (Institute of Medicine, 2010)

The RDA has historically included a "safety factor" over and above estimated nutrient requirements to account for variability in needs. In the new DRIs, the calculation of the safety factor is formalized. When there is sufficient information, an Estimated Average Requirement (EAR) is established, representing the amount of a nutrient that would meet the actual *requirement* for half of the people in a given population group. The RDA is derived by adding two standard deviations to the EAR. (In many cases, the standard deviations are not known with certainty and are based on estimates.) Thus, the RDA is always higher than the EAR, and the RDA remains the desirable target for individual nutrient intake. In some cases, there is not sufficient information to establish an EAR and an RDA. In those cases, an Adequate Intake (AI) is established instead. The AI is based on the amount of a given nutrient estimated to be consumed by groups of "apparently healthy people who are assumed to be maintaining an adequate nutritional state." (Institute of Medicine, 2006)

The RDA and the AI are intended as targets for individual intakes, and the EAR is a tool used by researchers to determine whether a population is at risk of inadequacy or deficiency. The UL, or Tolerable Upper Intake Level, is the "highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group." (Institute of Medicine, 2006)

DIETARY REFERENCE INTAKES: EAR, RDA, AI, UL

EAR (Estimated Average Requirement)	Used to determine risk of deficiency for a population.
RDA (Recommended Dietary Allowance)	Target for intake of the individual. Defined as the EAR plus 2 standard deviations.
AI (Adequate Intake)	Target for intake of the individual when no RDA is established.
UL (Tolerable Upper Intake Level)	Upper level shown to be safe for use in a healthy population.

If people fall short of the RDA or the AI, they are falling short of the nutrient intake recommended for individual health. If a population falls short of the EAR, that population may be at actual risk of inadequacy or deficiency. To illustrate the difference in values, the table below shows the EAR, the RDA, and the UL for vitamin C and vitamin E for men and women. (Institute of Medicine, 2006)

EAR, RDA, AND UL FOR VITAMINS C AND E

NUTRIENT	EAR	RDA	UL
Vitamin C			
Women	60 mg	75 mg	2000 mg
Men	75 mg	90 mg	2000 mg
Vitamin E			
(all adults)	12 mg	15 mg	1000 mg

LOW INTAKE OF VITAMIN E

National survey data shows that 93 percent of Americans (of all ages and both sexes) get less than the EAR for vitamin E from their diets. (Moshfegh, Goldman, et al., 2005) Obviously, few people get the full RDA for vitamin E. If we are to take the RDAs seriously—and they are clearly meant to be taken seriously—we have a national problem with vitamin E consumption. A simple multivitamin could fill that gap, as could a separate supplement of vitamin E.

LOW INTAKE AND LOW SERUM LEVELS OF VITAMIN C

Vitamin C is a nutrient that is easy to get from normal diets, provided people eat some fruits and vegetables, yet national survey data shows that about one-third of Americans get less than the EAR for vitamin C from their diets. (Moshfegh, Goldman, et al., 2005) Almost half have vitamin C intakes that fall below the RDA and therefore could benefit from a multivitamin or a separate supplement of vitamin C to fill that gap.

Smokers need more vitamin C than other people, and higher recommendations are established for them—recommendations which more than two-thirds of adult smokers fail to meet. (Moshfegh, Goldman, et al., 2005) The greatest need is for smokers to quit, but in the meantime they should at least ensure that they are obtaining adequate amounts of the vitamins they need.

There is evidence that the current RDAs for vitamin C may actually be too low, which would make the shortfalls even greater. Dr. Mark Levine and coworkers at the National Institutes of Health have conducted depletion-repletion studies in men and women, measuring plasma levels, tissue levels, and urinary excretion of vitamin C over a wide range of intakes. In one study, seven young men were admitted to a hospital and put on a depletion diet until their serum levels fell very low without overt signs of scurvy. The men then were given repletion doses of vitamin C, allowing time for equilibration at each dose. The doses given were 30, 60, 100, 200, 400, 1000, and 2500 mg per day. The study lasted four to six months, depending on how long it took each person to reach a steady state on each dose. "Six of seven volunteers noted mild fatigue and/or irritability at depletion, without scurvy. Symptoms disappeared within several days of the 30- or 60-mg daily dose. Although fatigue and irritability have myriad causes, vitamin C deficiency without scurvy should be an additional consideration. Since fatigue and irritability are common symptoms and were so easily reversible, physicians should ask patients with these symptoms about vitamin C ingestion from foods or supplements." (Levine, Conry-Cantilena, et al., 1996) Urinary excretion did not occur until the dose reached 100 mg per day. The authors suggest that 200 mg would be a suitable RDA for vitamin C.

A similar depletion-repletion study was conducted in 15 young women who were hospitalized for five to seven months, depleted until serum vitamin C levels were very low, and then given increasing doses of vitamin C from 30 to 2500 mg per day, allowing the subjects to reach a steady state at each dose. The researchers concluded that the RDA for vitamin C for young women should be increased to about 90 mg, instead of the current level of 75 mg. However, they added: "Vitamin C, 200 mg daily, from fruits and vegetables might be needed in place of 100 mg of pure vitamin C, as it is possible that bioavailability from foods is less than that from pure vitamin C." (Levine, Wang, et al., 2001)

One of the first signs of poor vitamin C status is low energy. A study of serum levels of vitamin C in the 2003-2004 National Health and Nutrition Examination Survey (NHANES) found that seven percent of the population had serum levels so low that they could be considered deficient in vitamin C. Sixteen percent of

adults "had vitamin C concentrations that are associated with low energy and weakness as a result of inadequate intake of vitamin C. More than 20 percent of adults showed marginal vitamin C status, placing them at risk of vitamin C deficiency." (Schleicher, Carroll, et al., 2009)

LOW INTAKES OF SEVERAL VITAMINS

The NHANES data show shortfalls in several nutrients, not just in vitamins C and E. These data are summarized in the USDA report *What We Eat in America*. (Moshfegh, Goldman, et al., 2005) The report shows the percentage of each age and sex group that gets less than the EAR for many nutrients, but it does not directly show what percent gets less than the RDA. However, it is possible to calculate the approximate percentage of a population that falls below the RDA using the percentile levels of intake shown in the report. The following table shows both values—the percentage whose intakes fall below the EAR (from the report) and the approximate percentage whose intakes fall below the RDA (calculated from the percentile levels of intake shown in the report).

PERCENTAGE WITH VITAMIN INTAKES BELOW THE EAR OR RDA

VITAMIN AND POPULATION	PERCENT BELOW EAR	PERCENT BELOW RDA
VITAMIN A		
Men	57%	80%
Women	48%	75%
VITAMIN E		
Men	89%	Over 95%
Women	97%	Over 97%
VITAMIN C FOR NONSMOKERS		
Men	36%	45%
Women	32%	45%
VITAMIN C FOR SMOKERS		
Men	69%	75%
Women	84%	90%
NIACIN		
Men	3%	5%
Women	5%	20%
Women over 70	13%	35%
VITAMIN B-6		
Men 50-70	16%	30%
Men over 70	23%	35%
Women 19-50	22%	30%
Women 51-70	33%	50%
Women over 70	49%	60%

More than half of adults fail to obtain even the EAR for vitamin A from their diets, let alone the RDA. This shortfall could easily be remedied with a multivitamin containing a modest amount of vitamin A, preferably as a mixture of retinol and beta-carotene.

A large percentage of women fail to obtain enough B-6 from their diets to meet the RDAs or even the EAR. There is new evidence to suggest, however, that the recommended intakes for vitamin B-6 may be too low. Researchers examined blood levels of B-6 in relation to intake in a large national survey and concluded that intakes considerably higher than the current recommendations would be needed to avoid low blood levels in some population groups. Specifically, the authors concluded that vitamin B-6 intakes of three to 4.9 mg per day appeared to be more consistent with the defini-

tion of a Recommended Dietary Allowance than the current RDAs. RDAs are intended to meet the needs of 97 to 98 percent of the population for which they are established. The current RDAs of two mg or less for vitamin B-6 may not meet this objective. Thus, the gap in adequacy may be much greater than indicated by the table on page 8. (Morris, Picciano, et al., 2008)

These nutrient shortfalls are reason enough for using a multivitamin. Achieving recommended intakes is a desirable objective, and dietary supplements can help meet that goal.

LOW INTAKES OF IRON, ZINC, AND MAGNESIUM

A large fraction of the population also fails to consume recommended amounts of various minerals, and these shortfalls can have meaningful consequences. Low intakes of iron in women of childbearing age can have a negative impact on their ability to perform physical work as well as on cognitive function, and low intakes of zinc can have a detrimental effect on immune function, especially in the elderly.

PERCENTAGE WITH INTAKES OF SOME MINERALS BELOW THE EAR OR RDA

POPULATION GROUP	PERCENT BELOW EAR	PERCENT BELOW RDA
MAGNESIUM		
Men	64%	80%
Women	67%	80%
IRON		
Girls 14-18	16%	70%
Women 19-50	16%	85%
ZINC		
Men 51-70	20%	35%
Men over 70	30%	50%
Women 19-50	12%	25%
Women 51-70	18%	35%
Women over 70	36%	55%

Poor iron status affects cognitive function and behavior. Women of childbearing age are susceptible to iron deficiency and iron deficiency anemia. In a study of 149 women ages 18 to 35, those who were *not* iron deficient at baseline performed better on cognitive tasks and completed them faster. Women with iron deficiency anemia had the poorest performance, and women with iron deficiency but not anemia were intermediate between the two extremes. After 16 weeks of iron supplementation (100 mg ferrous sulfate), there was a five- to seven-fold improvement in cognitive performance and an improvement in speed of completing the tasks. "Iron status is a significant factor in cognitive performance in women of reproductive age. Severity of anemia primarily affects processing speed, and severity of iron deficiency affects accuracy of cognitive function over a broad range of tasks." (Murray-Kolb & Beard, 2007)

Iron deficiency, even without anemia, affects work capacity. In a study of 41 untrained women who were iron-depleted but not anemic, supplementation with 100 mg ferrous sulfate for six weeks improved the time to complete a 15-kilometer test on a stationary cycle and improved oxygen uptake. This suggests that iron deficiency "impairs adaptation in endurance capacity after aerobic training in previously untrained women. This impairment can be corrected with iron supplementation." (Brownlie, Utermohlen, et al., 2004)

Iron deficiency is believed to affect up to 16 percent of premenopausal women in the United States, because "suboptimal iron consumption and menstrual bleeding lead to negative iron balance." (McClung, Karl, et al., 2009) Women who engage in regular physical activity may be at greater risk, since such activity has a negative effect on iron stores. About 15 percent of the individuals serving in the U.S. military are female—amounting to over 340,000 women. "Maintaining optimal iron status in this population is critical because of the known contribution of iron nutrition to physical and cognitive performance." (McClung, Karl, et al., 2009) Iron deficiency reduces hemoglobin levels and

diminishes the ability to do physical work. Endurance and cognitive function may also be affected. During an eight-week study of 219 female soldiers, iron status declined during basic training. An iron supplement (100 mg ferrous sulfate) attenuated the decline, improved mood, and improved physical performance, compared to women who did not receive an iron supplement. (McClung, Karl, et al., 2009)

LOW INTAKES OF CALCIUM

Calcium is a nutrient that is hard to get in adequate amounts from normal diets, except for people who consume large amounts of dairy products. Dietary Reference Intakes for calcium were established by the Food and Nutrition Board in 1997 and revised in 2010. The recommendations are relatively high, equivalent to three or four servings of dairy products per day for many age groups. For example, the following table shows the Adequate Intakes (AIs) for calcium established in 1997 and the RDAs established in 2010 for teens and adults. (Institute of Medicine, 2006, 2010)

DIETARY REFERENCE INTAKES ESTABLISHED FOR CALCIUM

POPULATION GROUP	AI, 1997	RDA, 2010
Teenage boys and girls	1300 mg	1300 mg
Men and women, age 19-50	1000 mg	1000 mg
Men, age 51-70	1200 mg	1000 mg
Women, age 51-70	1200 mg	1200 mg
Men and women over age 70	1200 mg	1200 mg

National survey data show that about 90 percent of teenage girls, over two-thirds of women ages 19-50, and over 90 percent of women over 50 fall short of reaching these levels of calcium from diet alone. (Moshfegh, Goldman, et al., 2009) Men do somewhat better, but still fall short. Over 40 percent of men 19-50 and over 80 percent of men over 70 fail to get recommended amounts of calcium from diet alone. Obviously, the vast majority of girls, women, and older men could benefit from calcium supplementation. Most calcium supplements provide about 500 mg per tablet, plus some vitamin D. One tablet in the morning and one in the evening would virtually ensure adequate calcium intake and also provide a boost in vitamin D.

MULTIPLE SHORTFALLS

The previous tables show what percentage of the population falls short of obtaining recommended amounts of individual nutrients. Few analyses have ever reported how many people fall short in multiple nutrients, but one did. Many years ago, some researchers undertook an exhaustive analysis of the findings of the 1977-78 USDA National Food Consumption Survey, which included information on three-day dietary records from more than 21,500 people. Their analysis found that only 12 percent of the population consumed 100 percent of the RDA (averaged over three days) for *all seven* of the following nutrients: protein, calcium, iron, vitamin A, thiamin, riboflavin, and vitamin C. When they added three more nutrients to the list (vitamin B-6, vitamin B-12, and magnesium), they found that *not a single person* got 100 percent of the RDA for all 10 nutrients. (Crocetti & Guthrie, 1982) It would be very interesting to see such an analysis of current nutrition survey data; the results would undoubtedly be similar.

SUPPLEMENT USE IMPROVES DIETARY ADEQUACY

Researchers from the Department of Agriculture observed that "a large proportion of older adults do not consume sufficient amounts of many nutrients from foods alone" and examined whether supplement use helped fill the gaps. (Sebastian, Cleveland, et al., 2007) They confirmed that supplement use permitted more than 80 percent of supplement users to meet Estimated Average Requirements (EAR) for

eight nutrients, but some still fell short while others exceeded the UL for some nutrients.

Recognizing that "low intake of nutrients is associated with poor health outcomes," other researchers also examined whether supplement use helped people meet recommended levels of intake of several nutrients. (Burnett-Hartman, Fitzpatrick, et al., 2009) In a study of over 6,000 people, they found that supplement users were much more likely than non-users to achieve recommended intakes of calcium, vitamin C, and magnesium. Supplement users were also more likely than non-users to exceed the UL for these nutrients.

A recent analysis examined total calcium intakes from diet and supplements recorded in NHANES 2003-2006. Calcium supplements were used by more than half of men over 50 and women over 30, and the supplements contributed markedly toward achieving adequate intakes. (Bailey, Dodd, et al., 2010) In women over 50, the prevalence of inadequate calcium intake was about 92 percent when considering diet alone but decreased to 61 percent when the contribution of supplements was included. In these same groups, the prevalence of vitamin D supplementation was also substantial and contributed markedly toward adequacy.

Another recent analysis of data from NHANES 2003-2006 examined the contribution of dietary supplements and fortified foods to requirements for many nutrients by the U.S. population. (Fulgoni, Keast, et al., 2011) They found, for example, that 46 percent of the population fell short of the EAR for vitamin C, when considering intake only from naturally-occurring vitamin C in foods. The percentage falling short of the EAR was reduced to 37 percent when fortification was taken into account and was reduced to 25 percent when dietary supplement use was taken into account. For vitamin E, 93 percent of the population fell short of the EAR, when considering intake only from naturally-occurring vitamin E in foods. The percentage falling short of the EAR was reduced to 91 percent when fortification was taken into account and was reduced to 60 percent when supplementation was taken into account. Thus, fortification and supplementation both made a significant contribution to meeting nutrient requirements.

RATIONALITY OF NUTRITIONAL SUPPLEMENTS

Dietary improvement is a desirable goal, but changing dietary patterns is extremely difficult. On the assumption that it is better for people to obtain recommended amounts of vitamins and minerals than to limp along with low intakes, a multivitamin with minerals which can be purchased for less than a dime a day would clearly fill a number of known nutrient gaps. Additional calcium with vitamin D is also advisable for a large fraction of the population.

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Who Recommends Dietary Supplements?

Some Prominent Nutrition Experts, Some Professional Organizations, and Even Government Reports

ADVICE FROM DR. WALTER WILLETT AND DR. MEIR STAMPFER OF HARVARD:

What vitamins should I be taking, Doctor?

Dr. Walter Willett and Dr. Meir Stampfer, two prominent physician-researchers at Harvard Medical School and the Harvard School of Public Health, have offered the advice excerpted below on the use of nutritional supplements. (Willett & Stampfer, 2001)

> **"Given the greater likelihood of benefit than harm, and considering the low cost, we conclude that a daily multivitamin that does not exceed the RDA of its component vitamins makes sense for most adults..."**

> **"Substantial data suggest that higher intakes of folic acid, vitamin B-6 and vitamin D will benefit many people, and a multivitamin will ensure an adequate intake of other vitamins for which the evidence of benefit is indirect. A multivitamin is especially important for women who might become pregnant; for persons who regularly consume one or two alcoholic drinks per day; for the elderly, who tend to absorb vitamin B-12 poorly and are often deficient in vitamin D; for vegans, who require supplemental vitamin B-12; and for poor urban residents, who may be unable to afford adequate intakes of fruit and vegetables."**

> **"Although one could measure blood levels to identify those who would benefit most from multivitamins, this would be much more expensive than simply recommending that all adults take a supplement (at a typical cost of $20 to $40 per year). Education regarding nutrition is vitally important, but it has been far less effective than supplementation or the fortification of food in raising blood folic acid levels."**

> **"However, a vitamin pill is no substitute for a healthful lifestyle or diet, because foods contain additional important components, such as fiber and essential fatty acids. In particular, a vitamin supplement cannot begin to compensate for the massive risks associated with smoking, obesity, or inactivity. The cost of a multivitamin supplement is so low—similar to that of about a quarter of a serving of fruit or vegetables—that it is unlikely to displace healthful foods in most persons' budgets."**

RECENT REITERATION OF MULTIVITAMIN ADVICE

Drs. Willett and Stampfer recently reiterated their multivitamin advice in a joint letter with Dr. Bruce Ames and Dr. Joyce McCann, following a National Institutes of Health Conference. (Ames, McCann, et al., 2007) The conference reviewed the evidence on multivitamin/mineral (MVM) supplements and concluded that there was not sufficient evidence to recommend for or against the use of MVM supplements for the prevention of chronic disease. (NIH State of the Science Conference on Multivitamins, 2006) This review, however, was limited to evidence from randomized controlled trials (RCTs) which included only 63 of the 11,261

available reports. By so limiting the scope of the NIH review, much relevant epidemiologic and mechanistic evidence was omitted from consideration, according to the authors of this letter. Their bottom line:

> **"Of course, everyone would agree that all persons should be encouraged to eat a good diet, but we are far from achieving this goal, especially among the poor. In most cases, a simple way to improve micronutrient status is to take an MVM. However, even if one eats an ideal diet and takes an MVM, some vitamins can remain below recommended concentrations in some groups... A significant fraction of Americans have micronutrient intakes below the Estimated Average Requirement. Why establish values such as the Estimated Average Requirement and not take simple steps to eliminate deficiencies? Because MVMs are cheap, readily available, and nontoxic, why not recommend that people take an MVM, particularly because much epidemiologic, biochemical, and other evidence points to the need for an adequate supply of vitamins and minerals for optimum function on many levels? At a minimum, taking an MVM is good insurance."** (Ames, McCann, et al., 2007)

ADVICE FROM TWO OTHER HARVARD PHYSICIANS

Dr. Kathleen M. Fairfield and Dr. Robert H. Fletcher of Harvard Medical School and the Harvard School of Public Health reviewed the benefits of vitamins in protecting against chronic disease and concluded that a multivitamin would be prudent for virtually all adults. The physicians observed that "a large proportion of the general population" has less-than-optimal intakes of a number of vitamins, exposing them to increased disease risk. They emphasized that the cost of routinely using a multivitamin is small—about $20 to $30 per year for brand-name products or as little as $10 annually for the large, economy-size container of a store-brand product. (Fairfield & Fletcher, 2002; Fletcher & Fairfield, 2002)

HEALTH PROFESSIONALS RECOMMEND DIETARY SUPPLEMENTS

The Council for Responsible Nutrition and the CRN Foundation sponsored numerous surveys of physicians, nurses, and other health professionals from 2007 to 2009—the "Life...supplemented" Healthcare Professionals (HCP) Impact Studies. (Dickinson, Bonci, et al., 2012; Dickinson, Boyon, et al., 2009; Dickinson, Shao, et al., 2011) The surveys were conducted and analyzed by Ipsos Public Affairs. In addition to the published articles reporting results of these surveys, the "Life...supplemented" website provides summary information. (CRN, 2012) Physicians surveyed included primary care physicians, ob/gyns, cardiologists, dermatologists, and orthopedists. Other health professionals surveyed included nurses, nurse practitioners, pharmacists, and dietitians. The surveys asked, among other things, whether various healthcare professionals "ever recommend dietary supplements" to their patients or clients, and the reasons for such recommendations. The following table shows the percentage of each professional group that responded positively to this question, and the top reasons they gave for recommending dietary supplements.

PERCENTAGE OF HEALTH PROFESSIONALS WHO "EVER RECOMMEND" DIETARY SUPPLEMENTS TO PATIENTS OR CLIENTS, AND TOP REASONS FOR SUCH RECOMMENDATIONS

HEALTH PROFESSIONALS	PERCENT WHO "EVER RECOMMEND" DIETARY SUPPLEMENTS TO PATIENTS/CLIENTS	TOP REASONS FOR RECOMMENDING DIETARY SUPPLEMENTS
Physicians n=900 (primary care, ob/gyn, other)	79%	Bone health, overall health/wellness, joint health, heart health, healthy cholesterol
Orthopedists n=300	91%	Bone health, joint health, musculoskeletal pain, overall health/wellness
Cardiologists n=300	72%	Healthy cholesterol, heart health, overall health/wellness, bone health
Dermatologists n=300	66%	Skin/hair/nails, overall health/wellness, bone health, anti-aging
Nurses n=277	82%	Overall health/wellness, bone health, flu/colds, joint health, immune health, healthy cholesterol
Nurse practitioners n=300	96%	Bone health, overall health/wellness, fill nutrition gaps, women's health, joint health
Pharmacists n=300	93%	Joint health, bone health, flu/colds, eye health, lower cholesterol
Dietitians n=300	97%	Bone health, fill nutrition gaps, overall health/wellness, healthy cholesterol, heart health

ADDING A "SUPPLEMENT FLAG" TO FOOD GUIDE PYRAMIDS

Scientists at the USDA Human Nutrition Research Center on Aging at Tufts University have given careful thought to the nutritional needs of the elderly. Older people have lower energy needs and tend to eat less. A national survey showed that about 40 percent of people over the age of 70 consumed less than two-thirds of the recommended energy intake, making it difficult for them to get recommended amounts of nutrients. Calcium, vitamin D, and vitamin B-12 are of particular concern for the elderly. The researchers emphasize the importance of educating older Americans to select nutrient-dense foods within all the food groups. To assist in nutrition education, these scientists developed a modified Food Guide Pyramid for the elderly. It sits on a base of water, emphasizing the need for at least eight glasses of water daily. Symbols are added to encourage the consumption of more fiber-rich grains, fruits, vegetables, and legumes. "Finally, a flag should be placed on the top of the 70+ Food Pyramid indicating that supplements of calcium, vitamin D and vitamin B-12 are frequently appropriate to promote optimal health." (Russell, Rasmussen, et al., 1999)

In a book about diet and health, Dr. Willett offers a "Healthy Eating Pyramid" that places more emphasis on whole grains, decreases the emphasis on dairy products, and relegates refined grain products as well as red meats and butter to the tip of the pyramid, along with sweets and fats—to be consumed "sparingly." A sidebar accompanies the pyramid, recommending "multiple vitamins for most." (Willett, 2001) The current website for *The Nutrition Source*, a publication of the Harvard School of Public Health, also shows an updated "Healthy Eating Pyramid" with a sidebar that recommends: "Daily multivitamin plus extra vitamin D (for most people)." (HSPH, 2012)

ADVICE FROM *DIETARY GUIDELINES FOR AMERICANS*

Dietary Guidelines for Americans, first published by the U.S. Department of Agriculture and the Department of Health and Human Services in 1980, must by congressional mandate be updated every five years. All editions of the *Dietary Guidelines* emphasize maintaining a healthy weight and choosing foods sensibly. Of the three most recent editions, the 2005 guidelines express the strongest concern about low intakes of some nutrients. (Department of Agriculture and Department of Health and Human Services, 2005) The nutrients of concern include the following:

- For adults: calcium, potassium, fiber, magnesium, vitamin A (as carotenoids), vitamin C, and vitamin E.
- For children and adolescents: calcium, potassium, fiber, magnesium, and vitamin E.

The 2000 and 2005 editions also recognize special needs for supplements for certain population groups. (Department of Agriculture and Department of Health and Human Services, 2000, 2005) These include:

- B-12 supplements for people over the age of 50, because their absorption of B-12 from food may not be efficient.
- Synthetic folic acid from fortified foods or supplements for women of childbearing age who may become pregnant and for those in the first trimester of pregnancy.
- Vitamin D from fortified foods or supplements for older adults, for people with dark skin, and for people not exposed to sufficient sunlight.

The 2010 *Dietary Guidelines for Americans* recognize that the probability of adequacy is tenuous for numerous vitamins and minerals and note that "in some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less than recommended amounts." (Department of Agriculture and Department of Health and Human Services, 2010; Dietary Guidelines Advisory Committee, 2010)

POSITION OF THE ACADEMY OF NUTRITION AND DIETETICS

The Academy of Nutrition and Dietetics (formerly the American Dietetic Association) advocates meeting nutritional needs through wise selection of a wide variety of foods, but has adopted a policy statement recognizing that additional nutrients from supplements "can help some people meet their nutrition needs as specified by science-based nutrition standards such as the Dietary Reference Intakes." (Marra & Boyar, 2009) The policy statement notes: "Many Americans do not consume the amount and types of foods necessary to meet recommended micronutrient intakes," perhaps in part because only about three to four percent of Americans follow the recommendations of the *Dietary Guidelines for Americans*. (King, 2007)

The statement acknowledges that multivitamin and mineral supplements "can be an effective way to increase nutrient intakes to meet recommended levels of multiple nutrients... In some cases such as with calcium, an additional supplement may be considered

to help meet recommended intakes, particularly in at-risk groups (e.g., older adults) where supplementation has been shown to have positive outcomes." (Marra & Boyar, 2009)

The policy statement also mentions a number of special needs that can be met by supplements:

- Supplemental vitamin D for infants, children, and teens who do not consume large amounts of milk fortified with vitamin D.
- Folic acid for women of childbearing age who may become pregnant.
- Folic acid and a multivitamin with iron for many pregnant women.
- Supplemental B-12 and vitamin D for people over age 50.
- Vitamin D for people with low exposure to sunlight and for people with dark skin, who have a decreased ability to synthesize vitamin D from sunlight.

OLDER AMERICANS ACT

The Nutrition Program established by the Older Americans Act provides congregate meals (senior dining) and meals on wheels (home-delivered meals) to older Americans who are at high nutritional risk. When Congress re-authorized the Older Americans Act in 2006, it included "sense of Congress" language encouraging nutrition providers to consider whether people participating in the program would benefit from a multivitamin-mineral supplement. This notion has been opposed by some on the grounds that the cost of supplements would take away from the amount of food or the number of meals that could be provided. (Marra & Wellman, 2008) However, it is difficult to imagine what other expenditure would provide more nutritional impact for those who are already at risk.

A brand-name multivitamin with minerals can be purchased at a retail store for about seven cents a day. If store brands are purchased or if products are bought on sale, the price, even at retail, can be cut substantially. Products distributed through a Federal feeding program would undoubtedly be purchased in bulk at even more of a savings. Adding a multivitamin/mineral supplement to a Federal feeding program may be controversial, but it deserves careful consideration and a realistic cost/benefit analysis.

COST OF A MULTIVITAMIN WITH MINERALS OR A FORTIFIED BREAKFAST CEREAL

This table shows the cost of a daily multivitamin with minerals, compared to the cost of a serving of a fortified breakfast cereal. The cereal will, of course, provide calories as well as additional nutrients. Prices were obtained in supermarkets and drug stores in the upper Midwest in early 2012.

PRODUCT	COST PER DAY	COST PER MONTH
Store-brand multivitamin with minerals	$0.05 per day	$ 1.50 per month
Brand-name multivitamin with minerals	$0.07 per day	$2.17 per month
Fortified breakfast cereal 1 oz. (no milk)	$0.31 per day	$9.28 per month
Fortified breakfast cereal with 1/2 cup milk	$0.46 per day	$13.80 per month

Bottom Line

Most people would benefit from adding a multivitamin and mineral supplement to their daily dietary intake, to ensure adequacy of a number of nutrients that are often not consumed in recommended amounts. A multivitamin would supply the extra vitamin B-12 and vitamin D recommended for the elderly. A multivitamin or a fully fortified breakfast cereal would supply the extra folic acid recommended for women of childbearing age.

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Who Uses Dietary Supplements? Most People Do.

Dietary supplements are used by the majority of adults in the United States. Usage is higher in women than in men and increases with age and education. Supplement users tend to adopt other healthy habits such as engaging in physical exercise, trying to eat a healthy diet, seeing a physician regularly—suggesting that supplement use is an integral part of an overall interest in wellness.

In some nutrition surveys, users of dietary supplements have been shown to also have somewhat higher nutrient intakes from food, indicating that they pay more attention to their diets. However, the magnitude of the difference in dietary nutrient intake is small, and the intakes of many users as well as nonusers of dietary supplements fall short of recommended levels for a number of vitamins and minerals. (Murphy, White, et al., 2007; Sebastian, Cleveland, et al., 2007)

In a study of a multi-ethnic cohort of more than 100,000 healthy people, 56 percent of the men and 72 percent of the women said they used a supplement at least once a week. The most commonly used supplement was a multivitamin, followed by vitamin C and vitamin E. Among women, calcium was also commonly used. In general, usage increased with age, education, and physical activity. The authors note that higher use among those with more education "may imply a greater awareness of the role of nutrition in good health." (Foote, Murphy, et al., 2003)

In the 2003-2006 National Health and Nutrition Examination Survey (NHANES), involving more than 20,000 respondents, 54 percent of the adults surveyed said they had used a dietary supplement within the past month. (Bailey, Gahche, et al., 2011)

The majority of people reported using only one dietary supplement, generally on a daily basis. The most frequently reported dietary supplement was a multivitamin-multimineral, used by 33 percent of adults. Botanical supplement use was reported by about 20 percent of adults. Dietary supplement usage was higher among women than men, and in adults the prevalence of usage increased with age, reaching 66 percent in men over 70 and 75 percent in women over 70. Among adults, usage was highest in those with more than a high school education (61 percent) and lowest in those with less than a high school education (37 percent).

PREVALENCE OF DIETARY SUPPLEMENT USE DURING THE PAST MONTH IN NHANES 2003-2006

Adult Populations	Any supplement	Multivitamin/ mineral	Botanical
19-30	39%	27%	13%
31-50	49%	35%	18%
51-70	65%	44%	20%
Over 70	71%	46%	17%

In the 1999-2000 NHANES, a national survey of almost 5,000 adults, 52 percent of the subjects said they had used a dietary supplement in the past month. (Radimer, Bindewald, et al., 2004) The prevalence of use was over 60 percent in adults who were age 50 or greater and in people with more than a high school education. Almost half of supplement users took only one product, 23 percent took two, 13 percent took three, and 17 percent took four or more. The most commonly used supplement was the multivitamin (used by 35 percent of the population), followed by vitamin E at 13 percent and vitamin C at 12 percent.

Supplement use is positively related to several health-related characteristics. (Radimer, Bindewald, et al., 2004) This suggests that many people use supplements as one component of a larger effort to adopt a healthy lifestyle. People with a low Body Mass Index (BMI) are more likely to use supplements than people who are obese, and people who engage in moderate or vigorous physical activity are more likely to be supplement users than people who avoid physical activity. Supplement use is more common among people who say their health is excellent than among people who say their health is poor. Nonsmokers and former smokers are more likely to be supplement users than are current smokers. In other words, people do not become supplement users in a vacuum; they adopt supplement use in an effort to improve their health, and they are also likely to adopt other healthy habits.

An annual survey of consumer use of dietary supplements is conducted by the Council for Responsible Nutrition (CRN), a trade association of the dietary supplement industry. Each survey includes a national sample of about 2,000 adults. The 2011 CRN Consumer Survey on Dietary Supplements found that 69 percent of those surveyed identified themselves as supplement users. (CRN, 2011) This figure has remained fairly constant for several years. The percentage who described themselves as supplement users was 66 percent in 2010, 65 percent in 2009, 64 percent in 2008, 68 percent in 2007, and 66 percent in 2006. (CRN, 2009, 2010)

The prevalence of dietary supplement use has increased over time. For example, five national surveys conducted between 1972 and 2006 found that usage among older adults (over age 50) more than doubled during that period from 27 percent to 67 percent. Usage among younger adults (under age 50) was lower than for older adults, but approximately doubled over time, increasing from 22 percent to 45 percent in the five surveys. (Bailey, Gahche, et al., 2011; Block, Cox, et al., 1988; Koplan, Annest, et al., 1986; NCHS, 1999; Radimer, Bindewald, et al., 2004) The following table illustrates this trend. Figures are approximate, since age groupings vary in the five reports.

APPROXIMATE PERCENTAGE OF ADULTS UNDER AND OVER AGE 50 USING DIETARY SUPPLEMENTS, NHANES SURVEYS, 1972 TO 2006

NHANES SURVEY	% ADULTS ≤50	% ADULTS >50
NHANES I, 1971-74 (Block, et al.)	22%	27%
NHANES II, 1976-80 (Koplan, et al.)	33%	39%
NHANES III, 1988-94 (NCHS)	40%	46%
NHANES 1999-2000 (Radimer, et al.)	45%	60%
NHANES 2003-06 (Bailey, et al.)	45%	67%

A survey of supplement use among more than 18,000 women in Iowa found that usage increased from 66 percent in 1986 (when the women were in their 50s and 60s) to 85 percent in 2004 (when the women were in their 70s and 80s). At the latter date, 27 percent of the women said they used four or more products. Over 60 percent of them used a multivitamin, and about the same number used a calcium supplement. A little over 30 percent said they used vitamin E, and almost 30 percent said they used vitamin C. The authors "suggest that the use of dietary supplements by older individuals could be beneficial in countering

age-related declines in food and nutrient intakes and in maintaining adequate nutriture for nutrients for which absorption declines with age." (Park, Harnack, et al., 2009)

HEALTH PROFESSIONALS USE DIETARY SUPPLEMENTS

Health professionals are as likely as the general population to use dietary supplements. A survey of women physicians found that 64 percent used vitamin or mineral supplements at least occasionally, and 47 percent used the supplements at least five days a week. (Frank, Bendich, et al., 2000) Two surveys of health professionals enrolled in an online course on dietary supplements reported high levels of supplement use (over 80 percent), perhaps reflecting the interest that led them to enroll in the course. (Gardiner, Woods, et al., 2006; Kemper, Gardiner, et al., 2007)

A survey of 900 physicians and almost 300 nurses found that 51 percent of the physicians and 59 percent of the nurses were regular users of dietary supplements. (Dickinson, Boyon, et al., 2009) Similarly, a survey of 900 physician specialists found that 37 percent of cardiologists, 50 percent of orthopedists, and 59 percent of dermatologists were regular supplement users. (Dickinson, Shao, et al., 2010; Dickinson, Shao, et al., 2011) When occasional and seasonal use were included, the usage figures were naturally even higher. At least occasional dietary supplement use was reported by 72 percent of physicians and 89 percent of nurses in the earlier study and by 56 percent of cardiologists, 73 percent of orthopedists, and 75 percent of dermatologists in the later study. A third survey of registered dietitians, nurse practitioners, and pharmacists had similar results. (Dickinson, Bonci, et al., 2012) All three surveys were sponsored by the Council for Responsible Nutrition as part of the "Life...supplemented" consumer wellness initiative. The following table shows the percentage of health professionals surveyed who reported that they personally use dietary supplements.

PERCENTAGE OF HEALTH PROFESSIONALS WHO REPORT PERSONAL USE OF DIETARY SUPPLEMENTS

Profession	Regular User	Occasional	Seasonal	Former	Never Used
Physicians n=900 (family care, ob/gyn, other specialties)	51%	19%	2%	14%	14%
Orthopedists n=300	50%	19%	4%	11%	16%
Cardiologists n=300	37%	17%	3%	18%	25%
Dermatologists n=300	59%	13%	3%	8%	17%
Nurses n=277	59%	27%	3%	8%	3%
Nurse practitioners n=300	71%	21%	3%	4%	1%
Pharmacists n=300	62%	22%	2%	8%	6%
Dietitians n=300	74%	20%	2%	3%	1%

Eighty-one percent of the dietitians surveyed said most people have gaps in their diets that can be filled with vitamins and other dietary supplements, and nine out of ten of them said they take supplements themselves and recommend them to their clients. (Dickinson, Bonci, et al., 2012) The most commonly used supplement reported by dietitians was a multivitamin, but many dietitians also reported using omega-3 fish oils, herbal or botanical supplements, or fiber. The main reasons they gave for using dietary supplements were for bone health (58 percent), for overall health/wellness (53 percent), and to fill nutrition gaps (42 percent).

Bottom Line

The majority of adults in the United States use dietary supplements as part of a healthy lifestyle, and health professionals are just as likely as members of the general public to use them. Dietary supplement use is generally not undertaken in a vacuum, but is one of many actions people take in an effort to improve overall wellness.

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What Do Essential Nutrients Actually *Do*?

The functions of vitamins and essential minerals are well known, and each of them plays one or more key roles in maintaining the daily functions basic to health and life itself. These functions are accomplished in every cell and every organ of the body, every minute of every day, from birth to death.

Some of these functions may ultimately provide some protection against chronic diseases such as cancer and heart disease. However, it is their more mundane but vital roles in metabolism that cause vitamins and minerals to be defined as "essential nutrients." The following is intended as a simplified reminder of the immense scope of these basic functions.

Vitamins and essential minerals are components of enzymes and cofactors the body needs to accomplish the everyday miracles of constantly keeping the heart beating, the blood flowing, the muscles flexing, the bones strong, the digestive system churning efficiently, the cells dividing, the eyes sparkling, the skin protecting our outer and inner surfaces, countless membranes controlling what goes into and out of every cell and tissue, the kidneys filtering the blood and adjusting blood pressure, the lungs drawing in life-giving oxygen and expelling other gases, the nerves snapping, and the brain cogitating.

The collective magnitude of these activities is illustrated by the fact that a large fraction of the body's total energy expenditure is devoted to maintaining these functions. This portion of the total daily energy requirement is known as the basal metabolic rate (BMR), and it accounts for 50 to 70 percent of the body's total daily energy expenditure. (Gropper, Smith, et al., 2009)

The essential nutrients are critical to the performance of these functions. An essential nutrient is a substance the body must have in order to function, but which it cannot make for itself. Therefore, the nutrient must be obtained from outside sources, namely foods. There are 13 vitamins (which by definition are essential), 15 essential minerals or electrolytes, nine essential amino acids, and a couple of essential fatty acids. Given an adequate supply of calories (from a mixture of fats, carbohydrates, and protein) and plenty of water, the body can use these essential nutrients to mix and match the various other components of foods and turn them into its own personal energy supply as well as continually creating new cells and tissues, blood and bone, muscles and brain, skin and hair. The essential nutrients in many cases are the catalysts or cofactors that make these operations possible.

The cells in the adult body are not the ones we were born with, since all of the body cells and tissues are constantly turning over—being worn out and repaired or replaced with new ones. Some tissues, like the cells lining the intestinal tract, turn over very rapidly—about every three days. The red blood cells turn over about every 120 days, and newly manufactured ones continually take the place of the old ones. Some other body cells and tissues may last for years, but even those are subject to constant repair.

Needless to say, any fault or faltering in these processes could have a direct impact on the body's ability to function. The nature of the impact will depend on which nutrients are in short supply and what tissues are affected.

B VITAMINS: THE POWERHOUSE

Many of the B vitamins are involved in energy production, every second of every day. They are coenzymes that make it possible for the body to convert carbohydrates, fats, and proteins into usable energy

that can be used to run the system, much like a power plant turns fuel into usable electricity that can run household appliances. Metabolic systems such as the Krebs cycle and the electron transport chain form the basis of the body's power plant, which exists in every cell and is dependent on several of the B vitamins, especially thiamin, riboflavin, niacin, and pantothenic acid.

The energy-related B vitamins work together as a team, passing electrons, carboxyl groups, or phosphates around with lightening speed in order to produce energy exactly when and where it is needed. Each vitamin in this team has its own particular function in the process, and each must fulfill its role in order for adequate energy to be produced.

People with inadequate intakes of these B vitamins have low energy, which is apparent not only in a decreased capacity for work but also in effects on cognitive function and "nerve." In a historic 1942 article urging the enrichment of white bread with thiamin (vitamin B-1) and other B vitamins, two prominent nutrition researchers asserted that "a first result of deficiency of thiamin is loss of courage and the will to do or die." (Williams & Wilder, 1942) This assertion may have been hyperbole arising from the pressures of the war effort, but it was grounded in an appreciation of the fundamental impact of the B vitamins on a person's mood and capability, as well as physical energy.

BUILDING BLOOD AND OTHER CELLS AND TISSUES

Many of the B vitamins are involved in synthesizing the basic building blocks of the body. They are components of the "one-carbon cycle," which generates methyl groups used in the synthesis of compounds such as amino acids, proteins, enzymes, neurotransmitters, hormones, and DNA. The key B vitamins involved in manufacturing these basic components include folate (folic acid), vitamin B-12, and vitamin B-6. They are critical to the existence and function of all cells, but are especially vital in supporting fast-growing tissues such as blood cells, the cells lining the gastrointestinal tract, and the rapidly growing fetus.

...the cells in the adult body are not the ones we were born with...

Red blood cells are made in the bone marrow, and they begin their life as large cells. Given an adequate supply of folic acid and vitamin B-12 for DNA manufacture and cell division, the large cell splits into smaller ones, which are precursors of the red blood cells (erythrocytes). If folic acid and B-12 are not sufficient to support normal DNA production and cell division, the large cell fails to split properly and remains "megaloblastic" (large). This eventually results in megaloblastic anemia, in which the red blood

cells are large but are reduced in number (because they failed to split normally and evolve into normal erythrocytes) and are inefficient in performing their basic functions of delivering hemoglobin and oxygen to the tissues. (Gropper, Smith, et al., 2009; Smolin & Grosvenor, 2010)

Iron is the critical component of hemoglobin, whose function is to carry oxygen from the lungs to the heart, and then from the heart to all the tissues of the body. If iron is in short supply, then too little hemoglobin is produced, and the red cells are pale and small (microcytic). Accordingly, the anemia that eventually results from iron deficiency is called microcytic anemia. Iron is also the critical component of myoglobin, a sister compound to hemoglobin, which provides oxygen to muscle cells. (Gropper, Smith, et al., 2009; Smolin & Grosvenor, 2010)

The effects of iron deficiency can be observed long before any actual anemia develops, and those effects include reduced physical work capacity and impaired cognitive function. (Institute of Medicine, 2006)

It is difficult to fully comprehend the extent of the biosynthesis that occurs in the body—the extent to which we are the product of our own metabolic pathways. The author Annie Dillard, in her beautiful book *Pilgrim at Tinker Creek,* contemplates this phenomenon, using the nephrons of the kidney as a case in point:

> **"The Henle's loop is an attenuated oxbow or U-turn made by an incredibly tiny tube in the nephron of the kidney. The nephron in turn is a filtering structure which produces urine and reabsorbs nutrients...There is no way to describe a nephron; you might hazard into a fairly good approximation of its structure if you threw about fifteen yards of string on the floor. If half the string fell into a very narrow loop, that would be the Henle's loop...But the heart of the matter would be a very snarled clump of string... which is the glomerulus...This is the filter to end all filters...Now the point of all this is that there are a million nephrons in each human kidney. I've got two million glomeruli, two million Henle's loops, and I made them all myself, without the least effort. They're undoubtedly my finest work."** (Dillard, 1974)

CALCIUM AND VITAMIN D FOR MANY FUNCTIONS, NOT JUST BONES

Calcium and vitamin D are both needed in adequate amounts in order to facilitate the absorption of calcium from food and in order to maintain essential levels of calcium for many metabolic functions. Calcium is of course a critical component of bone. Getting generous amounts of calcium and vitamin D can help build greater bone mass during the growth years, help slow bone loss during aging, and even help prevent or delay fractures. However, building bones is only one aspect of calcium's function. Calcium is also a critical component of extracellular and intracellular fluids, and the

body puts a higher priority on maintaining a steady state of calcium in extracellular and intracellular fluids than on retaining calcium in bones. In fact, the body treats the bones as a reservoir from which calcium can be withdrawn as needed to replenish the circulating supply. In a nutshell, this is why the bones are so vulnerable to low calcium intakes.

Calcium in the blood, muscle, and other tissues is essential for the contraction and dilation of blood vessels, neural transmission, and glandular secretion. Calcium is also essential for muscle contraction, and muscle contraction is vital to existence. The muscles of the heart contract and relax and contract again every second of every day, whether we are awake or asleep, reading or running, working or relaxing. The muscles of the arteries and veins react to the pumping of the heart and keep the blood flowing to the furthest reaches of the toes and fingers and back again, around and around and around. The muscles of the gastrointestinal tract actively push food through the system, permitting the body to take in the nutrients it needs and eliminate unwanted waste, hour after hour and day after day. The muscles of the diaphragm contract and relax, pulling life-giving oxygen into the lungs and expelling other gases, without ceasing.

The body strictly maintains a steady level of circulating calcium to fulfill these functions, even if that means taking calcium from bones, so it is important to get enough calcium every day to maintain the circulating level and also to maintain bone strength. Most people don't do a very good job of this, and the bones pay the price.

VITAMIN C FOR COLLAGEN: HOLDING EVERYTHING TOGETHER

The bones, of course, are not stacked one on top of the other in a precarious balance. They are firmly tied together and their muscles are firmly attached by

connective tissue—tendons and ligaments made of collagen. Collagen is a strong, smooth, white connective tissue that cushions the bones at intersections and joints so they move smoothly, that holds muscle bundles in place so they can effectively move the limbs, and that keeps the teeth firmly in place in the gums. Collagen, like bone, is made by the body from scratch, a manufacturing process which requires vitamin C.

When vitamin C is low, strong collagen will not be produced and maintained, "resulting in symptoms such as poor wound healing, the reopening of previously healed wounds, bone and joint aches, bone fractures, and improperly formed and loose teeth. Connective tissue is also important for blood vessel integrity. A vitamin C deficiency therefore causes weakened blood vessels and ruptured capillaries, which leads to symptoms such as tiny bleeds around the hair follicles, bleeding gums, and easy bruising." (Smolin & Grosvenor, 2010)

ANTIOXIDANT PROTECTION

In the course of normal metabolism, the cells and tissues are exposed to oxidation, which can be beneficial or can cause damage. Oxidation occurs when an electron is lost, and an oxidized molecule can be reduced if another nearby compound donates an electron. A substance with an unpaired electron is a "free radical." Numerous antioxidants are present in the blood and in the cells and membranes, and they can donate an electron when necessary. They are then rapidly regen-

erated by other antioxidants. The antioxidant defense system includes vitamin C, vitamin E, and some enzymes containing trace minerals such as selenium and zinc.

Vitamin C is a water-soluble antioxidant capable of scavenging free radicals and protecting against lipid oxidation. Vitamin E is a fat-soluble, chain-breaking antioxidant that can prevent the spread of free-radical reactions, especially in lipids. It scavenges free radicals and protects polyunsaturated fatty acids within membranes. Selenium is a component of many enzymes including glutathione peroxidase, and zinc is a component of superoxide dismutase, an enzyme that helps protect cells from free radical damage. (Institute of Medicine, 2006)

VITAMIN A FOR EYESIGHT AND OTHER FUNCTIONS

Vitamin A is essential for normal vision, gene expression, reproduction, development of the fetus, growth, and immune function. One of the earliest signs of low vitamin A status is night blindness (slow adaptation to the dark). Vitamin A activity is provided by retinol from animal sources and numerous carotenoids from plant sources. Carotenoids are the natural pigments in deeply colored fruits and vegetables, and the most common in the U.S. diet are alpha-carotene, beta-carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin. (Institute of Medicine, 2006)

Vitamin A is critical for the development and maintenance of healthy epithelial tissue, including the skin and the lining of internal surfaces such as the GI tract. The epithelial cells in the eye are "particularly susceptible to damage. The mucus in the eye normally provides lubrication, washes away dirt and other particles, and also contains a protein that helps destroy bacteria. When vitamin A is deficient, the lack of mucus and the buildup of keratin cause the cornea to dry and leave the eye open to infection." (Smolin & Grosvenor, 2010) This can lead to rupture of the cornea and permanent blindness. In the developing world, vitamin A deficiency is the leading cause of blindness in children under the age of five, and also increases their risk of infection and mortality.

ZINC FOR GROWTH AND IMMUNE FUNCTION

Zinc is the most abundant trace element in the cells, where is it integral to the functioning of more than 300 enzymes. (Smolin & Grosvenor, 2010) It is essential for growth and development. Impaired rate of growth in young children is often related to zinc insufficiency, and a modest level of zinc supplementation has been shown in some studies to help correct it. Zinc supplementation can contribute to healthier pregnancies and improved immune function. (Institute of Medicine, 2006)

NUTRIENT EFFECTS ON ENZYME FUNCTION AND DNA

Many of the vitamins function as cofactors for enzymes, and many of the essential minerals are integral components of the hundreds of enzymes that are functioning in the body all the time. The rates of reaction are governed by enzyme kinetics—the rate at which enzymes bind with their target compounds or their cofactors, accomplish their work, and then release the product. This rate can vary from one individual to another. Just as some people can jump high and some people can't, some people have very efficient metabolisms and others don't. Since vitamins are the cofactors that help enzymes to function, it may sometimes be possible to boost enzyme function by giving additional amounts of some vitamins.

Dr. Bruce Ames is a prominent biochemist who believes generous intakes of vitamins can "tune up" the metabolism and thus improve health or even delay

aging. (Ames, 2004) According to Dr. Ames: "Americans' intake of the 40 essential micronutrients (vitamins, minerals, and other biochemicals that humans require) is commonly thought to be adequate. Classic deficiency diseases, such as scurvy, beriberi, pernicious anemia, and rickets, are rare. The evidence suggests, however, that much chronic metabolic damage occurs at levels between the level that causes acute micronutrient deficiency disease and the recommended dietary allowances (RDAs). In addition, the prevention of more subtle metabolic damage may not be addressed by current RDAs. When one input in the metabolic network is inadequate, repercussions are felt on a large number of systems and can lead to degenerative disease. This may, for example, result in an increase in DNA damage (and cancer), neuron decay (and cognitive dysfunction) or mitochondrial decay (and accelerated aging and degenerative diseases)... A tune-up of micronutrient metabolism should give a marked increase in health at little cost." (Ames, 2004)

...when nutrients are in short supply, they are allocated by the body to vital functions such as energy production, possibly at the expense of functions important to long-term health...

It is known that there are genetic mutations that affect key enzymes, and many of these mutations result in a lower rate of reaction for the enzyme. Dr. Ames continues: "About 50 human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity." The B vitamins are prominent among these coenzymes. Dr. Ames predicts that, with a better understanding of the genomics involved, "it will become possible to customize vitamin therapies to suit the genotypic, and thus more specific, needs of individuals, instead of treating the phenotype." (Ames, Elson-Schwab, et al., 2002)

Dr. Ames has proposed that, when nutrients are in short supply, they are allocated by the body to vital functions such as energy production, possibly at the expense of functions important to long-term health. This allocation is a form of triage, and it could occur in part through altering the binding affinity of an enzyme for its vitamin or mineral cofactor. "The consequences of such triage would be evident at all levels," he says. "For example, in metabolic reactions, enzymes involved in ATP synthesis would be favored over DNA-repair enzymes; in cells, erythrocytes would be favored over leukocytes; and in organs, the heart would be favored over the liver." According to Dr. Ames, there is a need "to set micronutrient requirements high enough to minimize DNA and mitochondrial damage." End points such as avoidance of DNA damage could be used as indicators for establishing Estimated Average Requirements (EARs) for optimal health. In the meantime, he suggests that it would be prudent to recommend general use of a multivitamin to improve intakes of critical nutrients and protect against age-related diseases. (Ames, 2006)

"The triage theory posits that, when the availability of a micronutrient is inadequate, nature ensures that micronutrient-dependent functions required for short-term survival are protected at the expense of functions whose lack has only longer-term consequences, such as the diseases associated with aging." (McCann & Ames, 2009)

A recent study suggests that multivitamins may slow the aging of chromosomes. Telomeres are tails at the ends of chromosomes (repeat sequence TTAGGG)

that protect the chromosomes from degradation. The length of the telomere decreases with each round of cell division, which may eventually lead to the decline or death of the cell. "Therefore, telomere length has been proposed as a marker of 'biological aging.' Consistent with this hypothesis, preliminary epidemiologic studies have related shorter telomeres to higher mortality and higher risk of some age-related chronic diseases. Experimental evidence suggests that oxidative stress and chronic inflammation contribute to the attrition of telomeres. Several micronutrients, such as antioxidant vitamins and minerals, can modulate the states of oxidative stress and chronic inflammation and therefore may affect telomere length." (Xu, Parks, et al., 2009) In a study of 586 women in the Sister Study (healthy sisters of breast cancer patients), researchers examined the association of multivitamin use with telomere length. Sixty-five percent of the women used multivitamins at least once a month, and 74 percent of the supplement users took them on a daily basis. In general, the use of multivitamin supplements was associated with longer telomere length. Daily users had five percent longer telomeres than non-users, a difference which corresponds to about 9.8 years of age-related telomere loss. (Xu, Parks, et al., 2009) Protection against telomere aging has also been associated with other nutrients, including marine omega-3 fatty acids. (Farzaneh-Far, Lin, et al., 2010)

Bottom Line

Vitamins and essential minerals are constantly utilized by the body in producing energy to keep the system operating, in synthesizing and maintaining blood and skin and muscle and bone, in making DNA and proteins and enzymes to support cell growth and reproduction, and in supporting the physical and cognitive capabilities that make life both possible and enjoyable. Without adequate amounts of all of these nutrients, energy, productivity, and mental function decline. Some nutrients may also provide protection against the development of chronic disease, but that would be an added benefit and is not the reason they are considered essential. It is worth some effort to ensure adequate nutrient intakes to optimize function and promote overall health. That effort includes trying to get the best possible diet and may also include the rational use of nutritional supplements to fill nutrient gaps.

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Nutritional Supplements and Mortality

A human life is, ideally, long and complex. Its length and quality are impacted by a myriad of factors, including a person's genetic makeup, place of birth, family situation, economic status, educational achievement, avoidance of smoking and excessive drinking, access to medical care, social networks, type of employment, recreational choices, physical fitness, body weight, and dietary habits.

Some of these factors, such as one's place of birth, are accidents of fate. For example, a baby born today in the U.S. has a life expectancy of about 78 years. (CDC, 2011) Despite this "official" figure, some individuals will die young and a certain number will live to be 100 years of age or older.

Genetic factors play a role in a person's susceptibility to specific diseases and may thus affect life expectancy. Some chronic diseases such as heart disease, specific cancers, hypertension, and diabetes tend to run in families, and a person's risk of having such a disease is greater if the grandparents, parents or siblings have it. This is why physicians ask patients about their family history of disease, in order to identify patients who may be at elevated risk.

In contrast to one's genetic makeup, other factors such as the avoidance of smoking reflect personal choices and are subject to modification. Smoking has a huge impact on health status, increasing the risk of developing lung cancer by 13-fold in women who smoke and 23-fold in men who smoke, compared to nonsmokers. Smoking also has an important but less dramatic impact on heart disease, increasing risk in smokers by two to four-fold, compared to nonsmokers. (CDC, 2012)

In the U.S., there are around 2.5 million deaths per year, or less than 0.1 percent annually out of a total population of about 300 million. This represents "total mortality," or deaths from all causes. A few controversial but highly publicized studies have suggested that multivitamins or single vitamins and minerals can have a negative impact on total mortality. Given the fact that these nutrients are essential to the normal functioning of the body and to life itself, it seems highly unlikely that they could have an overall negative effect, when used within the very wide range of safe levels of intake.

TOTAL MORTALITY AND CAUSE-SPECIFIC MORTALITY

Clinical trials are never designed specifically to study effects of an intervention on "total mortality." In the nutrition arena, the studies are usually designed to evaluate whether giving people more of a specific vitamin or mineral or fatty acid can reduce the incidence of heart disease or cancer or bone fracture in the study population, compared to giving people a placebo. The desired outcome is an effect on a specific disease or condition, not on all possible diseases, since no intervention or preventive measure could possibly affect all of them. Data on total mortality is generally included in the report of the trial, but not as a main outcome.

Population studies (epidemiological studies), on the other hand, are designed to examine in great detail the health and lifestyle habits of large populations over long periods of time, seeking data on nutrients or habits that may promote general health, reduce disease incidence, or prevent premature mortality.

Heart disease and cancer are the two leading causes of death in the U.S., together causing many more deaths than the next eight causes combined. (CDC, 2011) Deaths from cancer or heart disease represent "cause-specific mortality," or mortality related to a

specific class of diseases, rather than "total mortality." Note that, despite the predominance of heart disease and cancer as leading causes of death, there are more deaths from miscellaneous "other causes" than from either of these.

TEN LEADING CAUSES OF DEATH IN THE U.S.

CAUSE	NUMBER OF DEATHS, 2009
Heart disease	599,413
Cancer	567,628
Chronic lower respiratory diseases	137,353
Stroke (cerebrovascular disease)	128,842
Accidents (unintentional injuries)	118,021
Alzheimer's disease	79,003
Diabetes	68,705
Influenza and pneumonia	53,692
Kidney diseases	48,935
Intentional self-harm (suicide)	36,909
All other causes	600,280

Because heart disease and cancer are responsible for so many deaths in the U.S. and other developed nations, reducing the incidence of and mortality from these two diseases could potentially deliver substantial public health benefits and potential savings in health care costs. Lifestyle choices including dietary habits are believed to have a large impact on a person's risk of these and other diseases. The *Dietary Guidelines for Americans* urge people to maintain a healthy weight, be physically fit, and make better dietary choices in order to promote health and help prevent disease. (Department of Agriculture and Department of Health and Human Services, 2010)

How much could dietary choices affect the risk of disease or mortality? Not as much as a strong genetic predisposition or personal choices about smoking, but enough to have a substantial impact. One report on

major dietary patterns and the risk of coronary heart disease in male health professionals evaluated the risk reduction that might be attributed to a "prudent diet" and the increased risk that might be attributed to a "Western diet." (Hu, Rimm, et al., 2000) The prudent diet was characterized by higher intakes of vegetables, fruit, legumes, whole grains, fish, and poultry. The Western diet was characterized by higher intakes of red meat, processed meat, refined grains, sweets and desserts, French fries, and high-fat dairy products. Men who consumed the most prudent diets had a 30 percent reduced risk of heart disease, expressed as a Relative Risk of 0.70 (RR 0.70), compared to men who had the least prudent diets. Conversely, men who consumed the most Western diets had a 64 percent increased risk of heart disease (RR 1.64), compared to men whose diets were the least "Western" in overall pattern. (Hu, Rimm, et al., 2000)

Many studies have examined the impact on disease or mortality of consuming certain foods or nutrients. Two classic studies back in 1993 found that men and women who took at least 200 IU of supplemental vitamin E for at least two years had about a 40 percent

reduced risk of heart disease, compared to people who took no vitamin E supplement. (Rimm, Stampfer, et al., 1993; Stampfer, Hennekens, et al., 1993) A recent report on whole grain intake and mortality in the Iowa Women's Health Study indicated that women with the highest consumption of whole grains had about a 20 percent reduced risk of mortality, compared to women with the lowest consumption of whole grains. (Jacobs, Andersen, et al., 2007) These findings are summarized in the following table.

INCREASE OR DECREASE IN RISK DUE TO CERTAIN DIETARY PRACTICES

PERCENTAGE INCREASE OR DECREASE	DIETARY HABITS OR PRACTICES
-20%	Decrease in total mortality in Iowa women with highest dietary consumption of whole grains
-30%	Decrease in risk of heart disease in men who consumed a "prudent diet"
-40%	Approximate decrease in risk of heart disease in men or women who used at least 200 IU vitamin E for at least 2 years
+65%	Increase in risk of heart disease in men who consumed a "Western diet"

These few examples illustrate that dietary patterns or specific food or nutrient intakes can potentially affect disease risk or mortality to an important degree—in these cases increasing or decreasing risk by 20 to 65 percent. Even very small effects on disease or mortality can be important, when extrapolated to the whole population, when the differences are real and the causes are well understood. However, the possibility also exists for a very small purported effect, or an effect not plausibly related to a given nutrient or product, to be blown out of proportion. This seems to have occurred in at least three well-publicized studies relating to vitamins and total mortality. All three analyses have significant limitations. Is it possible that the authors have blown their findings out of proportion? Or could they simply be wrong?

VITAMIN E AND TOTAL MORTALITY

A meta-analysis presented at a 2004 meeting of the American Heart Association (AHA) and highlighted by the President of AHA concluded that there was an increased risk of "all-cause mortality" in clinical trials using vitamin E at levels of 400 IU or more per day. (Miller, Pastor-Barriuso, et al., 2005) The study created an enormous storm of controversy, and even though it was later rebutted, the notion that harm could come from vitamin E was planted in the mind of the public by the media blitz that accompanied the meta-analysis.

The meta-analysis combined the results of 19 highly disparate clinical trials on vitamin E. (Miller, Pastor-Barriuso, et al., 2005) The analysis included studies that used vitamin E alone and studies that used vitamin E in combination with one or more nutrients. It included studies that used vitamin E in a very wide range of doses, from a minimum of 16.5 IU per day to a maximum of 2000 IU per day. The studies were done on highly divergent populations, including lifelong smokers, people with a recent myocardial infarction (MI), people at high risk of cardiovascular disease or coronary artery disease, people with bowel cancer, dialysis patients, and people with Alzheimer's disease or Parkinson's disease. Only a few studies were done in healthy people.

Based on the results of this mish-mash of studies, the authors concluded that nine out of eleven trials that utilized 400 IU per day or more showed a small (about four percent) increase in all-cause mortality, while the eight low-dose trials (less than 400 IU per day) showed a small (about two percent) decrease in all-cause mortality.

The authors of the vitamin E meta-analysis recognized that the high-dose trials "were often small and were performed in patients with chronic disease. The generalizability of the findings to healthy adults is uncertain." Nevertheless, generalize they did. They concluded that vitamin E at levels of 400 IU or more per day "may increase all-cause mortality and should be avoided." (Miller, Pastor-Barriuso, et al., 2005)

In 2006, the National Institutes of Health (NIH) convened a State-of-the-Science Conference on Multivitamin/Mineral Supplements and Prevention of Chronic Disease. (NIH State of the Science Conference on Multivitamins, 2006) In preparation for the conference, NIH commissioned an evidence report prepared by researchers at Johns Hopkins University for the Agency for Healthcare Research and Quality. (Huang, Caballero, et al., 2006) The evidence report reviewed the scientific data pertaining to nutritional supplements and disease risk, including the evidence relating to vitamin E and mortality. The report concluded that, based on the available data "along with consideration of biological plausibility, we find no convincing evidence to suggest vitamin E supplement use increases risk of death per se." (Huang, Caballero, et al., 2006)

The statistical treatment applied in the vitamin E meta-analysis was criticized by many scientists, including three from the M.D. Anderson Cancer Center in Texas who published an alternative analysis in 2009. The new analysis included some studies published after the Miller meta-analysis, for a total of 22. The conclusion of the re-analysis was that "vitamin E is unlikely to affect all-cause mortality, and that this is true regardless of dose." (Berry, Wathen, et al., 2009)

Thus, a single questionable meta-analysis, highlighted at a scientific meeting and avidly covered by the media, created the impression that vitamin E increases the risk of dying, when in fact adequate intakes are essential to life itself. National surveys show that over 90 percent of U.S. adults fail to get recommended amounts of vitamin E from their usual food intake. Most people could benefit from a modest supplement of vitamin E, either as part of their daily multivitamin or as a separate supplement.

ANTIOXIDANTS AND TOTAL MORTALITY

A meta-analysis published in 2007 purported to show that antioxidants used in clinical trials increased total mortality. (Bjelakovic, Nikolova, et al., 2007) The analysis included 68 clinical trials using beta-carotene, vitamin A, vitamin C, vitamin E, or selenium, either singly or in combination, at a wide range of doses. Overall, the 68 studies of antioxidants showed "no significant effect on mortality." (Bjelakovic, Nikolova, et al., 2007)

However, the authors apparently were not content with this overall result, so they proceeded to pick and choose among the 68 trials, dividing them into two subgroups.

"Facts are stubborn, but statistics are more pliable."
—Mark Twain

The authors claimed that some of the study designs posed a high risk of bias. The 21 studies with a purported high risk of bias included some highly regarded large clinical trials. As a group, these studies found that antioxidant interventions *decreased* mortality by about nine percent (RR 0.91). In contrast, the 47 studies identified by the authors as having a low risk of bias found that intervention with beta-carotene, vitamin A, or vitamin E *increased* mortality by about five percent (RR 1.05). Even after manipulating the studies in this manner, however, the authors found no influence of vitamin C or selenium supplementation on mortality.

The authors concluded: "Treatment with beta-carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study." (Bjelakovic, Nikolova, et al., 2007)

...the impact of antioxidants on the conditions that a study was designed to evaluate is a more reliable indication of risk and benefit than their impact on total mortality...

A comprehensive re-examination of the studies included in the antioxidant meta-analysis was published in 2010. (Biesalski, Grune, et al., 2010) The authors found that 36 percent of the trials reported a positive outcome of the intervention, indicating a benefit of antioxidant supplementation on the disease being studied. Sixty percent of the trials had a null outcome, showing neither a positive or negative effect on the disease of interest, and only three studies (four percent) had a negative outcome. The authors emphasize that the impact of antioxidants on the conditions that a study was designed to evaluate is a more reliable indication of risk and benefit than their impact on total mortality, which by definition includes a multitude of diseases and conditions, many of which are not related in any way to the potential effects of antioxidants.

THE IOWA WOMEN'S HEALTH STUDY

The Iowa Women's Health Study is a large observational study started in 1986 which enrolled about 40,000 women for the purpose of evaluating the association between the distribution of body fat and disease incidence. Measures collected included Body Mass Index (BMI), waist circumference, and waist-to-hip ratio. A questionnaire asked for information about education, smoking, alcohol use, leisure time physical activity, hormone replacement therapy, and reproductive history. Information was collected on the women's history of cancer, heart disease, hypertension, or diabetes. A food frequency questionnaire was also administered. At enrollment, the women were between the ages of 55 and 69. (Folsom, Kushi, et al., 2000)

In the years since its initiation, the Iowa Women's Health Study has been the subject of many scientific publications exploring various aspects of the available data, including publications relating to dietary habits and dietary supplement use. After initial enrollment in the study in 1986, the women were surveyed again in 1997 and 2004, and this longitudinal data provides a rich source of information on lifestyle habits, disease incidence, and mortality in this large cohort.

A 2011 article reported on dietary supplement use and total mortality in 38,772 participants in the Iowa Women's Health Study. (Mursu, Robien, et al., 2011) The authors reported a small (2.4 percent) increased risk of mortality in women who used a multivitamin and a small (3.8 percent) decreased risk of mortality in women who used a calcium supplement. They also reported on the risk of mortality among users of other specific nutritional supplements. In 1986, at baseline, 63 percent of the women were supplement users, and by 2004 the prevalence of supplement use had increased to 85 percent.

The article was published in the *Archives of Internal Medicine*. The editors of the journal highlighted the article by designating it as part of their "less is more" series showing that in some cases less health care results in better health. They also invited a commentary from the authors of the controversial meta-analysis on antioxidants and mortality. This triple-play created a considerable media buzz and resulted in enhanced coverage—somewhat like the burst of attention given to the meta-analysis on vitamin E and mortality in 2004.

The authors of the 2011 article purported to compare mortality in dietary supplement users *versus* nonusers, but in fact they provided no data on mortality among true nonusers of dietary supplements. (Mursu, Robien, et al., 2011) Instead, they provide data on mortality among users of each specific dietary supplement compared to *all other women in the study.*

For example, there were 12,769 users of multivitamins and 17,428 users of calcium supplements in 1986. The authors compare mortality in multivitamin users to mortality in the 25,474 women who did not use multivitamins—even if the women were using other dietary supplements, such as calcium. Similarly, the authors compare mortality in users of calcium supplements to mortality in the 20,735 women who did not use calcium—even if the women were using other dietary supplements such as multivitamins. In no case are users of any specific supplement compared to the 14,443 women who actually used *no* dietary supplements. (Mursu, Robien, et al., 2011)

Thus, the effect of any specific supplement on mortality is confounded by the possible effects (negative or positive) of other supplements. The authors say multivitamins slightly increased total mortality, while calcium slightly decreased total mortality—but each was being compared in part against the other. The confounding is exacerbated by the fact that many of the women were taking numerous dietary supplements. At baseline, 25 percent of the women used two or three supplements, eight percent used four or five supplements, and seven percent used six or more. (K. Park, Harnack, et al., 2009)

The article reports a negative effect of iron supplementation, but the doses associated with the negative effects are extremely high and are likely related to iron treatments medically prescribed by physicians to correct anemia or some other underlying problem. The four categories of iron dosage were: less than 50 mg per day, 50 to 200 mg per day, 200 to 400 mg per day, and over 400 mg per day. For comparison, the Recommended Dietary Allowance (RDA) for iron is only 8 mg per day for women over the age of 50 and 15 to 18 mg for women of childbearing age.

The authors of this report on the Iowa Women's Health Study advise against "the general and widespread use of dietary supplements" and recommend that supplements be used only "with strong medically based cause, such as symptomatic nutrient deficiency." (Mursu, Robien, et al., 2011) Such advice is not justified by their weak and highly confounded findings and is inconsistent with the current public health emphasis on the need for people to actively take responsibility for their own health, including the pursuit of healthy lifestyles. Waiting for symptomatic nutrient deficiency before adopting prudent dietary improvement or supplementation is counter to good sense and contrary to good public health policy.

RESULTS OF OTHER STUDIES ON MULTIVITAMINS AND MORTALITY

The Iowa Women's Health Study results are at variance with the results of several large studies that reported on multivitamins and total mortality. None of

the other studies found a negative impact on mortality, and some found beneficial effects when taking account of consistent longterm use or the combination of a multivitamin with other supplements. For example, in the Multiethnic Cohort Study of over 180,000 people, there was no association between multivitamin use and total mortality. (S. Y. Park, Murphy, et al., 2011) Likewise, a report on the Women's Health Initiative involving more than 160,000 postmenopausal women found no association between multivitamin use and total mortality. (Neuhouser, Wassertheil-Smoller, et al., 2009) In a study of more than 77,000 people in Washington State, any use of a multivitamin (at least once per week for at least a year) was not related to total mortality, although *regular* use (six or seven times a week for 10 years) was associated with a decrease in mortality. (Pocobelli, Peters, et al., 2009) In a study of more than one million people enrolled in a study sponsored by the American Cancer Society, there was no effect on total mortality of using a multivitamin for five years or more; but there was a decreased risk of total mortality in people who used a multivitamin in combination with additional vitamin C or E for five years or more. (Watkins, Erickson, et al., 2000) The following table summarizes these results.

EFFECT OF MULTIVITAMINS ON TOTAL MORTALITY IN FOUR LARGE STUDIES

EFFECT	POPULATION	STUDY
None	Over 180,000 people	Multiethnic Cohort Study
None	Over 160,000 postmenopausal women	Women's Health Initiative
None*	Over 77,000 people	Washington State study
None	Over one million people	American Cancer Society study

* Except beneficial effect with consistent longterm use

HARVARD COMMENTARY ON THE IOWA STUDY RESULTS

Researchers at the Harvard School of Public Health have carefully considered the report on the Iowa Women's Health Study and have concluded that it contains "major flaws." (HSPH, 2011) Among the major flaws in the study, Harvard researchers point to the fact that the authors of the study did not exclude women who already had various diseases or conditions at the beginning the study, including cancer, heart disease, or diabetes. Also, the study did not include any analysis related to the length of time the women had been using particular supplements.

The Harvard researchers observe: "Some scientists believe there is not enough evidence to recommend for or against taking a daily multivitamin, because there isn't yet enough data from randomized controlled trials. That's a reasonable but short-sighted point of view since it may never be possible to conduct randomized trials that are long enough to test the effects of multiple vitamins on risks of cancers, Alzheimer's disease, and other degenerative conditions." (HSPH, 2011)

Historically, recommendations for intakes of various vitamins were based on the amounts needed to avoid deficiency diseases, but the Harvard researchers note that current research suggests a broader role for these nutrients. For example, shortfalls in many micronutrients can lead to DNA damage, which in turn can cause or accelerate the diseases of aging. "This would make chronic conditions such as cancer, heart disease, vision loss, and a host of others a new type of deficiency disease." (HSPH, 2011)

More than 90 percent of Americans fail to get recommended amounts of vitamin D and vitamin E in their diets and also have shortfalls in other nutrients. Many older people have difficulty absorbing adequate amounts of dietary vitamin B-12, and thus the Institute

of Medicine and the Dietary Guidelines for Americans both recommend that people over the age of 50 eat foods fortified with B-12 or take a supplement of B-12. The Centers for Disease Control and Prevention (CDC) recommend that all women of childbearing age consume 400 micrograms of folic acid in addition to the amount of this vitamin they may obtain from their foods. The Harvard researchers conclude: "For these reasons, we believe a daily multivitamin-multimineral pill offers safe, simple micronutrient insurance, and the findings from the latest study don't change our recommendation." (HSPH, 2011)

Bottom Line

There is an abundance of evidence indicating that people who eat good diets and obtain adequate or even generous intakes of essential nutrients have better health that people who do not. Some of these health effects relate to improved normal body functions, such as having more energy, more endurance, better cognitive function, and improved disease resistance. Other effects may relate to a reduced incidence of some chronic diseases, including heart disease and cancer. A few scientists have jumped on "total mortality" as a measure of the overall impact of specific nutrients or nutritional supplements. Such analyses should be interpreted with caution, especially when the purported effects are very small and not related to the known mechanisms of action of the nutrients involved.

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Calcium and Vitamin D for the Bones

There is no question that a generous intake of calcium plus vitamin D will help build optimum bone mass during childhood and adolescence and will also slow the rate of bone loss that naturally occurs with aging. These combined effects help protect against the development of osteoporosis, a disease caused by failure to build adequate bone mass or by progressive bone loss during aging. Osteoporosis by definition is a condition in which bone mass is sufficiently compromised to result in bone fragility. Most people do not get enough calcium or vitamin D from diet alone, and in many individuals osteoporosis is only recognized when a fracture occurs. Substantial research has shown supplements to be effective in maintaining or increasing bone density.

More than 99 percent of the body's calcium is found in the bones and teeth. While the bones have an obvious structural role, they also serve as the body's reservoir for calcium, since bone calcium can be mobilized and used to maintain the steady state necessary for muscle contraction and nerve transmission. Bone is not a static tissue, but is constantly being resorbed and reformed. The balance determines whether bone is being added or lost in any particular person at any particular time. In growing children, the rate of bone formation is greater than the rate of bone resorption. In healthy young adults, the two processes are roughly balanced. During aging, the rate of formation falls behind the rate of resorption, and there is generally a net loss of bone.

OBSERVATIONS OF AN EXPERT: DR. ROBERT P. HEANEY

Dr. Robert P. Heaney of Creighton University, an internationally recognized expert on calcium and bone health, explains that bone is formed from structural materials such as calcium, phosphorus, and protein, all of which must be obtained from outside sources—that is, from dietary intake. A growing body must obtain these materials in adequate amounts from the diet. Even after growth has stopped, these substances must continue to be provided, because calcium and other components of bone are used for other functions and are lost from the body in considerable quantities every day. These losses must be offset by more intake. Otherwise, the body will treat the bones as a nutritional reserve and extract calcium from them to satisfy other needs. (Heaney, 2000)

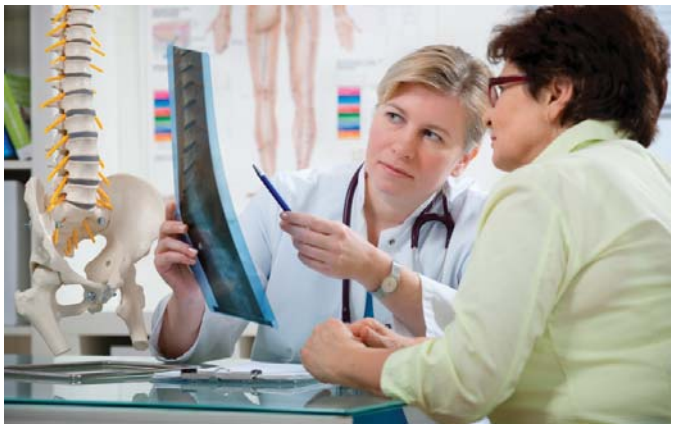
...the current levels of calcium intake in children are not sufficient to fulfill their genetic potential for building bone mass.

"In the past 25 years there have been at least 139 published reports in English exploring the relationship between calcium intake and bone status," according to Dr. Heaney. Almost all the randomized controlled trials in adults showed that increasing calcium intake reduced or stopped age-related bone loss, or reduced the rate of bone fractures, or both. All of the trials in children and adolescents showed that consuming supplemental calcium (from supplements or from dairy products) increased bone growth.

What conclusions can be drawn from these controlled studies? First, the current levels of calcium intake in children are not sufficient to fulfill their genetic potential for building bone mass. Also, current intakes

among adults are not sufficient to protect the "bone capital" they have amassed during their lifetime. Dr. Heaney says "increasing calcium intake across the life span will enhance bone acquisition during growth, stabilize bone mass at maturity," and minimize bone loss during aging. (Heaney, 2000)

In addition to the controlled studies, there have been more than 86 observational studies on the association between calcium intake and bone mass. About three-fourths of these "support the hypothesis that increased calcium intake protects the skeleton." (Heaney, 2000) Taken together, all the available studies firmly establish that high calcium intakes are important throughout life, that most Americans are not getting enough calcium, and that shortfalls of calcium intake have a major impact on bone health.



What about the role of calcium in treating people who have already suffered significant bone loss? "With the stimulus of growth long past, and with some of the bony scaffolding already destroyed by prior bone loss, supplemental calcium alone does not usually restore lost bone. However, high calcium intakes play a crucial and often little appreciated role as an adjuvant to formal therapeutic regimens." Dr. Heaney suggests that it would be prudent to include 1600 to 2400 mg per day of calcium as part of any treatment regimen directed at increasing bone mass. (Heaney, 2000)

Dr. Heaney has also emphasized the critical importance of the interaction of calcium and vitamin D in bone health and possibly in other conditions. Both are needed to ensure sufficient calcium absorption to meet the body's needs. Also, "population intakes of both nutrients are recognized to be inadequate and to be in need of improvement." (Heaney, 2008a)

THE NIH CONSENSUS CONFERENCES ON OSTEOPOROSIS

The National Institutes of Health convened consensus conferences on osteoporosis in 1984, 1994, and 2000. All emphasized the importance of calcium intakes as well as other actions to reduce the risk of osteoporosis. The Consensus Conference on Osteoporosis Prevention, Diagnosis, and Therapy convened by NIH in 2000 had this to say about calcium and osteoporosis: "Calcium is the nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis. Sufficient data exist to recommend specific dietary calcium intakes at various stages of life." Yet only about 25 percent of teenage boys, around 10 percent of teenage girls, and approximately half of older adults actually consume the recommended amounts of calcium, according to the consensus conference report. The consensus conference also emphasized the role of vitamin D, which is required for optimal calcium absorption. (NIH, 2000)

Randomized clinical trials have demonstrated that adequate calcium intake from diet or supplements increases bone mineral density. In some trials, combined supplementation with vitamin D and calcium has resulted in significant reductions in hip fracture and other fractures. The panel recommends that calcium and vitamin D also be given in conjunction with any drug therapy for osteoporosis. Other recommendations for prevention and treatment include getting plenty of weight-bearing exercise and avoiding falls. (NIH, 2000)

SURGEON GENERAL'S REPORT ON BONE HEALTH AND OSTEOPOROSIS

In a major report issued in 2004, the U.S. Surgeon General concluded: "Physical activity and calcium and vitamin D intake are now known to be major contributors to bone health for individuals of all ages. Even though bone disease often strikes late in life, the importance of beginning prevention at a very young age and continuing it throughout life is now well understood.... It is never too late for prevention, as even older individuals with poor bone health can improve their bone health status through appropriate exercise and calcium and vitamin D intake." (Department of Health and Human Services, 2004)

INCIDENCE OF OSTEOPOROSIS

According to the nonprofit National Osteoporosis Foundation (NOF), about 10 million Americans already have osteoporosis, and another 34 million have low bone mass that puts them at risk for osteoporosis. (National Osteoporosis Foundation, 2012) Every year, there are more than two million fractures due to osteoporosis. The cost of treating these fractures in 2005 was $19 billion, which amounts to $52 million a day.

The NOF notes that "many Americans do not get the amount of calcium they need every day." (National Osteoporosis Foundation, 2012) NOF's recommended solution for this problem is for people to modify their dietary habits to increase consumption of dairy products and other foods providing calcium, but it is recognized that "calcium-fortified foods and calcium supplements are helpful for people who are unable to get enough calcium in their diets." Vitamin D is also critical, and it is hard to get enough vitamin D from foods alone. The skin makes vitamin D in response to sunlight, but concerns about skin cancer have led many people to stay out of the sun, cover up, or use sunscreen or sunblock, thus dramatically limiting vitamin D production. Therefore, NOF recommends that "people who do not get enough vitamin D should consider taking a supplement." (National Osteoporosis Foundation, 2012)

EXPANDED HEALTH CLAIM APPROVED BY FDA

The Food and Drug Administration (FDA) is authorized by law to permit "health claims" in food labeling regarding nutrients scientifically demonstrated to reduce the risk of a disease. One of the first health claims approved by FDA in 1993 was for the role of calcium in protecting against osteoporosis. (FDA, 1993) In 2008, FDA revised the calcium health claim to permit mention of the fact that vitamin D also plays a critical role in maintaining bone health and protecting against osteoporosis. (FDA, 2008) The claim is permitted for foods or dietary supplements that provide at least 200 mg of calcium per serving; if vitamin D is included, the product must provide at least 80 International Units per serving. The FDA regulation permitting the claim suggests model language such as:

> "Adequate calcium and vitamin D throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis."

REVISING RECOMMENDATIONS FOR CALCIUM AND VITAMIN D

In the years since new Dietary Reference Intakes (DRIs) for calcium and vitamin D were initially established in 1997, there has been extensive research suggesting that higher recommendations may be warranted, especially for vitamin D. (Dawson-Hughes, Heaney, et al., 2005; Holick, 2006; Vieth, 2004; Vieth, Bischoff-Ferrari, et al., 2007) As a result of this new evidence, the Institute of Medicine convened an expert panel to consider whether the official values should be revised. (Institute of Medicine, 2009; Yetley, Brule, et al., 2009).

RECOMMENDATIONS OF THE INSTITUTE OF MEDICINE

After two years of deliberations, the panel issued new DRIs for calcium and vitamin D in November 2010. (Institute of Medicine, 2010) The new report adopts Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for both nutrients, in place of the Adequate Intakes (AIs) established in 1997. Quantitatively, the RDAs for calcium are very similar to the former AIs for calcium, while the new RDAs for vitamin D are substantially higher than the earlier AIs.

NEW DIETARY REFERENCE INTAKES FOR CALCIUM, 2010

POPULATION GROUP	CALCIUM EAR	CALCIUM RDA
Boys and girls 9 to 18	1100 mg	1300 mg
Men 19 to 50	800 mg	1000 mg
Women 19 to 50	800 mg	1000 mg
Men 51 to 70	800 mg	1000 mg
Women 51 to 70	1000 mg	1200 mg
Men over 70	1000 mg	1200 mg
Women over 70	1000 mg	1200 mg

NEW DIETARY REFERENCE INTAKES FOR VITAMIN D, 2010

POPULATION GROUP	VITAMIN D EAR	VITAMIN D RDA
Children and adults to age 70	400 IU	600 IU
Adults over 70	400 IU	800 IU

The EAR "is the average daily nutrient intake level that is estimated to meet the nutrient needs of half of the healthy individuals in a life stage or gender group. Although the term 'average' is used, the EAR is actually an estimated *median* requirement. Therefore, by definition, the EAR exceeds the needs of half of the population and is less than the needs of the other half." (Institute of Medicine, 2010)

The RDA is derived from the EAR. Specifically, the RDA is the EAR plus two standard deviations and is intended to cover the needs of virtually all (97.5 percent) of the healthy population. (Institute of Medicine, 2010)

The new DRI committee on calcium and vitamin D also established a Tolerable Upper Intake Level (UL) for calcium of 2500 mg per day for children and for adults up to age 70, but a lower UL of 2000 mg per day for men and women over the age of 70. An upper level of 4000 IU was set for vitamin D for children and adults in all age groups. ULs for both nutrients apply to total dietary intake.

CALCIUM AND VITAMIN D INTAKES ARE BELOW RECOMMENDED LEVELS

National surveys show that calcium and vitamin D intakes are below recommended levels—not just for some people, but for most people, and especially for women. (Moshfegh, Goldman, et al., 2009)

RDAs for calcium in boys and girls ages nine to 18 are higher than for any other age group—1300 mg per day, which is the equivalent of about four glasses of milk per day. Over 80 percent of boys ages nine to 13 and almost 60 percent of boys ages 14 to 18 fail to achieve this level of intake. Among girls in this age range, the situation is even worse, with about 90 percent of girls falling short of the RDA. Clearly almost all teenage girls and many teenage boys would benefit from supplemental calcium to ensure adequate bone strength and growth.

Recommendations for calcium in adults in the age range 19 to 50 are a little lower—1000 mg per day, which is the equivalent of about three glasses of milk per day. However, *more than two-thirds of adult women in this age group fail to get the recommended amount of calcium.* About half of these women get 800 mg or less, and about a quarter of them get 600 mg or

less. Men in the age range 19 to 50 do a little better, with "only" about 40 percent falling short of the RDA for calcium. Most adult women are not getting enough calcium to maintain healthy bones, and the same is true of a large fraction of men. A calcium supplement would certainly help to fill these gaps.

RDAs for calcium in women over age 50 and in men over age 70 are higher—1200 mg per day—and a larger percentage of them fall short of this level. *More than 90 percent of women over 50* fail to achieve recommended intakes of calcium, along with *more than 80 percent of men over 70*. This has unmistakable consequences for bone health, and a calcium supplement would be an easy and inexpensive option for increasing intake.

The situation with vitamin D intake is similar. At least 90 percent of men and women fall short of the EAR and the RDA for vitamin D, considering only dietary intake. (Moshfegh, Goldman, et al., 2009) Multivitamins with vitamin D and calcium supplements with vitamin D can help address these shortfalls. Vitamin D is also synthesized in the body in response to sunlight, so dietary intake is not the only source. Blood levels of an intermediate form of vitamin D (25OHD) are considered a valid measure of overall vitamin D status, reflecting the contribution of both dietary intake and sun exposure.

HALF OF WOMEN OVER 50 HAVE LOW BONE MINERAL DENSITY

The National Osteoporosis Risk Assessment study showed that almost half of women over 50 have undiagnosed low bone mineral density. In other words, they are unknowingly at risk of bone fractures. The study measured the bone mineral density of more than 200,000 postmenopausal women 50 years of age or older with no previous diagnosis of osteoporosis. The women were recruited from more than 4,000 medical practices in 34 states, and the average age at the time of recruitment was 65 years. Forty percent of the women had low bone mineral density (osteopenia but not osteoporosis) and an additional seven percent had bone mineral density so low as to constitute osteoporosis. During the year following recruitment into the study, the women with osteopenia had twice the rate of bone fracture and the women with osteoporosis had four times the rate of bone fracture, compared to women with normal bone density. (Siris, Miller, et al., 2001)

The National Osteoporosis Risk Assessment study "reaffirms the existence of a large population of women expected to live well into the 21st century who are at risk for future fracture. It also affirms the immediacy of risk…; the risk of fracture is not a decade or more in the future but, rather, exists at the time of the diagnosis." (Siris, Miller, et al., 2001)

HELPING WOMEN COMPLY WITH CALCIUM RECOMMENDATIONS

More than 100 women with low bone density were included in an osteoporosis education program and were counseled by a dietitian. Six months later, 77 percent of the women were adhering to calcium recommendations and 91 percent were using calcium supplements. Barriers to full adherence included the participants' uncertainty about identifying good sources of calcium,

as well as concerns about weight gain and fat content of some calcium-rich foods. "The only significant independent predictor of calcium adherence at follow-up was use of a calcium supplement." (French, Vernace-Inserra, et al., 2008)

Researchers in Cleveland examined barriers to calcium supplement use in 185 women ages 20 to 64 who visited suburban clinics. (Tyler, Werner, et al., 2008) Calcium supplement use was higher among women who used multivitamins, who believed themselves to be at some risk of osteoporosis, and who were older. Ninety-six percent of those who never used supplements said they would consider taking a calcium supplement if their physician recommended it. The authors suggest that these barriers "seem amenable to focused and brief office-based interventions that could increase the number of women meeting calcium intake guidelines." (Tyler, Werner, et al., 2008)

NOT JUST A WOMEN'S ISSUE

Osteoporosis can also strike men, particularly older men. It has been estimated that "one in five men over the age of 50 will suffer an osteoporotic fracture during their lifetime, and men who sustain fractures have an increased mortality risk." (Khosla, 2010) In fact, the incidence of osteoporosis-related fracture in men is similar to that of myocardial infarction and exceeds that of lung and prostate cancers combined. (Binkley, 2009) Clearly it is just as critical for men to obtain adequate amounts of calcium and vitamin D as it is for women.

POTENTIAL EFFECTS BEYOND BONE

Some studies suggest that improved calcium and vitamin D intakes could have benefits beyond their effects on bone. These benefits could potentially affect conditions such as cancer and hypertension, as well as numerous other health risks.

A study of calcium and cancer in the NIH-AARP Diet and Health Study found that cancers of the digestive system, especially colorectal cancers, were lower in men and women with higher intakes of calcium. The study evaluated calcium intake from foods or supplements in more than 36,000 men and more than 16,000 women who developed cancer over a period of seven years. (Park, Leitzmann, et al., 2009) Other epidemiological studies have reported an effect of vitamin D in lowering colorectal cancer. (Giovannucci, 2006) Such an effect was not observed in the Women's Health Initiative. (Wactawski-Wende, Kotchen, et al., 2006) However, many of the women in that study did not actually take the calcium and vitamin D supplements they were assigned to take. (Jackson, LaCroix, et al., 2006)

A recent review attempted to define optimal vitamin D serum levels associated with multiple health outcomes. The authors assert that "a large majority of the U.S. population could benefit from vitamin D supplementation, which is a simple, highly affordable, and well-tolerated strategy that could reduce osteoporosis and fractures and could probably reduce falls associated with lower-extremity weakness, could improve dental health, and reduce the incidence of colorectal cancer in older adults." (Bischoff-Ferrari, Giovannucci, et al., 2006) They suggest that the optimal serum vitamin D level is at least 75 nanomoles per liter (nmol/L), and ideally 90

to 100 nmol/L. An intake in adults of at least 1000 IU (25 mcg) of vitamin D is needed to bring vitamin D concentrations in at least 50 percent of the population up to 75 nmol/L. They urge an increase in currently recommended levels of intake for vitamin D. (Bischoff-Ferrari, Giovannucci, et al., 2006) A benefit-risk assessment indicates that the recommended increased intakes of vitamin D can be considered both beneficial and safe. (Bischoff-Ferrari, Shao, et al., 2010)

Improved vitamin D status may protect cardiovascular health. Recently published epidemiological studies have suggested that vitamin D status (measured by serum 25-hydroxyvitamin D levels) is inversely associated with the risk for cardiovascular events and related deaths. (Dobnig, Pilz, et al., 2008; Giovannucci, Liu, et al., 2008; Wang, Manson, et al., 2010)

Researchers in New Zealand have published a meta-analysis and other findings suggesting the possibility that calcium supplementation may increase the risk of cardiovascular events, including myocardial infarction (MI). (Bolland, Avenell, et al., 2010; Bolland, Grey, et al., 2011) In contrast, a systematic review and meta-analysis by other researchers at Brigham and Women's Hospital in Boston reported that calcium supplements appear to have minimal cardiovascular effects and that vitamin D supplements may reduce cardiovascular risk. (Wang, Manson, et al., 2010) Both groups agree that additional research is warranted to clarify the effects of these nutrients on cardiovascular endpoints.

Harvard Medical School and the Brigham and Women's Hospital are currently undertaking a large, long-term clinical trial funded by the National Institutes of Health on the effect of 2000 IU vitamin D supplementation (and/or 1 gram of omega-3 fatty acids from fish oil) on both cardiovascular and cancer outcomes (the VITAL or Vitamin D and Omega-3 Trial). (VITAL Study, 2012)

NEED FOR A BROADER APPROACH TO CLINICAL TRIALS

In a major lecture delivered in 2008, Dr. Robert Heaney of Creighton University noted that clinical trials tend to measure single outcomes of nutritional interventions, even when the nutrients are known to affect multiple metabolic systems. (Heaney, 2008b)

Dr. Heaney explains, "If one takes vitamin D as an example, one notes at the outset that there are credible scientific data suggesting that vitamin D has an effect on blood pressure, insulin sensitivity, bone density, fall frequency, osteoporotic fracture risk, calcium absorption efficiency, resistance to infection, periodontal disease, and the development of various epithelial cancers, to mention only some." (Heaney, 2008b) How could one design a clinical trial to measure a composite of these effects?

As an example, Dr. Heaney points to a review article on the aggregated effects of vitamin D on BMD (bone mineral density), bone fracture rate, colon cancer risk, tooth attachment loss in periodontal disease, and lower extremity neuromuscular function. (Bischoff-Ferrari, Giovannucci, et al., 2006) Dr. Heaney urges the development of a global functional index for various nutrients or combinations of nutrients, to permit more effective research into nutritional benefits.

KEY SCIENTIFIC STUDIES

The conclusions and recommendations mentioned earlier are based on a large number of clinical trials, some of which are summarized below, with more recent studies cited first.

To study the effect of calcium supplementation alone (without vitamin D), researchers gave 1200 mg of calcium or a placebo to 930 men and women for a period of four years. During treatment, there were significantly fewer fractures in the calcium group. Not

surprisingly, the benefit was maintained only while the treatment continued and was not maintained during the six or seven years of follow-up after treatment was discontinued. (Bischoff-Ferrari, Rees, et al., 2008)

In a study in Australia, 323 men at least 40 years old were given 600 mg or 1200 mg of calcium supplementation, or a placebo, for two years. Bone mineral density increased in the men receiving 1200 mg but not in the men who got only 600 mg of calcium. The authors conclude that the effects of 1200 mg of calcium on bone mineral density in men are similar to the effects observed in postmenopausal women. (Reid, Ames, et al., 2008)

In 96 adolescent girls with low calcium intakes, supplementation for 18 months with about 500 mg of calcium increased bone mineral density at "all skeletal sites" and improved other markers of bone health, compared to girls given a placebo. The supplement was given as calcium citrate malate dissolved in fruit juice. Two years after the treatment was discontinued the benefits were no longer evident, indicating that ongoing supplementation is required to maintain the effects. (Lambert, Eastell, et al., 2008)

In a study of more than 36,000 postmenopausal women who were already enrolled in the Women's Health Initiative, researchers studied the effect of 1000 mg of calcium and 400 IU of vitamin D on fracture rates. The supplements were meant to be taken for a period of seven years, but many women failed to comply, and there was widespread calcium supplement use (and thus high overall calcium intake) in the placebo group, a limitation acknowledged by the study authors. Overall, there was no effect on fracture rates, but in women in the treatment group who actually took the supplement there was a significant decreased risk of hip fracture. (Jackson, LaCroix, et al., 2006)

In another study in Australia, 1,460 women over the age of 70 were given 1200 mg of calcium per day or a placebo for a period of five years. Overall, there was no benefit, possibly because more than 40 percent of the subjects failed to comply with the treatment. Among 830 patients who actually took 80 percent or more of their tablets (calcium or placebo), the calcium group had a significantly reduced risk of fracture. They also had improved measurements of bone density and bone strength. The authors conclude that calcium supplementation in this group was ineffective as a public health intervention because of poor compliance, but was effective in those women who took the supplements. (Prince, Devine, et al., 2006)

Researchers at the USDA Human Nutrition Research Center on Aging at Tufts University studied bone density in almost 400 men and women over 65 years of age. The subjects were given 500 mg of calcium plus 700 IU of vitamin D per day, or a placebo, for a period of three years. The group that received calcium and vitamin D experienced a significantly lower rate of bone loss and fewer nonvertebral fractures, compared to the placebo group. The researchers conclude that supplementation with calcium and vitamin D "may substantially reduce the risk of nonvertebral fractures among men and women 65 years of age or older." (Dawson-Hughes, Harris, et al., 1997)

A four-year study of calcium supplementation conducted in New Zealand confirmed that the beneficial effects of calcium supplements are maintained over several years of regular use. In this study, 78 women who were at least three years beyond menopause were assigned to calcium (1 gram per day) or a placebo. The rate of total body bone loss was lower in the calcium group than in the placebo group. In addition, calcium supplementation was associated with a lower fracture rate. In the placebo group, seven women experienced nine fractures during the study, while there were only

two fractures in the group getting 1 gram of calcium daily. (Reid, Ames, et al., 1995)

A study from France showed that calcium and vitamin D supplementation can not only decrease bone loss and reduce the incidence of fractures, but may slightly *increase* bone mass, even in the very old. For a period of 18 months, more than 3000 women over the age of 69 received 1.2 grams of calcium and 800 IU of vitamin D a day, or a placebo. In the supplemented group, there were 43 percent fewer hip fractures. Most surprisingly, bone density actually increased slightly in the group of elderly women who received the supplement. The authors concluded that "it may never be too late to prevent hip fracture." (Chapuy, Arlot, et al., 1992)

Researchers in The Netherlands conducted a meta-analysis of 33 studies on calcium and bone mass in adults 18 to 50 years of age. The intervention trials indicate that a calcium supplement of about 1000 mg per day in premenopausal women "can prevent the loss of more than 1 percent of bone per year" at most bone sites. This could have a substantial impact on bone mass around the time of menopause. (Welten, Kemper, et al., 1995)

WHAT WOULD IT COST TO INCREASE CALCIUM INTAKE?

Increasing daily calcium intake by 1000 mg per day can be accomplished by using a dietary supplement, consuming foods fortified with calcium, or ingesting more dairy products. All three are considered to be roughly equivalent in terms of the bioavailability of the calcium they contain. (Institute of Medicine, 1997)

Food sources of calcium tend to be more expensive than dietary supplement sources. Of course, they also provide nutrients other than calcium, as well as calories. The cost of adding 1000 mg of calcium to the diet would be about six cents a day for a calcium carbonate antacid (without vitamin D), around 14 to 18 cents a day for calcium tablets with vitamin D, about 30 cents a day for calcium chews with vitamin D, approximately a dollar a day if the calcium comes from lowfat milk, and over a dollar a day if the calcium comes from calcium-fortified orange juice. Most of these prices are for national brands of each product. Purchasing store brands or buying on sale would decrease the cost.

COST OF 1000 mg OF CALCIUM FROM DIETARY SUPPLEMENTS, MILK, OR FORTIFIED ORANGE JUICE

This table shows the amount of each product that would need to be consumed to provide 1000 mg of additional calcium per day, and the cost for each product. Prices are for products purchased from supermarkets and drug stores in the upper Midwest early in 2012.

PRODUCT	COST PER DAY	CALORIES	VITAMIN D
Store-brand dietary supplement, calcium carbonate, two tablets provide 1000 mg calcium, plus vitamin D	$ 0.14	—	yes
Brand-name dietary supplement, calcium carbonate, two tablets provide 1000 mg calcium, plus vitamin D	$ 0.18	—	yes
Dietary supplement, soft calcium chews, two chews provide 1000 mg calcium, plus vitamin D	$ 0.32	40	yes
Antacid (and dietary supplement), calcium carbonate, chewable, two tablets provide 1000 mg calcium (no vitamin D)	$ 0.06	20	no
Lowfat milk, 1% fat, 3.3 cups provide 1000 mg calcium, plus vitamin D	$ 1.02	360	yes
Calcium-fortified orange juice, 3 cups provide 1000 mg calcium, plus vitamin D	$ 1.62	330	yes

Whether to change overall dietary habits to make room for additional high-calcium foods or simply to add a calcium supplement is a matter of personal choice. Adding a supplement may be the easiest and most inexpensive option, but any of these alternatives would be an economical and sound investment in long-term health for consumers.

Bottom Line

A generous intake of calcium, plus an appropriate amount of vitamin D, can significantly increase bone mass in growing children and young adults and can substantially decrease bone loss during aging. Most Americans do not get the amount of calcium recommended for optimal bone health, and shortfalls throughout life can result in fractures as people age. These fractures can be both costly and traumatic. It would make sense for most people to increase their calcium intake by 500 to 1000 mg per day, and one of the easiest and most economical ways to do this is to use a daily calcium supplement, preferably with vitamin D.

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Folic Acid Protects Against Some Birth Defects

One of the most exciting scientific developments in the past several decades is the finding that folic acid (one of the B vitamins) plays a critical role in protecting against neural tube birth defects (NTDs) such as spina bifida when taken by women of childbearing age before conception and during early pregnancy. Most of the clinical evidence is from studies using *multivitamins containing folic acid*, rather than the use of folic acid alone.

NTDs are very serious defects that occur in the United States and Canada in about one of every thousand births. Higher rates of incidence occur in Great Britain and Ireland and in northern Chinese populations. NTDs include conditions such as spina bifida (a failure of closure of the neural tube surrounding the spinal cord) and anencephaly (partial absence of the brain). Babies with spina bifida generally survive, but may require extensive surgical and medical care and may be permanently disabled. Babies with anencephaly do not survive.

Nutritional status is a key component affecting the occurrence of neural tube defects. Some studies have shown that women with higher dietary folate intakes had a lower risk of having a baby with an NTD. In other studies, women who took multivitamins containing folic acid had a lower risk of having a baby with an NTD than women who did not take multivitamins. These studies showed that it was critical that the supplement be used at least a month before conception and during at least the first month following conception. The neural tube of the fetus closes (or tragically fails to close) in the first month of pregnancy, at a time when many women are not yet aware they are pregnant.

In the U.S., approximately 3000 pregnancies are affected by NTDs each year, and worldwide these birth defects affect 300,000 or more pregnancies annually. (Berry, Li, et al., 1999; CDC, 2009) Scientific evidence makes it clear that supplementation with a multivitamin containing folic acid could prevent a large fraction of these defects.

Food Folate vs Folic Acid

Folate is the form of this B vitamin that occurs naturally in foods. It must be modified by an enzyme in the intestine before it can be absorbed. Only about half the folate in foods is absorbed.

Folic acid is the synthetic form of this B vitamin that is used in nutritional supplements, fortified foods, and clinical trials.

It is very efficiently absorbed by the body.

NOTE ON ABBREVIATIONS

The recommended daily quantity of folic acid for women of childbearing age is 400 micrograms per day (equivalent to 0.4 mg per day). The abbreviation of the term “microgram” for purposes of nutrition labeling is “mcg,” while the scientific abbreviation is “µg.” In this document we will use the abbreviation “mcg.”

RECOMMENDATION OF THE PUBLIC HEALTH SERVICE

In 1992, the U.S. Public Health Service considered the available evidence and recommended that “all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs.” (CDC, 1992)

RECOMMENDATION OF THE FOOD AND NUTRITION BOARD

In its 1998 report on recommendations for the B vitamins, the Food and Nutrition Board of the Institute of Medicine outlined the evidence relating to folic acid and neural tube defects. (Institute of Medicine, 1998) A number of scientific studies have shown that women who took a folic acid supplement of 360 to 800 mcg per day, *in addition to their usual diet* providing 200 to 300 mcg of dietary folate per day, had a reduced risk of having a baby with a neural tube defect.

In addition to protecting against neural tube defects such as spina bifida, multivitamins and fortified foods containing folic acid have been shown in some studies to prevent other types of birth defects, including cleft palate and cleft lip and some cardiovascular malformations, according to the Food and Nutrition Board.

Based on this evidence, the Food and Nutrition Board issued new dietary recommendations for folic acid in 1998, recognizing the need for women of childbearing age to get *supplemental folic acid***,** over and above the amounts that are naturally present in foods. (Institute of Medicine, 1998)

Recommendation for Women Capable of Becoming Pregnant

The Food and Nutrition Board of the Institute of Medicine recommends "that women capable of becoming pregnant consume 400 mcg of folate daily from supplements, fortified foods, or both in addition to consuming food folate from a varied diet. At this time the evidence for a protective effect from folate supplements is much stronger than that for food folate."

FDA HEALTH CLAIM AND MANDATORY ENRICHMENT

In 1996, FDA concluded that the evidence was strong enough to support a health claim that may be used in the labeling of foods and dietary supplements containing the B vitamin folic acid. The claim may state that "healthful diets with adequate folic acid may reduce a woman's risk of having a child with a brain or spinal cord birth defect." (FDA, 1996a)

Beginning in 1998, FDA required that folic acid be included among the nutrients added to enriched grain products such as flour, breads, and pasta. Previously, only iron, thiamin, riboflavin, and niacin were added to enriched grain products. The level of folic acid fortification is relatively modest (140 mcg per 100 grams of product), about twice the level of folate that is naturally present in whole wheat. (FDA, 1996b)

The level of folic acid fortification selected by FDA was initially expected to deliver an additional 80 to 100 mcg of folic acid to the daily diets of women of childbearing age, but the actual increase in the amount consumed appears to be higher than that, and blood levels of folate have increased substantially. CDC has documented a decline of 26 percent in the incidence of NTDs since mandatory enrichment—a very important

gain, even if it does not match the impact that would be predicted if women got the full recommended amount of supplemental folic acid. (CDC, 2004)

An analysis of folic acid intake in the 2003-2006 National Health and Nutrition Examination Survey found that 42 percent of adults consumed folic acid only from enriched grain products and not from ready-to-eat cereals or supplements; 18 percent consumed both enriched grains and ready-to-eat cereals; 25 percent consumed ready-to-eat cereals and dietary supplements containing folic acid; and 15 percent consumed all three sources of folic acid. The usual amount of folic acid consumed by the four groups was 138, 274, 479, and 635 mcg per day, respectively. (Yang, Cogswell, et al., 2010) Clearly, most people who do not consume folic acid supplements are not reaching daily intakes of 400 mcg per day.

ISSUES RELATING TO MANDATORY ENRICHMENT

Because of the closely inter-related functions of folic acid and vitamin B-12, there is continuing concern about the significance of raising population intakes of folic acid without also raising population intakes of vitamin B-12, and there is discussion of the possibility of adding vitamin B-12 to the enrichment package. (Green, 2009) Also, there is controversy about the potential effect of folic acid enrichment on the progression of some cancers, especially colorectal cancer. Folate is required for cell division and growth. This applies to cancer cells as well as to healthy cells, and antifolate drugs are used in cancer treatment. It has been suggested that folic acid supplementation may help protect against the initiation of cancer, but may facilitate the growth or progression of precancerous cells once they are present. (Mason, Cole, et al., 2008; Smith, Kim, et al., 2008) However, recent analysis of a very large cohort of over 500,000 people found that higher folic acid intakes from diet or from supplements were associated with a decreased risk of colorectal cancer, and this association was similar in the periods before and after mandatory enrichment. (Gibson, Weinstein, et al., 2011) There will be ongoing monitoring and research to clarify the impact of enrichment on all segments of the population.

RECOMMENDATION OF THE U.S. PREVENTIVE SERVICES TASK FORCE

In 2009, the U.S. Preventive Services Task Force reviewed and reiterated its recommendation that "all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid." This is classified as a grade A recommendation. (U.S. Preventive Services Task Force, 2009) The purpose of this recommendation is to reduce the risk of having a baby with a neural tube birth defect. According to the Task Force, these birth defects, which include spina bifida, are the most common birth defects in the U.S., occurring in about one in every 1000 pregnancies.

CDC RECOMMENDATION FOR CONTINUED EMPHASIS ON SUPPLEMENTATION

According to a CDC report on a 2007 Gallup survey of folic acid supplement knowledge and use, most women were aware of folic acid, but less than half of women of childbearing age reported daily consumption of a supplement containing folic acid. Young women (age 18 to 24) were least likely to be using such a supplement. According to the report, "These findings warrant the continued promotion of folic acid consumption among all women of childbearing age and especially among women aged 18-24 years. Folic acid education that promotes consumption of folic acid from various sources (e.g., supplements containing folic acid and fortified foods), in addition to foods rich in folate, can increase the possibility of all women consuming the recommended amount of 400 mcg." (CDC, 2008)

KEY CLINICAL TRIALS

The evidence on folic acid and birth defects began developing in England in the early 1980s, when Dr. R. W. Smithells and coworkers, in a multicenter clinical trial, gave a multivitamin supplement containing folic acid to women who had already had a previous pregnancy affected by an NTD and who wanted to become pregnant again. The multivitamin provided 360 mcg (0.36 mg) of folic acid per day. The rate of recurrence of NTDs in the supplemented group was one percent, compared to five percent in women who did not receive a supplement. The protective effect was thus an 80 percent reduction in the incidence of NTDs. (Smithells, Nevin, et al., 1983; Smithells, Sheppard, et al., 1980)

Smithells' study was a carefully conducted clinical trial, but it was not a randomized placebo-controlled trial, since the institutional review board overseeing the research would not allow any of the women to be given a placebo instead of the multivitamin. To definitively confirm or refute these results, and to determine whether folic acid was the nutrient responsible for the reduction in NTDs, a large, multicenter, randomized controlled trial was initiated in 1983 by the U.K. Medical Research Council.

In 1991, the Medical Research Council reported that a supplement of 4 mg (4000 mcg) of folic acid had a protective effect of 72 percent against the recurrence of NTDs in 1,195 women who had already experienced at least one affected pregnancy. The relatively high dose of folic acid was chosen to assure that any beneficial effect would be found and not missed because of too low a dose. The degree of protection was similar to that achieved by Smithells' use of a low level of supplementation (0.36 mg of folic acid in a multivitamin). There were 21 NTDs in 602 pregnancies in the control groups, and six NTDs in 593 pregnancies in the supplemented groups. The researchers concluded that "public health measures should be taken to ensure that all women of childbearing age receive adequate dietary folic acid." (MRC Vitamin Study Research Group, 1991)

...all women planning pregnancy should receive a vitamin supplement containing folic acid.

Another randomized controlled trial was initiated in Hungary in 1984, when a multivitamin supplement containing folic acid (0.8 mg) or a placebo was offered to Hungarian women planning a pregnancy as part of the Hungarian Family Planning Program. By the time the study was concluded in 1991, there had been about 2,000 pregnancies in the supplement group and about the same number in the control group. There were no NTDs in the supplement group, compared to six in the placebo group. In addition, there were fewer malformations of all types in the supplement group compared to the placebo group (13 per 1,000 pregnancies, compared to 23 per 1,000). The researchers concluded: "Given the results of this study, we think that all women planning pregnancy should receive a vitamin supplement containing folic acid." (Czeizel & Dudas, 1992)

A public health program in China was undertaken from 1993 to 1995 in which women were asked to take a supplement of 400 mcg of folic acid daily from the time of their premarital medical examination until the end of their first trimester of pregnancy. The program involved almost 250,000 women. In the northern region of China, where there is a high incidence of NTDs, there were about five neural tube defects per 1,000 births among women who did not receive the supplement. This was reduced to one per 1,000 (a reduction of 80 percent) among women who were supplemented. In the southern region of China, the rate of NTDs was much lower—about one per 1,000 births for unsupplemented women. This was reduced to 0.6 per 1,000 births (a reduction of about 40 percent) in women who received the supplement. This study demonstrates that folic acid supplementation helps prevent NTDs in areas of high incidence as well as in areas of low incidence. (Berry, Li, et al., 1999)

Another study in 18 counties of China confirmed the effectiveness of a multivitamin with folic acid in reducing the incidence of NTDs. Incidence was 0.35 per 1,000 pregnancies in the multivitamin group and 1.8 per 1,000 pregnancies in the control group—a protective rate of about 80 percent. The authors conclude that a multivitamin supplement containing folic acid taken from two months before conception through the end of the second month of pregnancy and taken more than five times per week can significantly reduce the risk of NTDs. (Chen, Song, et al., 2008)

EPIDEMIOLOGIC STUDIES ON MULTIVITAMINS AND BIRTH DEFECTS

Three out of four epidemiological studies published in 1988 and 1989 showed a protective effect of multivitamin supplements with folic acid in women who took the supplement at least one month before and three months after conception (the periconceptional period). The supplement provided a 60 to 70 percent protection against NTDs. (Bower & Stanley, 1989; Mills, Rhoads, et al., 1989; Milunsky, Jick, et al., 1989; Mulinare, Cordero, et al., 1988)

In early 1993, researchers published the results of a case-control study done in Boston, Philadelphia, and Toronto. In women who used multivitamins containing folic acid for at least 28 days before and 28 days after conception, the supplement had a strong protective effect against NTDs. The authors suggest that "daily periconceptional intake of 0.4 mg of folic acid (the dose most commonly contained in over-the-counter multivitamin preparations) reduces the risk of occurrent NTDs by approximately 60 percent." (Werler, Shapiro, et al., 1993)

In a case-control study conducted by the California Birth Defects Monitoring Program, 549 mothers of infants or fetuses with neural tube birth defects were paired with 540 mothers of infants without birth defects. Using a vitamin containing folic acid in the three months *before conception* had a protective effect against NTDs. The women who used a supplement had 35 percent less risk of having babies with a neural tube defect. (Shaw, Schaffer, et al., 1995)

The epidemiologic evidence indicates that *multivitamin* use by the mother not only protects against NTDs, but may also protect against other types of birth defects, including cleft lip and cleft palate, as well as a variety of other defects. (Moyers & Bailey, 2001; Shaw, Schaffer, et al., 1995)

The prevalence of NTDs was relatively high in South Carolina, and a public health program was initiated "to prevent recurrence of NTDs among high-risk mothers with the use of folic acid during the periconceptional period." During the six years from 1992 to 1998, there was a 40 percent reduction in the incidence of neural tube defects and an increase in the use of folic acid by women during the critical months just before and after conception. The number of NTDs declined from 1.89 per 1,000 births to 0.95 per 1,000 births during this period. In 113 women who had already had one pregnancy affected by neural tube defects and who were given folic acid before and during their next pregnancy, there were no recurrences of NTDs in the subsequent pregnancy. In the general population, use of folic acid supplements increased among women of childbearing age during this period, from eight percent to more than 30 percent. These findings are "in agreement with the known protective effect of folic acid against these malformations." (Stevenson, Allen, et al., 2000)

A recent study of the rate of occurrence of NTDs in pregnancies that were conceived *after* folic acid enrichment of grain products was initiated in the U.S. suggested the possibility that mandatory fortification may be achieving a large fraction of the preventive effect that can be achieved, as it was intended to do. Previous population studies have found folic acid supplement use during the months before and after conception to be associated with a substantial decrease in the incidence of NTDs. This most recent population study found little evidence of such an association. The authors speculate that it is possible that folic acid intake in the U.S. "may have reached levels where nearly all folate-sensitive neural tube defects have been prevented." (Mosley, Cleves, et al., 2009)

Dr. Karen Bell and Dr. Godfrey Oakley of Emory University in Atlanta, Georgia, have developed a program for tracking folic acid fortification programs globally and for estimating the number of NTDs that are being prevented by such fortification. As of 2009, they indicate that 68 countries have instituted folic acid enrichment or fortification of wheat flour and/or maize flour. However, in most countries the level of fortification is not sufficient to provide most women with the recommended level of 400 mcg of folic acid daily. They conclude: "Seventeen years after folic acid was unequivocally shown to prevent spina bifida and anencephaly, we estimate that only about 10 percent of the birth defects in the world that can be prevented by folic acid are actually being prevented." (Bell & Oakley, 2009)

COST OF 400 mcg PER DAY OF FOLIC ACID

Women can easily add 400 mcg of folic acid per day to their dietary intake by using a multivitamin containing folic acid or by consuming a breakfast cereal fortified with 400 mcg of folic acid per serving. The cost of the multivitamin supplement would be less than a dime a day, and the cost of the fortified breakfast cereal would be about 31 cents per serving without milk or 46 cents per serving with milk. All are excellent bargains, providing critically important protection from neural tube birth defects as well as overall protection of women's health. Costs cited below are based on prices in supermarkets and drug stores in the upper Midwest early in 2012.

PRODUCT	COST PER DAY
Store-brand multivitamin/ mineral supplement	$ 0.05
Brand-name multivitamin/ mineral supplement	$ 0.07
Breakfast cereal fortified with 100% of the Daily Value of folic acid (cost of cereal alone, without addition of milk)	$ 0.31
Breakfast cereal fortified with 100% of the Daily Value of folic acid (cost of cereal plus 1/2 cup milk)	$ 0.46

Bottom Line

An abundance of data shows that women who get an extra 400 mcg of folic acid per day for one to three months prior to conception and one to three months after conception can substantially lower the risk of having a baby with a neural tube defect such as spina bifida or anencephaly. In most studies, the protective amount of folic acid was consumed in the form of a multivitamin supplement; a few studies provided folic acid as a single nutrient. For optimum protection of the fetus, it would be advisable for all women of childbearing age to consume a multivitamin containing 400 mcg of folic acid every day. Since many women do not take a multivitamin, food fortification programs have been adopted in many nations, including the U.S. These have reduced the numbers of babies born with neural tube birth defects, but not to the extent observed in women who used a supplement, so there is still an important role for multivitamins with folic acid in providing fuller protection against NTDs.

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Supporting Healthy Pregnancies and Healthy Children

Pregnancy strains the mother's physical and nutritional resources, and prenatal multivitamins with minerals are commonly recommended to help ensure that the baby's and mother's nutritional needs are met. The effect of multivitamins with folic acid in protecting against neural tube birth defects such as spina bifida is discussed in the previous section; but there are many other benefits of adequate nutrition in supporting healthy pregnancies and healthy children.

"Whatever the limitations of our current state of knowledge, it is apparent that pregnancy and lactation are periods during which good nutrition is exceptionally important. The infant is not protected from the inadequate diet of the mother." (Zeisel, 2009) Some of the nutrients known to be in short supply and critical to the health of the mother and the development of the infant include folate, choline, iodine, and DHA, among others. "We already know that a dollar invested in nourishing pregnant and lactating women results in a many-fold return in better infant outcomes. We are now uncovering some of the mechanisms responsible. While we are searching for specific supplements that optimize development, we should not forget to continue to invest in assuring that pregnant and lactating mothers have access to a good diet." (Zeisel, 2009)

MULTIVITAMIN SUPPLEMENTATION

The recommended intakes for many essential vitamins and minerals increase during pregnancy, and "health care providers generally recommend that pregnant women consume a standard prenatal multivitamin and multimineral supplement as insurance against inadequate micronutrient intake." (Picciano & McGuire, 2009) Because of the evidence that a multivitamin

with folic acid taken for a few months before and after conception can reduce the incidence of neural tube birth defects such as spina bifida, such supplementation is recommended for women of childbearing age by the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, the Institute of Medicine, and the National Healthy Mothers, Healthy Babies Coalition. Because of the known need for additional iron during pregnancy, the World Health Organization and the CDC recommend daily iron supplementation. In addition, the American Thyroid Association recommends that pregnant women get 150 mcg per day of supplemental iodine. (Picciano & McGuire, 2009)

The following table shows Recommended Dietary Allowances (and Adequate Intakes) for a number of vitamins and minerals, many of which are needed in higher amounts during pregnancy and lactation.

RECOMMENDED DIETARY ALLOWANCES FOR WOMEN 19-50, SHOWING INCREASED RECOMMENDATIONS FOR MANY VITAMINS AND MINERALS DURING PREGNANCY AND LACTATION

VITAMINS & MINERALS	NON-PREGNANT	PREGNANT	LACTATING
Vitamin A	700 mcg	770 mcg	1300 mcg
Vitamin C	75 mg	85 mg	120 mg
Vitamin D	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
Vitamin E	15 mg	15 mg	19 mg
Thiamin	1.1 mg	1.4 mg	1.4 mg
Riboflavin	1.1 mg	1.4 mg	1.6 mg
Niacin	14 mg	18 mg	17 mg
Vitamin B-6	1.3 mg	1.9 mg	2.0 mg
Folate	400 mcg	600 mcg	500 mcg
Vitamin B-12	2.4 mcg	2.6 mcg	2.8 mcg
Pantothenic acid*	5 mg	6 mg	7 mg
Biotin	30 mcg	30 mcg	35 mcg
Choline*	425 mg	450 mg	550 mg
Calcium	1000 mg	1000 mg	1000 mg
Chromium*	25 mcg	30 mcg	45 mcg
Copper*	900 mcg	1000 mcg	1300 mcg
Iodine	150 mcg	220 mcg	290 mcg
Iron	18 mg	27 mg	9 mg
Selenium	55 mcg	60 mcg	70 mcg
Zinc	8 mg	11 mg	12 mg

* Nutrients with Adequate Intakes rather than RDAs are marked with an asterisk

In a study of pregnancy outcomes in more than 400 low-income women, researchers at the University of Medicine and Dentistry of New Jersey found that women who took multivitamins with minerals during pregnancy were less likely to suffer a preterm delivery or to have a low-birth-weight infant. The authors conclude that "in low income, urban women, use of prenatal multivitamin/mineral supplements may have the potential to diminish infant morbidity and mortality." (Scholl, Hediger, et al., 1997)

IODINE SUPPLEMENTATION

"The fetus is totally dependent in early pregnancy on maternal thyroxine for normal brain development." (Becker, Braverman, et al., 2006) Thus, adequate iodine intake by the mother during pregnancy is critical for neural development in the fetus, and insufficiency can result in brain damage to the infant. *Average* iodine levels in women of childbearing age appear to be adequate in the U.S., but many women have inadequate levels. The American Thyroid Association "recommends that women receive 150 microgram iodine supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 mcg of iodine." (Becker, Braverman, et al., 2006)

The Recommended Dietary Allowance (RDA) for iodine for women of childbearing age is 150 mcg per day, but the RDA for iodine during pregnancy is 220 mcg per day—almost 50 percent more. Thus, a woman who becomes pregnant is suddenly faced with an

increased need for iodine to support her own health as well as that of the fetus. The RDA for iodine during lactation is even higher—290 mcg per day. Iodine is a component of the thyroid hormone, which is necessary for neural development. Severely low maternal thyroid levels during pregnancy can cause "irreversible brain damage with mental retardation and neurologic abnormalities" in the infant. "Whether mild-to-moderate maternal iodine deficiency produces more subtle changes in cognitive and/or neurologic function in the offspring is uncertain," but many researchers believe even moderate deficiency "may affect the cognitive and motor function of children." (Zimmermann, 2009)

Researchers in New Zealand studied the effects of mild iodine deficiency in children 10 to 13 years of age. Iodine deficiency in New Zealand has recently re-emerged as a problem due to "lower concentrations of iodine in milk because of the discontinuance of iodine-containing sanitizers in the dairy industry, declining use of iodized salt, and an increased consumption of processed foods not made with iodized salt." In the study, 184 children were given an iodine tablet (150 mcg iodine) or a placebo for 28 weeks. The iodine supplement significantly improved scores on cognitive tests, suggesting "that mild iodine deficiency could prevent children from attaining their full intellectual potential." (Gordon, Rose, et al., 2009)

IRON SUPPLEMENTATION

In a study of 513 low-income pregnant women in Cleveland, iron supplementation (30 mg iron as ferrous sulfate) during pregnancy led to higher average birth weights and a lower incidence of low-birth-weight infants. The authors suggest that prenatal iron supplementation "deserves further examination as a measure to improve birth weight and potentially reduce health care costs." (Cogswell, Parvanta et al., 2003)

An analysis of data from the Third National Health and Nutrition Examination Survey showed that 73 percent of pregnant women and 60 percent of lactating women had used supplements containing iron during the previous month. This compared to very low levels of use among nonpregnant women—only nine percent among adolescents and 23 percent among women over 18. Use of supplements that contain iron was associated with a lower prevalence of iron deficiency among women 19 to 50. (Cogswell, Kettel-Khan, et al., 2003)

"In the United States, the prevalence of third trimester anemia among low-income pregnant women is 29 percent and has not improved since the 1980s." The authors studied whether low-income women would adhere to advice to use iron-containing prenatal multivitamin/mineral supplements. Among 244 pregnant women receiving care at a public prenatal clinic, 74 percent took the supplements as prescribed. (Jasti, Siega-Riz, et al., 2005)

COMPLIANCE WITH RECOMMENDATIONS FOR PRENATAL SUPPLEMENTS

While prenatal supplements are routinely recommended or prescribed, not all pregnant women comply with these recommendations, especially among women who are African-American or Hispanic. Researchers convened 12 focus groups to explore motivators and barriers to prenatal supplement use among minority women. Motivators for supplement use included experiencing positive effects, having access to a convenient supply, affordability of the supplements, reinforcement by health care providers, and having a social network that reinforced the importance of daily intake. (Tessema, Jefferds, et al., 2009)

Bottom Line

Nutrient needs are increased during pregnancy and lactation, and a prenatal multivitamin with minerals is commonly prescribed to ensure that needs are met. Support from the healthcare provider as well as from a woman's social network is needed to help ensure compliance with this recommendation.

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Supporting Healthy Aging

There is substantial scientific evidence suggesting that generous intakes of a variety of nutrients can help protect vision, lung function, neurological function and cognitive ability, skin and muscle integrity, and immune function in the aging population.

"At the beginning of the 20th century, fewer than half of all Americans lived past 65 years; now over 80 percent have this expectation. Presently, 13 of every 100 Americans are age 65 years or older; this proportion will increase to 20 of every 100 by the year 2030." (Bales & Wang, 2004)

NUTRITIONAL SHORTFALLS IN THE ELDERLY

"The percentage of older adults among the world's population continues to increase." While obesity is a problem for many, undernutrition "continues to be prevalent in approximately 25-40 percent of older adults worldwide." (Silver, 2009) Undernutrition is "associated with poor health outcomes—from inadequate diet quality and having micronutrient deficiencies, to loss of lean body and skeletal muscle mass... as well as inflammatory stress, compromised immune function, impaired wound healing, increased susceptibility to infections, impaired physical performance, functional dependencies, depression, and being homebound. Moreover, undernutrition reduces overall quality of life and is associated with increased mortality risk. Finally, undernutrition is a healthcare burden that continues to strain the economic resources of developing and developed countries.... Unfortunately, the most vulnerable older adults, i.e., older women, minorities, rural-living, and the poor are at greatest risk." (Silver, 2009) There is a need for more research on the benefit and cost of various strategies for improving nutrient intakes, body weight, and functionality in ways that are safe, clinically relevant, and cost-effective.

In Arizona, an extensive survey of the dietary habits of 1740 healthy adults over the age of 50 showed that more than 60 percent had deficient dietary intakes of vitamin D, vitamin E, folate, and calcium. Their intakes were not only below the *recommended* levels, but below the *average requirement*. In terms of dietary patterns, no more than 10 percent of the population met the Food Pyramid recommendations for grain or dairy products, and only about 50 percent met the daily recommendations for fruits and vegetables. (Foote, Giuliano, et al., 2000)

Researchers working in rural Iowa surveyed nutrient intakes of more than 400 elderly residents. All subjects were 79 years of age or older (average age 85) and were living in the community, not in an institution. More than half lived alone. "Eighty percent of subjects reported inadequate intakes of four or more nutrients." Folate, vitamin D, and calcium intakes were inadequate in most of this elderly population. "Multivitamin/mineral supplementation with additional calcium may be necessary for the old to achieve adequate nutrient intakes." (Marshall, Stumbo, et al., 2001)

AGE-RELATED MACULAR DEGENERATION

"Age-related macular degeneration (AMD) is a disease that affects the central vision. In the aging U.S. population, AMD is a major cause of visual impairment and blindness. The prevalence of AMD increases dramatically with age. Nearly 30 percent of Americans over the age of 75 have early signs of AMD and 7 percent have late-stage disease... This number is expected to triple with the increase in the aging population in the next 30 to 40 years." (Johnson, 2005) Low dietary and tissue levels of lutein and zeaxanthin are modifiable risk factors for AMD, as is obesity. These factors may be related in that obesity is associated with increased oxidative stress and increased inflammation. Also, dietary carotenoids are stored in body fat, which may act as a "sink" and thereby reduce the amount of lutein and zeaxanthin potentially available for the eye. (Johnson, 2005)

"Age-related macular degeneration (AMD) is a leading cause of blindness. Epidemiologic reports suggest that intake of foods rich in lutein protects against AMD. Lutein and its structural isomer, zeaxanthin, selectively accumulate in the retina and are particularly dense in the macular region where they are main components of macular pigment. Lutein functions as an antioxidant and blue light filter and may protect the macula from light-initiated oxidative damage. Oxidative stress is high in the eye because of repeated exposure to light and the high rate of oxidative metabolism in the retina," and this oxidative damage may play a role in the development of AMD. (Johnson, Chung, et al., 2008) Docosahexaenoic aid (DHA), a key omega-3 fatty acid, is also found in the retina and is a component of photoreceptors which are constantly being renewed and thus in need of a constant supply of DHA. (Johnson, Chung, et al., 2008)

"Age-related macular degeneration (AMD) is a burden to the elderly population, and its consequences are increasing because treatment options are limited. Prevention remains the best approach for decreasing the impact of this leading cause of blindness. Knowledge about modifiable factors related to AMD has increased considerably during the past decade, including most notably cigarette smoking, nutritional factors, obesity, and lipid levels." (Seddon, Gensler et al., 2004) One recently discovered risk factor for AMD is having an elevated level of C-reactive protein (CRP), a marker of systemic inflammation. (Seddon, Gensler, et al., 2004)

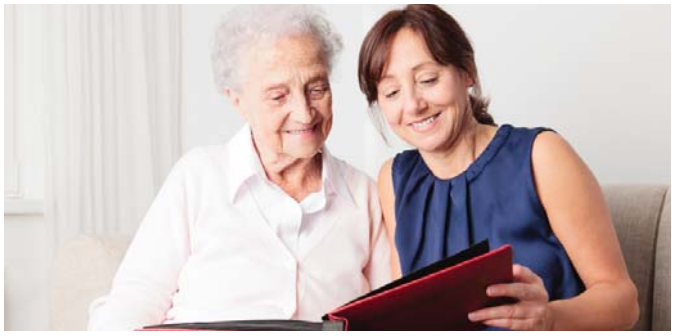
...It is estimated that if the 8 million individuals in the U.S. who are at high risk of developing advanced AMD received the AREDS formulation, more than 300,000 of the 1 million persons expected to develop advanced AMD... would avoid it...

AREDS is an 11-year, multicenter trial involving more than 3,600 people who had evidence of AMD when they entered the trial. Participants were assigned to one of four groups, with each group receiving antioxidant supplements, zinc supplements, both, or a placebo. The antioxidant supplement included 500 mg vitamin C, 400 IU vitamin E, and 15 mg beta-carotene. The zinc supplement included 80 mg zinc and 2 mg copper. The participants that received both the antioxidant and the zinc supplements were significantly protected from development of advanced AMD.

The researchers suggested that people over the age of 55 should have an eye exam including dilation of the eyes to evaluate their risk of developing advanced AMD. People at risk of AMD "should consider taking a supplement of antioxidants plus zinc such as that used in this study." (AREDS-8, 2001) However, the authors noted that supplementation with beta-carotene is not advised for smokers.

The protective effect of the AREDS antioxidant supplement was modest, but could have substantial population impact. "With this modest therapeutic effect of the AREDS formulation, the potential effect on public health of the disease burden of AMD is considerable. It is estimated that if the 8 million individuals in the United States who are at high risk of developing advanced AMD received the AREDS formulation, more than 300,000 of the 1 million persons expected to develop advanced AMD... would avoid it, and its associated vision loss, during the next 5 years." (Chew, Lindblad, et al., 2009)

The National Eye Institute at the National Institutes of Health (NIH) is currently undertaking an additional, multi-center, randomized clinical trial, called AREDS2, to assess the effects of supplementation with high levels of lutein and zeaxanthin and/or supplementation with the marine omega-3 fatty acids EPA and DHA on the risk of progression of AMD. The study is also intended to determine whether decreased levels of zinc or the omission of beta-carotene modifies the effect of the original AREDS formulation. (NIH National Eye Institute, 2010)



CATARACTS

Vitamin C is 60 times more concentrated in the lens of the eye than in blood plasma, and other antioxidants are also concentrated in the lens. Opacity of the lens of the eye is one of the first signals that cataracts are developing. Cataracts are a major cause of blindness throughout the world, and antioxidants are believed to play a role in protecting against cataracts. Scientists have suggested that the adequate provision of antioxidant vitamins might delay cataract development sufficiently to decrease the number of cataract operations in the United States by one-half. (Taylor, 1992)

"Age-related cataracts are an important public health problem globally and remain a leading cause of blindness worldwide, with surgical extractions increasing the medical care costs in many developed countries. The oxidation of proteins or lipids within the lens is known to be associated with the formation of age-related cataracts." (Yoshida, Takashima, et al., 2007) In a prospective study of more than 30,000 Japanese residents ages 45 to 64 years, researchers studied the association between vitamin C intake and five-year risk of cataract. Diagnosis of cataracts and extraction of cataracts during a five-year period were significantly lower in men and women with higher intakes of vitamin C. (Yoshida, Takashima, et al., 2007)

In the Age-Related Eye Disease Study (AREDS) sponsored by NIH, a high-dose antioxidant formulation showed no significant effect on the progression of cataracts. However, most of the participants in the study were using a national-brand multivitamin in addition to the study treatment, and subsequent analysis showed that use of the multivitamin provided significant protection against cataracts. (Milton, Sperduto, et al., 2006)

In the Blue Mountains Eye Study in Australia, the effect of antioxidant intake on the 10-year development

of age-related cataracts was studied in 2464 subjects. "Increasing vitamin C consumption was associated with a significantly reduced 10-year risk of incident nuclear cataract... A similar but nonsignificant trend was observed for vitamins A and E and zinc." The authors conclude that the study "provides evidence of long-term beneficial association between antioxidants, mainly vitamin C (either alone or in combination with other antioxidants), and nuclear cataract development, a well-known biological marker of aging." (Tan, Mitchell, et al., 2008)

In the Nutrition and Vision Project (NVP), the development of cataracts in almost 500 women over the age of 50 was studied in relation to their usual nutrient intake over a period of 13 to15 years prior to the visual exam. The prevalence of lens opacities was lower in women with higher intakes of vitamin C and in women who had used a vitamin C supplement for 10 years or more. "Results from the NVP provide further evidence that antioxidant nutrients are associated with risk of age-related lens opacification. Total vitamin C intake from diet and supplements was associated with a lower prevalence of nuclear opalescence." (Jacques, Chylack, et al., 2001) Vitamin C intake in the lowest quintile was as high as 140 mg per day, which is almost double the RDA for women. Yet the risk of lens opacity decreased in each quintile as vitamin C intake went up to 180, 240, and even 360 mg per day. It has been estimated that tissues in the human eye become saturated with vitamin C at intakes in the range of 200 to 300 mg per day. Vitamin E, lutein, and zeaxanthin also had protective effects, but these were not clearly independent of the vitamin C effect, since women with a high vitamin C intake tended to have higher intakes of the other nutrients as well. (Jacques, Chylack, et al., 2001)

Among residents of Beaver Dam, Wisconsin, the risk of developing a cataract over a period of five years was 60 percent lower in people who had used multivitamins or a supplement containing vitamin C or vitamin E for more than 10 years, compared to people who did not use such supplements. Use of supplements for a shorter period of time did not appear to have a protective effect. "Measured differences in lifestyle between supplement users and non-users did not influence these associations, nor did variations in diet as measured in a random subsample." (Mares-Perlman, Lyle, et al., 2000)

ANTIOXIDANTS AND THE LUNGS

"Reduced pulmonary function is an important predictor of mortality in the general population." (Schunemann, Grant, et al., 2001) Factors that affect pulmonary function are not completely understood, but exposure to excessive oxidation is believed to have a damaging effect. "Vitamin C and vitamin E are powerful antioxidants found in the lung where they protect against oxidative damage. Although vitamin E is predominantly membrane bound, there is a close interaction between vitamins C and E, because vitamin C not only functions directly as an antioxidant, but it also recycles the antioxidant capacity of oxidized vitamin E." (Schunemann, Grant, et al., 2001) Vitamin A and the carotenoids also have anti-inflammatory and antioxidant activity and play a role. "These compounds have been thought to protect against development of lung cancer and other respiratory illnesses." In a study of more than 1,600 adults in western New York, researchers examined the association between serum levels of these vitamins and lung function.

Lung function was found to improve as blood levels of the antioxidant vitamins increased, with the strongest impact being associated with vitamin E and beta-cryptoxanthin. (Schunemann, Grant, et al., 2001)

In a British study of lung function in 178 men and women 70 to 96 years of age who had respiratory symptoms, researchers found that for every extra milligram of vitamin E in the diet, there was an improvement in performance on two tests of lung function. (Dow, Tracey, et al., 1996) In another study of more than 2,600 people in the area of Nottingham, England, higher dietary intakes of vitamin C and vitamin E were associated with improved lung function. (Britton, Pavord, et al., 1995)

Exposure to ozone can cause inflammation in the lung and potentially damage it. In a study involving 31 healthy adults, researchers gave the participants 250 mg of vitamin C, 50 IU of vitamin E, and 12 ounces of a vegetable cocktail or a placebo for a period of two weeks. For the two weeks of the study and the week before it started, the participants followed a vitamin C-restricted diet. The subjects were then exposed to ozone for a period of two hours and lung function was tested. The ozone caused an inflammatory response in all of the groups, but those supplemented with antioxidants had less damage to lung function compared to the placebo group. This study suggests that antioxidant supplementation may be "a safe and effective strategy with which to decrease pulmonary function responses to this common air pollutant." (Samet, Hatch, et al., 2001)

NUTRITION AND BRAIN FUNCTION

In a long-term study of more than 3,000 Japanese-American men over 70 years of age living in Hawaii, researchers found that the use of vitamin C and vitamin E supplements significantly reduced the risk of dementia. In those without dementia, use of vitamin C or vitamin E supplements was associated with improved cognitive function. (Masaki, Losonczy, et al., 2000)

In a longitudinal study of aging, researchers from the University of New Mexico School of Medicine measured cognitive function in 137 people ages 66 to 90. Higher intakes of vitamin C, thiamin, riboflavin, niacin, and folate were correlated with better performance on various tests of cognitive performance. "Use of self-selected vitamin supplements was associated with better performance on a difficult visuospatial test and an abstraction test." (La Rue, Koehler, et al., 1997)

"Although severe vitamin deficiencies and congenital defects are rare, milder subclinical vitamin deficiencies are not uncommon in the elderly. Interest is increasing in learning the extent to which these mild, reversible deficiencies contribute to some decline in cognitive function in the later years of life." (Selhub, Bagley, et al., 2000) It is well established that deficiencies of the B vitamins involved in the single-carbon cycle have severe effects on brain function that can result in depression, dementia, and other disorders. Results of some studies "support the possibility that poor vitamin status is partially responsible for the cognitive decline seen in some elderly persons." (Selhub, Bagley, et al., 2000)

In an Australian study of the effects of a multivitamin supplement compared to a placebo in 50 healthy older men, eight weeks of supplementation reduced the overall score on a test for depression, anxiety and stress, and resulted in improvements in alertness and general daily functioning; the supplement included vitamins at levels above officially recommended intakes, as well as minerals, antioxidants, and herbal extracts. (Harris, Kirk, et al., 2011)

According to the authors of a study on Alzheimer's disease, "there is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease." (Sano, Ernesto, et al., 1997) They conducted a randomized, double-blind, multicenter study involving 341 patients. During the two-year study, patients received a monoamine oxidase inhibitor called selegiline, 2000 IU per day of vitamin E, both treatments, or a placebo. The researchers reported that treatment with vitamin E or with selegiline delayed progression of the disease, including "delays in the deterioration of the performance of activities of daily living and the need for care." (Sano, Ernesto, et al., 1997)

There is evidence to suggest that oxidative stress plays a role in the development of Alzheimer's disease, and there is clear evidence of oxidative damage in the brains of patients with the disease. A clinical trial of vitamin E and selegiline in patients with moderate Alzheimer's disease showed that these treatments slowed the rate of functional decline to a significant degree. The results raise the question whether vitamin E might also delay the decline in patients with milder cases of Alzheimer's disease, "and whether it may prevent dementia in elderly individuals who are minimally or not yet cognitively impaired." (Grundman, 2000) The Alzheimer's Disease Cooperative Study has initiated an additional trial to determine whether vitamin E can prevent or delay development of Alzheimer's disease in patients with mild cognitive impairment. (Grundman, 2000)

AGING OF THE SKIN

"During the course of skin aging, both skin function and appearance are affected. Changes in appearance are the most visible signs of aging and include wrinkles, irregular pigmentation, sagging...," thinning, and loss of elasticity. "Such changes in appearance have substantial negative effects on self-esteem and social wellbeing. Furthermore, appearance was shown to be an indicator of overall health status, and it has been shown that 'looking old for one's age' is associated with increased risk of mortality." (Cosgrove, Franco, et al., 2007) Researchers examined the association between nutrient intakes from foods (not from supplements) and the appearance of skin aging in more than 4,000 women who were over the age of 40 and who were included in the First National Health and Nutrition Examination Survey. Higher intakes of vitamin C and linoleic acid and lower intakes of fats and carbohydrates are associated with a lower appearance of skin aging, according to the authors. "Perhaps appealing benefits such as reducing skin-aging appearance may motivate healthy eating, and new campaigns to promote healthy dietary behaviors could consider this issue." (Cosgrove, Franco, et al., 2007)

Both animal and human studies have shown that supplementation with carotenoids, such as beta-carotene, lycopene, and lutein, can significantly reduce UV-light induced erythema (i.e., sun burn) of the skin. (Heinrich, Gartner, et al., 2003; McArdle, Rhodes, et al., 2004; Stahl, Heinrich, et al., 2000) Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema. (Aust, Stahl, et al., 2005) This does not appear to be due to a sunscreen effect, as these carotenoids do not filter out UV light the way sunscreens do, but instead involves an antioxidant effect. UV light generates free radicals in the skin which trigger an inflammatory response that leads to erythema. Carotenoids that are taken orally are absorbed and subsequently deposited in the subcutaneous layers of the skin, where researchers believe they quench the UV-generated free radicals, in turn preventing the inflammatory response that leads to erythema.

SELENIUM AND MUSCLE STRENGTH IN THE ELDERLY

"Aging is characterized by the loss of muscle strength, which in turn increases the risk of falls, hospitalization, disability, and mortality." (Lauretani, Semba, et al., 2007) Oxidative damage to muscle proteins, lipids, and DNA increases with age. Selenium plays an important role in muscle function, and selenium-containing enzymes help protect muscle cells (and other cells) from oxidative damage. The authors examined the association between muscle weakness and marginal selenium status in almost 900 men and women, age 65 and over, who were dwelling in the community in Tuscany, Italy. People in the lowest quartile of plasma selenium were at higher risk of poor hip strength, knee strength, and grip strength. (Lauretani, Semba, et al., 2007)

VITAMIN D AND FALLS

There is evidence that adequate vitamin D supplementation reduces the risk of falling in the elderly. A meta-analysis of eight randomized controlled trials found that supplementation with 700 to 1000 IU per day of vitamin D or achieving a serum level of at least 60 nmol/L of 25-hydroxyvitamin D reduced the risk of falling by about 20 percent. Lower levels of supplementation (200 to 600 IU per day) and lower serum levels of vitamin D were not protective. (Bischoff-Ferrari, Dawson-Hughes, et al., 2009)

CALCIUM, VITAMIN D, AND BONE DENSITY

Calcium and vitamin D are both essential to achieving maximum bone density and slowing bone loss during aging. Most people fail to get protective amounts of both nutrients, and supplementation even late in life can have a positive effect. The Surgeon General's report in 2004 observed: "It is never too late for prevention, as even older individuals with poor bone health can improve their bone health status through appropriate exercise and calcium and vitamin D intake." (Department of Health and Human Services, 2004)

NUTRITION AND IMMUNE FUNCTION

It is likely that improved nutrition could enhance resistance to infectious disease in the elderly. If immune function could be improved, the impact on quality of life and on the nation's health care costs could be substantial.

"In comparison with the general population, older Americans are twice as likely to visit the doctor and 3 times more likely to be hospitalized; their average hospital stays are twice as long, and they consume twice the number of prescription drugs." (High, 2001) Infection is one of the most common causes of sickness in the elderly, and older people are two to ten times more likely to die of infections than younger

adults. A review of clinical trials on nutritional interventions supports "use of a daily multivitamin or trace-mineral supplement that includes zinc (elemental zinc, >20 mg/day) and selenium (100 mcg/day), with additional vitamin E to achieve a daily dosage of 200 mg/day." (High, 2001) The article adds that health care providers should be aware of common drug/nutrient interactions, since the elderly are often heavy users of medications.

In a Boston study of 88 healthy people 65 years of age or more, vitamin E supplementation was found to improve some measures of immune function. Researchers at the USDA Human Nutrition Research Center on Aging indicated that the best responses were observed in people given 200 mg of vitamin E per day, versus 60 or 800 mg. (Meydani, Meydani, et al., 1997)

A study of vitamin E supplementation and respiratory infections in more than 600 elderly individuals in nursing homes reported a lower incidence of upper respiratory infections, including the common cold, in the group that was given 200 IU of vitamin E daily. Everyone in the trial (the placebo group as well as the vitamin E group) also received a supplement providing half the RDA for numerous vitamins and minerals throughout the trial. (Meydani, Leka, et al., 2004) In the course of this study, it was observed that more than 30 percent of the subjects had low serum zinc levels at the beginning of the study and also after a year of follow-up, despite the fact that they were given a supplement providing 50 percent of the RDA of essential vitamins and minerals, including zinc, during the trial. Compared to people with low zinc levels, the elderly with normal zinc levels had a lower incidence of pneumonia, fewer prescriptions for antibiotics, a shorter duration of pneumonia, fewer days of antibiotic use, and a lower rate of all-cause mortality. Zinc is a required cofactor for more than 300 enzymes and is "essential to the function of all highly-proliferating cells in the human body, especially the immune system." (Meydani, Barnett, et al., 2007)

A study by Dr. Ananda Prasad and coworkers also reported that zinc supplementation decreased the number of infections over a period of one year, compared to the placebo group, in people age 55 and over. (Prasad, Beck, et al., 2007)

In a review, Dr. Simin Meydani and other authors suggested that elderly people with low serum zinc levels might benefit from zinc supplementation. "Based on our careful review of the literature and given the upper safe limit of zinc, a dose of 30 mg elemental zinc per day might be adequate to improve immune function and to reduce the risk of infections." (Barnett, Hamer, et al., 2010)

A study of immune function in elderly residents of New Jersey showed that taking a daily multivitamin for one year resulted in a stronger immune system and higher blood levels of several vitamins. The researchers suggested that current recommendations for some micronutrients may be too low to support optimal immune function in healthy, independently living older adults. (Bogden, Bendich, et al., 1994)

In a two-year study in a nursing home in France, residents were given zinc and selenium *or* vitamin C, vitamin E, and beta-carotene; *or* all five nutrients; *or* a placebo. People who were supplemented with the min-

erals, with or without the vitamins, had significantly fewer respiratory infections and urogenital infections over the two-year period. (Girodon, Lombard, et al., 1997)

NUTRITIONAL SUPPLEMENTS SHOULD BE PROVIDED IN NURSING HOMES

Elderly persons residing in nursing homes may be particularly at risk of unrecognized inadequacies of vitamins and minerals because of difficulties in feeding and because they are already suffering from numerous diseases or disorders. While other nutritional problems observed in nursing homes may be difficult to remedy, micronutrient deficiencies can be avoided through inexpensive, safe supplementation. Dr. Connie Bales of the Duke University Medical Center emphasizes that "the benefits could be remarkable, with the potential for improvements in a number of vital functions, including but not limited to cognitive ability and immunocompetence." (Bales, 1995)

A study of Veterans Administration nursing homes found that 88 percent of the residents had dietary intakes below 50 percent of the RDA for three or more nutrients. Researchers observed that "essential nutrient inadequacies can lead to adverse effects on nearly all organ systems and can contribute to many of the physical and mental complications commonly seen in nursing home residents." (Rudman, Abbasi, et al., 1995) They urge nursing home administrators to assure that residents unable to feed themselves receive a multivitamin/mineral supplement daily to alleviate complications related to nutrient inadequacy such as the following:

- Inadequate intakes of calcium, phosphorus, and vitamin D predispose to bone loss and fractures, both of which are common in the nursing home population.
- Deficient intakes of copper, iron, folate, or vitamin B-12 can cause or contribute to anemia, which is present in 50 percent of residents.
- Deficiency in zinc predisposes to dermatitis, slow wound healing, and altered mental status.
- Pyridoxine (B-6) deficiency can cause or intensify anemia and affect the incidence of convulsions.
- Low intakes of thiamin or niacin can predispose to abnormal behavior or dementia.

While it is assumed that the RDAs apply to the nursing home population, some studies have shown that higher-than-RDA levels of some nutrients are required by some patients. "It would appear that in some nursing home patients, changes in absorption, transport, storage, metabolism and excretion are such that an intake at the RDA level does not result in a normal blood level." (Drinka & Goodwin, 1991) Further research is warranted, but in the meantime "it would appear prudent to place all nursing home residents on an inexpensive multiple vitamin containing the RDA and to consider placing the more debilitated residents on generic supplements containing several times the RDA of water soluble vitamins." (Drinka & Goodwin, 1991)

In an Australian study of the effectiveness of a multivitamin in 92 residents of an aged care facility, taking the multivitamin for six months was found to increase serum levels of vitamin D, vitamin B-12 and folate, compared to levels in residents given a placebo. Also, there was "an increase in bone quality and a trend toward a 63% lower rate of falls." (Grieger, Nowson, et al., 2009)

Dr. Bales has concluded, "While only a small proportion of the elderly population actually resides in nursing homes at any point in time, it is likely that many of us will pass that way at some point in our lives... Perhaps by moving forward with a common sense approach [supplementation] for dealing with remediable nutritional problems in the facilities where they occur, we could be doing ourselves and/or our loved ones a nutritional favor—in advance." (Bales, 1995)

Bottom Line

The elderly are at risk for nutrient inadequacy, and that inadequacy can have a specific negative impact on many aspects of their health. Antioxidant supplements have been shown to have a positive impact on eye diseases, lung function, skin, and cognitive dysfunction. Adequate nutritional status also affects the condition of the skin and supports muscle function. Calcium and vitamin D supplements can have a powerful impact on bone health, and it is never too late to benefit from improved intakes of these nutrients. Vitamin D can also reduce the risk of falls in older people. Vitamin and mineral supplements have been shown in some studies to improve immune function in the elderly. Low zinc intakes are associated with an increase risk of infections, including pneumonia. Generous intakes of some individual nutrients such as vitamin E have had a positive effect in decreasing upper respiratory infections. Some experts believe it makes sense to encourage the elderly to use multivitamin and mineral supplements. Some have also advocated providing a multivitamin and mineral product to the elderly in nursing homes, as a matter of policy, to avoid risking the consequences of inadequate intakes.

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Health Promotion and Disease Prevention: Philosophy, Observation, and Clinical Trials

Until the 1980s, dietary improvement and nutritional adequacy were of interest to policy makers and consumers primarily based on traditional models of health and nutrition. Good dietary patterns and adequate nutrient intakes based on the Recommended Dietary Allowances were considered the best guides to health, but chronic disease prevention through dietary modification was not a common topic of discussion, except for the American Heart Association's early championing of a relationship among saturated fat intake, blood cholesterol levels, and heart disease risk.

This situation began to change dramatically following publication of the 1977 report on *Dietary Goals for the United States*, prepared by the Senate Select Committee on Nutrition and Human Needs, positing a relationship between the affluent American diet and the incidence of numerous "killer diseases." (Senate Select Committee on Nutrition and Human Needs, 1977) This was followed by a cascade of other major reports on diet and disease, including the National Research Council's 1982 report *Diet, Nutrition and Cancer;* the Surgeon General's 1988 report *Nutrition and Health*; and the National Research Council's 1989 report *Diet and Disease.* (Department of Health and Human Services, 1988; National Research Council, 1982, 1989)

The reports asserted that improved dietary patterns, including increased intakes of fruits and vegetables and whole grains, could reduce the risk of chronic disease. They also featured extensive discussion of the components of these foods that were likely to be protective, including fiber and a number of antioxidant nutrients. The reports emphasized the importance of improved food patterns and downplayed the importance of increasing the intake of specific nutrients, but at the same time numerous clinical trials were undertaken specifically to evaluate the possibility that supplementation with some of the individual nutrients (especially antioxidants) might reduce the risk of cancer and heart disease. For example, by 1986 the National Cancer Institute was supporting more than 20 clinical trials on specific nutrients and potential cancer prevention. (Greenwald, Sondik, et al., 1986)

...many clinical trials have in fact demonstrated benefits against disease for specific nutrients... calcium...folic acid... omega-3 fatty acids...

DESIGN OF CLINICAL TRIALS

While countless epidemiological trials support the hypothesis that dietary improvement can reduce the risk of chronic disease, the design of clinical trials to test that hypothesis is a challenge. Nevertheless, many clinical trials have in fact demonstrated benefits against disease for specific nutrients. Calcium to protect against osteoporosis, folic acid to help prevent some birth defects, and omega-3 fatty acids to reduce the risk of heart disease are among these success stories. On the other hand, beta-carotene for cancer prevention, vitamin E for lowering heart disease risk, B vitamins for protecting against cardiovascular disease, and selenium and vitamin E for prevention of prostate cancer are among the disappointments, where clinical trials so far have largely failed to confirm the disease-related benefits suggested by earlier observational and other studies.

What factors in the design of clinical trials are responsible for success or failure? Does a negative trial mean the hypothesis of benefit has been disproven? Might a disappointing trial actually represent a failure to truly test the hypothesis suggested by epidemiology and other evidence? These are questions being intensely examined and vigorously debated within the scientific community. Some of the factors being considered are discussed in the following pages.

Clinical trials are done with single nutrients or a small number of nutrients:

The epidemiological evidence points to food patterns that are related to a lower risk of disease, but changing food habits over the long term is very difficult. Thus, researchers attempt to identify the specific nutrients that are most strongly associated with protective food patterns and then design clinical trials to test whether giving supplements of those nutrients will protect against disease. Is this a true test of the hypothesis? If diets rich in numerous carotenoids appear to be protective against lung cancer in the general population, does it follow that giving a single carotenoid (such as beta-carotene) for several years to older men who are lifelong smokers is likely to protect them against lung cancer?

Nutrients function in the body as an interdependent group, not primarily as individual stars. They play critical roles in metabolic systems, pathways, and cycles. Dr. Robert Heaney believes clinical trials and meta-analyses err when they focus on single nutrients without taking account of critical interactions. (Heaney, 2008) Dr. Frank Meyskens and Dr. Eva Szabo refer to the single-nutrient focus characteristic of clinical trials as the "four-legged stool problem." (Meyskens & Szabo, 2005) Nutrients are compared to the individual legs of a four-legged stool. Together, the four legs make a strong and functional unit, but tested individually, a single leg will not stand alone– and was never meant to stand alone. In order to design an effective nutritional intervention to be tested, it is necessary to understand which nutrients or other food components are essential to the overall functional package, and then to include all the limiting components in the intervention at appropriate levels.

Clinical trials are usually done in populations not screened for markers of nutrient status or markers of disease risk:

Subjects are generally recruited into clinical trials without regard to relevant markers of nutrient status, including for example their baseline blood nutrient levels, markers of antioxidant status, markers of inflammatory response such as CRP (C-reactive protein), or homocysteine levels. (Block, Jensen, et al., 2009; Jialal & Devaraj, 2005; Traber, 2007) Some have pointed out that this is equivalent to testing statins in people who do not have elevated cholesterol levels, or testing antihypertensive medications in people who do not have high blood pressure. (Halliwell, 2000; Heinecke, 2001)

Clinical trials are often done in diseased populations:

Even the leading causes of death from chronic disease occur at relatively low levels in the population. Thus, clinical trials are generally done in high-risk populations or in people who already have a disease, in order to increase the likelihood of having enough events over a period of several years to detect a difference

between the treatment group and the placebo group, if there is in fact a difference. Is this a true test of the hypothesis? If the hypothesis is that a lifetime of exposure to a nutrient (or a combination of nutrients) will reduce the risk of ever developing the disease, then testing the nutrient(s) in older or less healthy people within some brief window of time may not be a true test of prevention—and testing it in people who already have the target disease is definitely not. Is it close enough? That is the question. Some would say it is the best we can do. Others would say it is like the old story of the drunk looking for his keys under a street light. When a passerby stopped to help and eventually asked the drunk if he was certain he had dropped the keys in that spot, the man said, "No, I lost them over there, but the light's better here." Testing disease prevention in people who are already sick may be like looking for lost keys where the light is better, instead of where the keys are more likely to be found. (Drake & Colditz, 2009)

Clinical trials are often done in people already receiving state-of-the-art treatment for their disease:

The diseased or high-risk populations often selected for clinical trials have another characteristic that may limit the ability to observe an effect of a relatively mild intervention such as a vitamin supplement. These populations are already receiving all the medications considered to represent the standard of care for patients with their particular risk factors or diseases. Thus, in order to appear successful in a clinical trial, not only must the vitamin prevent progression of disease, it must provide benefits over and above those already being provided by the standard medical treatments the patients are receiving—and which they will continue to receive throughout the duration of the trial.

Combined primary endpoints:

Because of the relatively small number of deaths or serious events that are likely to occur during the course of a clinical trial, primary outcome measures are often combined events: death and nonfatal myocardial infarction (MI) and stroke, for example. In these cases, interventions will only be found successful if they have a benefit for the combined measure. If the intervention "only" prevents strokes, that may not be counted a success, but may only qualify as a secondary benefit. In some trials, the authors appear to bend over backwards to minimize some apparently real benefits, and an impression of failure is given where some success was actually observed.

Compliance and "intent to treat":

All subjects assigned to the treatment group are included in the analysis of effects of the treatment, whether or not they complied with the treatment regimen. This is the accepted statistical convention of analyzing data according to "intent to treat." Analysis of compliers is considered subgroup analysis and thus statistically questionable. Yet in the epidemiological studies that gave rise to the hypothesis, it was only the actual *use* of the supplement that contributed to the apparent benefit. Including noncompliers in the treatment group in analyzing clinical trials may be necessary for statistical purity, but may permit inappropriate conclusions to be drawn about the effects of nutritional treatments that are effectively applied. In some studies, beneficial effects have been shown in those people who actually took the assigned supplements. This is a meaningful result and should be recognized as such.

Relevance of epidemiologic data, apart from the results of clinical trials:

By the very nature of their design, most clinical trials test very narrow hypotheses—"a mile deep but only an inch wide," the saying goes. For example, a given

trial may test the effect of a single form of a single supplemental nutrient at a single dose, in a specific population, at a certain life stage, for a given period of time. All of the compromises that go into the design of clinical trials may, separately or together, make it more difficult or even impossible to detect a real benefit. While the current emphasis on "evidence-based medicine" tends to designate randomized clinical trials as the gold standard and minimize the relevance of even rigorously designed observational studies, the evidence for such a rigid hierarchy of study designs has been questioned. (Concato, 2004) It is important to recognize that failure to detect a benefit in a clinical trial does not necessarily negate the epidemiological data showing an apparent benefit, especially when the hypothesis tested in the clinical trial is not the same as the hypothesis suggested by the observational data.

Clinical trials travel in groups:

Strong epidemiological observations and thorough analysis of other supporting data is likely to result in the funding of not just one clinical trial, but numerous clinical trials—all initiated within a few years of each other and all being concluded within a few years of each other. Since the trials are concurrent, there is little or no opportunity for one trial to build on another in order to improve the study design.

Ethics of clinical trials:

In order for a clinical trial to be undertaken at all, there must be a critical balance between confidence and uncertainty. The treatment to be administered must be considered safe, and there must be enough confidence in a possible benefit to justify giving the treatment to thousands—often tens of thousands—of people. On the other hand, there must be sufficient uncertainty about a possible benefit so that it is not unethical to give half the subjects a placebo. Researchers undertake clinical trials in the expectation of finding a benefit. A trial that fails to find a benefit is a disappointment, but not necessarily the final word. As long as researchers in a subject area remain convinced of a likely benefit and as long as new trials are being initiated with a given substance or set of substances, the discussion is not over.

Terminology—"prevention" as a euphemism for "treatment":

In trials conducted in patients who already have the target disease, the administration of vitamins cannot truly be said to have the goal of "prevention." The term "secondary prevention" is commonly used to describe these trials in which an effort is made to prevent future progression or recurrence of the target disease. Realistically, "secondary prevention" is a euphemism for treatment effects. If the results of such trials are null, they do not indicate a failure of prevention, but a failure of treatment. The difference in terminology is important to the public perception of the findings. Hardly anyone would be surprised to tune in to the morning news and hear that a few B vitamins failed to be an effective treatment for MI or stroke. When the authors instead assert that the trial represents a failure of prevention, people are confused by this choice of language into believing that the trial actually tested prevention and that vitamins failed the test, when in truth the hypothesis of disease prevention with nutrients was likely not tested.

Where Next?

Many researchers remain convinced that improved dietary habits and some specific nutrient interventions are very likely to make large contributions to health promotion and disease prevention. Beneficial effects have already been demonstrated and are accepted as proven for calcium and vitamin D relating to bone health, for folic acid to protect against neural tube birth defects, and for dietary fiber and soluble fiber to

reduce the risk of cancer and heart disease. There is also persuasive evidence for an antioxidant cocktail to help prevent eye disease and for omega-3 EPA and DHA to reduce the risk of heart disease. At the same time, there is a dilemma posed by the series of null clinical trials relating to vitamin E and coronary artery disease, the B vitamins and cardiovascular disease, and antioxidants and cancer—trials apparently at odds with a large body of human observational evidence, supported by animal studies and a full understanding of the mechanisms by which these nutrients could be expected to have a beneficial effect.

Even after disappointing clinical trials on vitamin E and heart disease appeared, Dr. Daniel Steinberg expressed confidence in the antioxidant hypothesis, saying that the results "lead us to re-examine the question of what might be the appropriate nature of trials in humans, but they do not invalidate the large body of experimental evidence supporting the role for oxidative modification of LDL in atherogenesis." (Steinberg, 2000) Researchers such as Dr. Maret Traber and Dr. Balz Frei remain convinced that vitamin E is beneficial when taken before disease onset, as shown by some of the subgroup analyses in the Women's Health Study, and they also point out that 96 percent of American women and 93 percent of American men fail to consume even recommended amounts of vitamin E. (Traber, Frei, et al., 2008) They believe "the negative evidence regarding vitamin E supplements from randomized clinical trials is more a reflection of inadequate study design and methods of analysis than proof of failure of vitamin E in primary prevention." (Traber, Frei, et al., 2008)

Some researchers see disappointing clinical trials as a useful step toward better understanding of the questions to ask and the types of research designs to pursue in the future. While recognizing that "the most satisfying trials are those that deliver the goods," many researchers caution that null or unexpected results should not be viewed as failures, since such studies shed some light on the causes of disease and possible approaches to disease prevention. (Albanes, 2009)

Some researchers see disappointing studies as proof that clinical trials as presently designed are inappropriate for complex nutrient/disease interactions, and they call for some new thinking about the best way to scientifically evaluate such relationships. Some have wondered whether the scientific community is ready to rethink "the reductionist medical approach" when it comes to evaluating complex diet/disease or nutrient/disease relationships. (Meyskens & Szabo, 2005)

Dr. Heaney has been outspoken about the need for a new approach to research on nutrition and disease prevention, saying: "The field of nutrition must, I believe, apply the brakes to its mad, downhill rush to embrace a drug-based standard of proof, and instead, pause long enough to develop its own standards—standards that would involve both different designs and a differing approach to endpoints." (Heaney, 2008) He asserts that nutrition is important to health and to disease prevention, "despite the fact that the still growing number of failed trials of individual nutrients might suggest that no nutrient actually made much of a difference, a conclusion that is absurd on its face and ought to have alerted us to the possibility that there was something wrong with how we were investigating the matter." (Heaney, 2008)

Part of the solution, in Dr. Heaney's view, might involve the development of a global index of the various effects of specific nutrients on markers of health and disease—an outcome measure which would be complex but which would better reflect the multiple and related effects of nutrients on many metabolic systems. He argues that studying single nutrients apart from the host of other nutrients with which they interact is an exercise that is bound to fail. As a concrete

first step toward an improved nutrition research paradigm, he suggests that it "would be useful for the ASN [American Society for Nutrition], in collaboration with concerned governmental entities such as the USDA, to convene a workshop to address these structural issues." (Heaney, 2008) A workshop was convened at Creighton University in September 2008 to discuss these topics, and a report of the workshop appeared in *Nutrition Reviews* in 2010. (Blumberg, Heaney, et al., 2010)

The following sections will examine the concordance or discordance of epidemiologic evidence and clinical trials in several areas, including antioxidants and cancer, antioxidants and heart disease, and B vitamins and cardiovascular disease.

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Antioxidants and Cancer

By the 1980s, numerous epidemiologic studies had shown that people with higher intakes of antioxidant nutrients had a lower risk of many different types of cancer, and beta-carotene appeared to be especially promising. For example, Dr. Peter Greenwald of the National Cancer Institute observed that "about 20 studies in various parts of the world suggest an inverse association between eating foods containing vitamin A or beta-carotene and various types of human cancer; risk is thereby reduced 30-50 percent," and by 1986, the National Cancer Institute was already sponsoring 21 clinical trials. (Greenwald, Sondik, et al., 1986) Most involved vitamin A and/or beta-carotene, but some also involved vitamin E, vitamin C, folic acid, or other nutrients. These included the ATBC trial among male smokers in Finland, the CARET trial among asbestos workers and smokers in the U.S., and the Physicians Health Study in the U.S. Although the antioxidant hypothesis was in large part based on observations of benefit from fruit and vegetable intake, none of the studies were trials relating to fruit and vegetable intake.

Many researchers have criticized some aspects of the design and the assumptions of the clinical trials on antioxidants and cancer. Trials have been undertaken with single nutrients, rather than a constellation of nutrients that occur together in foods or that have similar functions. Trials have been undertaken in populations without measuring their antioxidant status and without regard to genetic factors that may affect their risk of cancer.

Dr. Frank Meyskens and Dr. Eva Szabo observe: "It is important to recognize that micronutrients or any other dietary components do not act in isolation, but as part of a package." If the total package is required for effective function, then testing just one component is likely to be futile. They continue: "A major issue to consider is whether the scientific community is willing to take a more public health approach in addition to rethinking the reductionist medical approach in the matter of diet and cancer. In other words, do we really need to know which components of food are the active agents if changes in diet will result in reduction of cancer incidence or risk in the population at large?" (Meyskens & Szabo, 2005)

BETA-CAROTENE, VITAMIN E, AND LUNG CANCER

In the Alpha Tocopherol and Beta Carotene Study (ATBC), a large randomized controlled study in Finland, supported by the National Cancer Institute, beta-carotene and vitamin E were given to over 29,000 long-term smokers for about six years. The men had a median age of 57 at the beginning of the trial, smoked a median of 20 cigarettes per day, and had been smoking for a median of 36 years. Vitamin E supplementation (50 mg per day) increased serum levels of alpha-tocopherol by 50 percent. Beta-carotene supplementation (20 mg per day) increased serum levels of beta-carotene by 17-fold. Beta-carotene was given in a water-soluble form that had a very high bioavailability The treatments were ineffective in reducing the risk of lung cancer. In fact, there was a modest increase in lung cancer risk in smokers who took beta-carotene. (ATBC Study Group, 1994) The increase in risk was strongest in subjects who smoked at least 20 cigarettes daily and in those who drank the most alcohol. (Albanes, Heinonen, et al., 1996)

In the Carotenoid and Retinol Efficacy Trial (CARET) in the U.S., beta-carotene and high-dose vitamin A were given to a large group of smokers and asbestos workers, and were not effective in reducing the risk

of lung cancer. In fact, smokers who took beta-carotene had a somewhat increased risk of lung cancer. (Omenn, Goodman, et al., 1996)

In a third large beta-carotene trial, the Physicians' Health Trial, more than 20,000 U.S. physicians were given 50 mg of beta-carotene every other day for a period of about 13 years. No benefit was observed against cancer or heart disease in this study. Neither were there any adverse effects. (Hennekens, Buring, et al., 1996)

These three studies raise a number of questions. Shortly after publication of the studies, experts who had carefully reviewed the data were cautious about concluding that beta-carotene may actually be harmful. (Erdman, Russell, et al., 1996) Instead, they urged consideration of several points, including the following, outlined by CARIG, the Carotenoid Research Interactive Group:

- Beta-carotene is believed to be protective against the very early stages of lung cancer development. Therefore, giving beta-carotene for only a few years to high-risk lifelong smokers and asbestos workers may have been too late for it to protect against lung cancer.
- Adverse effects in the ATBC trial were primarily seen in men with the greatest intake of alcohol. It is possible that an interaction of beta-carotene, smoking, and alcohol was responsible for the apparent adverse effects.
- Fruits and vegetables contain many carotenoids and other beneficial compounds. In retrospect, it may have been unrealistic to expect a single carotenoid to achieve protective effects on its own. Research should continue on a variety of carotenoids, including beta-carotene.

In an article reflecting on the beta-carotene studies, two researchers say: "The cancer prevention community was stunned in the early 1990s" by the results of the ATBC trial and the CARET trial. It is suggested that the results "may be related to the pharmacologic doses of beta-carotene used and the resultant supra-physiologic serum concentrations of beta-carotene. This explanation is consistent with the apparent protective effect of beta-carotene on lung cancer incidence and mortality reported in observational epidemiologic studies," as well as in some clinical trials. (Duffield-Lillico & Begg, 2004)

Vitamin E was not found to have an effect in reducing the risk of lung cancer in the ATBC trial, but a 19-year follow-up analysis of the subjects in the ATBC trial recently showed that the men who had relatively higher *baseline vitamin E* levels had about a 20 percent reduced risk of cancer and heart disease during the following two decades. (Wright, Lawson, et al., 2006)

SELENIUM, VITAMIN E, AND PROSTATE CANCER

A study of selenium and skin cancer reported no effect on that primary endpoint, but researchers found a marked decrease in risk of prostate cancer in men who received selenium. (Clark, Combs, et al., 1996) The ATBC trial, which found no effect of vitamin E against lung cancer, found that the men who received vitamin E had a lower risk of prostate cancer. These two findings, together with promising epidemiologic data, formed part of the basis for launching a massive new trial on prostate cancer in 2001 (the Selenium and Vitamin E Clinical Trial, or SELECT). The SELECT trial, involving over 35,000 men who were given 200 mcg of selenium and 400 IU of vitamin E, was discontinued in 2008 because the treatments were not having a significant effect. (Lippman, Klein, et al., 2009)

Surprisingly, later followup of the participants in the SELECT trial found evidence of an increased risk of prostate cancer, after the treatment was stopped, in the men who had been given vitamin E but not in the men who had received the combination of vitamin E and selenium. (Klein, Thompson, et al., 2011) The authors indicate that a biological explanation for this observation "is not apparent from these data." They suggest that caution should be used "when recommending or studying high doses of micronutrients." They add that these essential nutrients "are part of normal physiology, and a U-shaped dose response curve may exist where either deficiency or supra-physiological doses are harmful." (Klein, Thompson, et al., 2011)

The Physicians' Health Study II (PHS II) failed to find an effect on prostate cancer or total cancer when vitamins E and C were given to more than 14,000 male physicians (average age of 64 years at the beginning of the trial) for a period of about eight years. The physicians were given 400 IU of vitamin E every other day or 500 mg of vitamin C every day, or both, or a placebo. (Gaziano, Glynn, et al., 2009)

The authors of the SELECT reflected on possible reasons why selenium appeared to be protective in an earlier trial but not in the SELECT trial. They recognized the possibility that the effect seen in an earlier trial may have been due to chance. Also, the form of selenium used in the Clark trial was not the same as the form used in the SELECT trial. They also noted that most of the benefit observed in the Clark trial was in men with low baseline selenium levels. In the SELECT trial, 78 percent of the men had higher levels at baseline and therefore may have been sufficiently replete that there was no effect of additional selenium. (Lippman, Klein, et al., 2009)

In addition to considering a broader spectrum of nutrients for possible interventions, it may be important to screen study subjects according to some marker of oxidative stress or cancer risk.

Dr. Peter Gann, in an editorial that accompanied the SELECT and PHS II reports on prostate cancer, pointed out that PSA testing became widespread at about the time the study was initiated, catching potential prostate cancer at a very early stage and leading to treatment to prevent its progression. As a result, there were relatively few cases of prostate cancer diagnosed during the trial, and most were localized and not advanced. (Gann, 2009) Dr. Gann also raises the question whether it is time to stop focusing on intervention with single agents as an approach to primary prevention.

A recent comprehensive review on selenium and human health also emphasizes the fact that the SELECT trial included almost no men with selenium levels as

low as those in the Clark trial that found a benefit from selenium supplementation on prostate cancer risk. (Rayman, 2012) The review notes that the SELECT trial does not explain the potential effects of selenium on (1) risk of advanced disease, which was present in only 1 percent of cases; (2) prostate cancer mortality, since only one SELECT participant died of the disease; (3) current smokers, who represented only 7.5 percent of the study population; or (4) as noted earlier, men with low selenium status. According to the review, "the crucial factor that needs to be emphasized is the inextricable U-shaped link with selenium status," suggesting that various health benefits could be derived from supplementation of people with low status, while people with adequate or high selenium status are unlikely to benefit and may be affected adversely. (Rayman, 2012)

ANTIOXIDANTS AND CANCER IN MEN

In the SU.VI.MAX (*Supplementation en Vitamines et Mineraux Antioxydants*) study in France, almost 8,000 women and more than 5,000 men were given an antioxidant supplement for about 7.5 years. The supplement provided 30 mg vitamin E, 120 mg vitamin C, six mg beta-carotene, 100 mcg selenium, and 20 mg zinc. Total cancer incidence and all-cause mortality were reduced in men but not in women, possibly because the men had lower antioxidant status at baseline. (Hercberg, Galan, et al., 2004)

ANTIOXIDANTS AND CANCER IN CHINA

Several intervention trials were undertaken in China, where nutritional status was relatively low. The Linxian study involved almost 30,000 adults who were given an antioxidant supplement including 50 mcg selenium, 30 mg vitamin E, and 15 mg beta-carotene, from 1985 to 1991. The treatment led to decreased risk of cancer. (Blot, Li, et al., 1993) A recent report of a 10-year follow-up of the Linxian study found that people who had received the antioxidant supplement had lower gastric cancer mortality and lower total mortality in the 10 years following discontinuation of the supplement. (Qiao, Dawsey, et al., 2009)

Where Next?

In addition to considering a broader spectrum of nutrients for possible interventions, it may be important to screen study subjects according to some marker of oxidative status or cancer risk. The study of genomics also indicates that people with different genetic profiles may vary in the way they metabolize nutrients and in their susceptibility to disease. Dr. Bruce Ames has long held that genetic variations in metabolism and in enzyme kinetics can markedly affect both normal function and susceptibility to cancer. (Ames, Elson-Schwab, et al., 2002) A recent study on breast cancer found increased risk in women who had shortened telomeres (important for stabilizing genes) and low intakes of antioxidant vitamins. (Shen, Gammon, et al., 2009) Factors such as these could potentially affect the design of new clinical trials.

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Antioxidants and Heart Disease

Antioxidants help protect every cell and membrane in the body against the ravages of everyday living, and thus may help prevent diseases that result from accumulated damage due to oxidation.

Oxidation is not necessarily a bad thing. Many cycles in the body depend on an interlocking chain of reactions involving both oxidation—in which an electron is lost—and reduction—in which an electron is gained. Electrons are passed back and forth continually in countless metabolic reactions without generating "oxidative damage." However, the oxidation of some compounds (such as lipids) can be damaging and some oxidative reactions can produce "free radicals," which are dangerous because they set up a chain reaction that can rapidly damage a large number of molecules. One way to prevent oxidative damage is to surround the sensitive compound with "antioxidants" that can be offered up as targets of oxidation *instead of* the sensitive compound. Antioxidants are molecules that can easily and harmlessly give up or accept electrons. That is, antioxidants are *substances that are themselves easily oxidized and that are benign* in their oxidized form. Once oxidized, they are also readily reduced back to their active form, making them available for another round of protection.

In the antioxidant cycle, one antioxidant often hands off electrons to another. Antioxidants thus operate as a team, passing electrons back and forth as necessary in order to prevent unwanted oxidation of sensitive compounds. The antioxidant team includes vitamin E and vitamin C. Some minerals, such as selenium, are integral components of antioxidant enzymes and thus are recognized to serve an antioxidant function. Other food components have also been shown to be protective. These include carotenoids (such as beta-carotene, lutein, and lycopene), flavonoids, and polyphenols.

Vitamin E is the primary fat-soluble antioxidant in the body, and has been shown to protect lipids from peroxidation. This is particularly relevant to heart disease risk, since it is believed that the initiating factor that ultimately leads to atherosclerosis is the oxidation of LDL cholesterol and its incorporation into foam cells or fatty streaks deposited inside blood vessels.

Two studies published in 1993 created widespread excitement about the possibility that vitamin E supplementation could dramatically reduce the risk of heart disease. One was based on data from the Nurses' Health Study, involving more than 87,000 women. Dr. Meir Stampfer and colleagues at Harvard Medical School and the Harvard School of Public Health reported a 41 percent reduction in risk of heart disease among nurses who had taken vitamin E for more than two years. The average vitamin E intake in the lowest-risk group was 200 IU. The researchers noted that a beneficial effect of vitamin E on heart disease "is plau-

sible because of the substantial evidence indicating the importance of oxidation of LDL in atherosclerosis." (Stampfer, Hennekens, et al., 1993)

The second study was based on data from the Health Professionals Follow-up Study involving almost 40,000 men. Dr. Eric Rimm and colleagues at the Harvard School of Public Health and Harvard Medical School found that men who had taken vitamin E for more than two years had a 37 percent lower risk of heart disease, compared to men who had not taken supplements of vitamin E. The average level of vitamin E intake in the lowest-risk group was 400 IU. (Rimm, Stampfer, et al., 1993)

These studies, together with an abundance of other evidence, spurred a large number of clinical trials on vitamin E and heart disease. Two of these showed positive benefits from vitamin E, and these happen to be the two studies that used 800 IU for all or part of the study, a higher level than used in other trials. The most striking is the Cambridge Heart Anti-Oxidant Study (CHAOS), a randomized controlled trial that found that vitamin E supplementation was dramatically effective in reducing the incidence of heart attacks in patients who already had confirmed evidence of coronary disease. In this study, 1,000 men with heart problems were given 800 IU of vitamin E early in the study, lowered to 400 IU of vitamin E later in the study. Another 1,000 men were given a placebo. After 18 months, the number of heart attacks in the vitamin E group was only one quarter of the number in the placebo group. In other words, vitamin E reduced the risk of heart attack by 75 percent. (Stephens, Parsons, et al., 1996)

The WHS found a 24 percent reduction in cardiovascular death and a 26 percent decreased risk of major cardiovascular events in women over 65 with 600 IU every other day of vitamin E.

Another positive study is a study of patients with endstage renal disease requiring chronic hemodialysis. According to the authors of the study, "The cardiovascular-disease mortality rate in this patient group is estimated to be five to 20 times that of the general population," and the increased mortality is considered to be due in part to a high level of oxidative stress. In the SPACE trial (Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease), researchers tested the effect of 800 IU per day of vitamin E supplementation on cardiovascular disease in almost 200 patients over a period of two years. The authors concluded that vitamin E treatment has a significant protective effect against cardiovascular death and non-fatal myocardial infarction (MI). (Boaz, Smetana, et al., 2000)

In the Women's Health Study (WHS), natural source vitamin E (600 IU every other day) or a placebo was given to almost 40,000 apparently healthy women over a period of 10 years. *The study found a significant 24 percent reduction in cardiovascular death, and a 26 percent decreased risk of major cardiovascular events in women over 65.* The significant reduction in cardiovascular events in women over 65 was made up of a 34 percent reduction in MI and a 49 percent reduction in cardiovascular death. These meaningful benefits were minimized by the authors because these were considered to be subgroup analyses, and there was no overall protective effect in the primary *combined* endpoint of MI, stroke, and cancer risk. (Lee, Cook, et al., 2005)

Further analysis of the Women's Health Study also showed a benefit of vitamin E in decreasing the risk of venous thromboembolism (clot formation in a vein) by 21 percent. (Glynn, Ridker, et al., 2007)

However, most of the major clinical trials on vitamin E and heart disease have failed to identify beneficial effects, and there is intense debate over the reasons for these disappointing findings. Has the potential effect of vitamin E on heart disease risk been disproven, or is it yet to be properly tested?

TRIALS OF VITAMIN E AND HEART DISEASE MAY BE FATALLY FLAWED

In a 2007 commentary, Drs. Jeffrey Blumberg and Balz Frei suggested that the "clinical trials on vitamin E and cardiovascular diseases may be fatally flawed." They indicated that few investigators have confirmed the bioavailability and the effects on biomarkers of oxidative stress of the vitamin E doses and formulations used in the trials. "Further, no randomized controlled trials have employed cut-off values of vitamin E intake or status as inclusion criteria for enrollment eligibility.... Absent evidence of significant changes in vitamin E and oxidative stress status, the antioxidant hypothesis is not being tested!" (Blumberg & Frei, 2007)

Plasma C-reactive protein (CRP) may be a candidate to serve as a marker of risk. CRP is an inflammatory biomarker that predicts cardiovascular disease, and lowering elevated CRP with statins has been shown to reduce the risk of heart disease. Block and coworkers recently found that vitamin C reduced CRP levels in people whose CRP was 1.0 mg/L or more to an extent comparable to the lowering observed with statins. They suggest that "research on clinical benefits of antioxidants should limit participants to persons with elevations in the target biomarkers." (Block, Jensen, et al., 2009)

GOALS FOR FUTURE RESEARCH: DR. STEINBERG

Dr. Daniel Steinberg of the University of California at San Diego, a leading researcher in the area of antioxidants and heart disease, posed the question, "Is there a potential therapeutic role for vitamin E or other antioxidants in atherosclerosis?" His answer was, "Probably, but it is too soon to say." (Steinberg, 2000) Following are some of the points he emphasized.

"A large body of evidence supports the hypothesis that oxidation of low-density lipoprotein (LDL) plays an important causative role in the atherosclerosis of several different animal models." Also, many studies demonstrate that supplementation of humans with vitamin E has effects on "markers" for cardiovascular disease. However, clinical trials of vitamin E in patients with pre-existing heart disease have been disappointing. Dr. Steinberg says it is "most unlikely that further studies in similar patient populations will change the conclusion that was reached, namely, that these doses of vitamin E in patients like these (i.e., with established severe coronary disease) will be ineffective, at least within a 3-5 year period." (Steinberg, 2000) Dr. Steinberg suggests "we may not be doing the right kind of clinical trial," and offers three possible explanations for the negative results of several clinical trials:

1. Vitamin E may inhibit the early stages of atherosclerosis but have little or no effect on advanced lesions. The animal data show a benefit of antioxidants given at very early stages of atherosclerosis, not at late stages. Dr. Steinberg suggests intervention trials that focus on detecting and quantifying the development of new lesions. "The epidemiologic data showing decreased CHD risk in patients with higher intakes or higher plasma levels of vitamin E reflect lifetime exposure to diets associated with higher intakes of vitamin E (or long-term use of supplements).

There is no reason to expect that a 3-5-year treatment with supplemental vitamin E can duplicate the protective effect of a lifetime of exposure to, for example, a Mediterranean diet."

2. Vitamin E may not be the most potent antioxidant for this purpose. Other antioxidant compounds, including synthetics, need further study. "More basic research is needed on the issues of where antioxidant activities are needed *in vivo* and how antioxidants can best be transported to those sites. At the moment, most investigators assume that oxidation in the wall of the artery itself is the most relevant but this has never been firmly established."

3. There could be a true species difference such that antioxidants shown to be effective in animal models "will simply never have an effect on atherogenesis in humans." This is a possibility that should not be accepted until the first two explanations are thoroughly explored, but it cannot be ruled out.

Dr. Steinberg concluded that the disappointing results of several clinical trials "lead us to re-examine the question of what might be the appropriate nature of trials in humans, but they do not invalidate the large body of experimental evidence supporting the role for oxidative modification of LDL in atherogenesis." (Steinberg, 2000)

HOW MUCH VITAMIN E? JUST ENOUGH!

Do the disappointing results of some clinical trials mean that vitamin E status is not an important determinant of health and disease? Not at all. Back in 1994, the ATBC trial found no effect of supplemental vitamin E on lung cancer risk. (ATBC Study Group, 1994) However, a recent analysis of 19 years of follow-up reported that *the men who had higher vitamin E blood levels at baseline had a lower subsequent risk of cancer and of other diseases including heart disease over the next couple of decades.* (Wright, Lawson, et al., 2006) During 19 years of follow-up of more than 29,000 men included in the ATBC trial, more than 13,000 of the subjects have died, and extensive data is now available on baseline serum vitamin E levels related to overall mortality and to mortality from specific causes. It turns out that men in the higher quintiles of *baseline vitamin E* levels had about a 20 percent lower total mortality, cancer mortality, and cardiovascular mortality, as compared to men in the bottom quintile of serum vitamin E. Within the categories of cancer and cardiovascular disease, they had significantly lower mortality for lung cancer, prostate cancer, ischemic stroke, hemorrhagic stroke, and respiratory disease. These are exactly the kind of protective effects that would have been predicted from the observational studies. Data such as these will keep investigators searching for improved research designs that hopefully will permit a new generation of RCTs (or their equivalent) to more effectively explore nutrient/disease relationships and to produce results that better capture the whole picture.

In an editorial accompanying the report mentioned above, Dr. Maret Traber asked and answered the question, "How much vitamin E? . . . Just enough!" The Wright study found that disease risk was decreased as serum vitamin E levels increased from nine to 13 mg/L. However, "estimates of the vitamin E intake

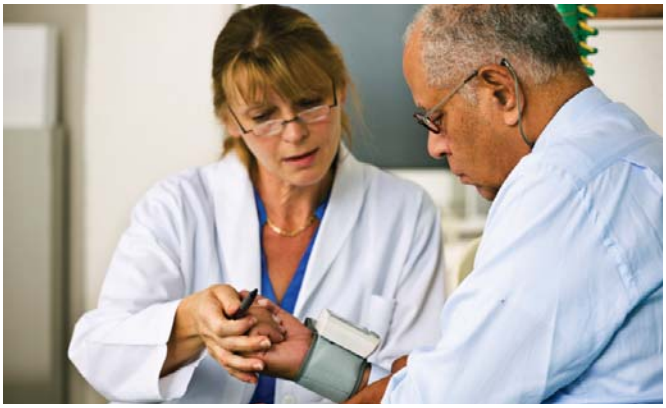
necessary to achieve a certain serum concentration of alpha-tocopherol have varied widely." In the ATBC baseline study, a dietary intake of about 12 mg was associated with serum levels of 11 to 12 mg/L. Traber observes, however, that "12 mg vitamin E is an amount that is greater than that estimated to be consumed by 93 percent of men and 96 percent of women in the United States." She suggests that "the vitamin E recommended dietary allowance of 15 mg/d may yield optimal serum concentrations to achieve significant reductions in chronic disease mortality. However, 15 mg/d may be a vitamin E intake that is achieved only with supplements, given the dietary habits of most Americans." (Traber, 2006)

KEY CLINICAL TRIALS

Following is a summary of numerous clinical trials on vitamin E and heart disease, in the U.S. and elsewhere.

In the GISSI (Gruppo Italiano per lo Studio della Sopravivenza nel'Infarto miocardico) trial in Italy, researchers gave 300 mg of vitamin E and/or one gram of omega-3 fatty acids or no supplement to over 11,000 patients who had survived an MI within the previous three months. The supplements were continued for an average of 3.5 years. The omega-3 fatty acid treatment reduced the risk of death, nonfatal heart attack, and stroke, but the vitamin E did not have a significant protective effect. The authors conclude that "the dose of vitamin E that is most effective and safe, as well as the minimum duration of treatment that is required to produce the postulated protective effects of vitamin E are still unknown." (GISSI, 1999)

The Alpha-Tocopherol Beta-Carotene Study (ATBC) was designed to test whether vitamin E and/or beta-carotene supplementation would reduce the risk of lung cancer in almost 30,000 smokers in Finland, but effects on coronary artery disease were also evaluated. In that study, neither supplement was found to protect against lung cancer or heart disease. Vitamin E appeared to have a protective effect against prostate cancer, colorectal cancer, and ischemic stroke, but increased the risk of hemorrhagic stroke. (ATBC Study Group, 1994) The Food and Nutrition Board of the Institute of Medicine in its report on Dietary Reference Intakes for antioxidant nutrients, noting that several other major trials using higher levels of vitamin E have not reported any increased risk of stroke, commented: "The unexpected finding of an increase in hemorrhagic stroke in the ATBC study was considered preliminary and provocative, but not convincing until it can be corroborated or refuted in further large-scale clinical trials." (Institute of Medicine, 2000)



In the Primary Prevention Project (PPP) in Italy, almost 4,500 people with at least one major risk factor for heart disease were given low-dose aspirin (100 mg) or vitamin E (300 mg) or both for three to six years. Aspirin lowered the frequency of cardiovascular events and cardiovascular deaths, but vitamin E did not. (PPP, 2001)

In the Heart Outcomes Prevention Evaluation study (HOPE), researchers enrolled more than 2,500 women and almost 7,000 men over 55 years of age who had existing heart disease or diabetes plus one additional risk factor for heart disease. They were given 400 IU of natural vitamin E (or a placebo) daily for a period of four to six years. Among the vitamin E group at

baseline, 53 percent had already had an MI and 26 percent had already undergone bypass surgery. There were no significant effects of vitamin E on the risk of later heart attacks, stroke, or death. This dose of the vitamin was "well tolerated, with no significant adverse events as compared with placebo." (Yusuf, Dagenais, et al., 2000)

The HOPE study was continued for another four years to further examine effects of vitamin E on heart disease and cancer risk. The results of the continued study, labeled HOPE-TOO, were published in 2005 and showed no benefit for cardiovascular or cancer risk, but some increase in risk of heart failure. During this extended study, ACE inhibitors were being recommended for all participants, based on the favorable outcome of the ACE inhibitor portion of the initial HOPE study. (Lonn, Bosch, et al., 2005)

In the Women's Antioxidant Cardiovascular Study (WACS), more than 8,000 female health professionals with a history of cardiovascular disease or with three or more risk factors were given 600 IU of vitamin E every other day, 500 mg vitamin C every day, 50 mg beta-carotene every day, or a placebo. There were no significant effects on cardiovascular events. (Cook, Albert, et al., 2007)

In the Physicians Health Study II, involving over 14,000 healthy men, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events (death, nonfatal MI, or stroke). This trial went on for eight years, but the authors point out that this may not have been long enough to encompass the "etiologic window" for heart disease. It is also important to note that the physicians in this trial were already 64 years old, on average, at the beginning of the study—perhaps past the age when true prevention would be operative, since it is believed that the process of atherosclerosis begins in youth. (Sesso, Buring, et al., 2008)

Bottom Line

Vitamin E, vitamin C, and other antioxidants have been linked in numerous observational studies to a decreased risk of various diseases, including heart disease. Some clinical trials have shown a benefit of vitamin E, at least in some subgroups, but most have not. Long-term follow-up of the men who participated in the ATBC trial showed a lower risk of cancer and heart disease over a period of 19 years in those who had higher serum vitamin E levels at baseline. It has been suggested that future studies should screen participants based on their initial antioxidant status and the presence of markers of oxidative or inflammatory risk, and researchers should confirm whether markers of oxidative risk are lowered, in addition to monitoring direct disease outcomes.

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B Vitamins and Cardiovascular Disease

An abundance of research suggests a relationship between blood homocysteine levels and heart disease risk, as convincingly summarized in a 1995 meta-analysis of 28 studies. (Boushey, Beresford, et al., 1995) Homocysteine is produced in the body as a byproduct of the one-carbon cycle, which generates methyl groups for the synthesis of innumerable compounds essential to life and health, including DNA itself. Homocysteine normally gets recycled and does not accumulate to a large extent. The nutrients directly involved as cofactors that keep the one-carbon cycle operating efficiently include several of the B vitamins, notably folate, vitamin B-6 and vitamin B-12. When these B vitamins (and some other compounds) are present in adequate amounts, homocysteine is kept at a relatively low level in the body. A number of observational studies found that populations with low homocysteine levels had a lower incidence of heart disease than populations with higher levels of homocysteine.

A recent trial illustrates the importance of distinguishing between effects of B vitamins in people depending on their baseline level of homocysteine.

It was clearly demonstrated that giving extra amounts of the B vitamins lowered homocysteine levels, and so it seemed likely that such supplementation would reduce the risk of cardiovascular disease in the population as a whole. Some researchers urged public health authorities to endorse widespread supplementation with these B vitamins, without waiting for results from a number of controlled studies that were undertaken to test the hypothesis that reducing homocysteine levels would also reduce the risk of cardiovascular disease. (Stampfer & Malinow, 1995) Numerous clinical trials on B vitamins, homocysteine, and heart disease or stroke were undertaken, involving tens of thousands of patients in several countries. In general, the interventions were undertaken in groups of older patients who had just suffered an event such as a stroke or a myocardial infarction (MI). One can reasonably question whether such trials are true tests of prevention.

A recent trial illustrates the importance of distinguishing between effects in people depending on their baseline level of homocysteine. In a clinical trial involving 506 people without diabetes and with no cardiovascular disease, B vitamins or a placebo were given for a period of three years. The vitamin supplement provided five mg folic acid, 400 mcg vitamin B-12, and 50 mg vitamin B-6. In this group of people at low risk for cardiovascular disease, the high-dose B vitamin supplementation reduced progression of early-stage subclinical atherosclerosis in those with a baseline homocysteine level of 9.1 micromole per liter or greater, but not in those with lower homocysteine levels. (Hodis, Mack, et al., 2009)

It is uncertain whether the clinical trials have sufficient statistical power to detect an effect, if there is one. Observational studies and nonrandomized trials generally overpredict the magnitude of an effect by as much as 50 to 100 percent. (Meyskens & Szabo, 2005) "Because sample sizes for clinical trials are generally based on the relative risks (or the equivalent) shown in observational studies, there is a high likelihood that randomized trials are consistently underpowered, thereby missing a small, but real effect." (Meyskens & Szabo, 2005)

An analysis by a collaborative group of researchers involved in B vitamin trials concluded that the homocysteine trials, in particular, "may not involve

a 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." (B-Vitamin Treatment Trialists' Collaboration, 2006) Other researchers have noted that the expected effect of the B vitamins on cardiovascular disease is in the range of 10 to 15 percent and the clinical trials were "generally underpowered" to detect such an effect. (Wald, Wald, et al., 2006) The latter group observed that, despite the problem of having low statistical power, reports from the studies "tend to inappropriately interpret non-significant effects as evidence of no effect."

KEY CLINICAL TRIALS

The VISP (Vitamin Intervention for Stroke Prevention) trial was undertaken in 3,680 patients who had already suffered a non-disabling stroke (cerebral infarction). (Toole, Malinow, et al., 2004) All of the patients "received best medical and surgical care plus a daily multivitamin containing recommended amounts of the non-study vitamins." The trial tested high-dose B vitamins or low-dose B vitamins as compared to placebo, over a 2-year period. The high-dose formula contained 25 mg pyridoxine (B-6), 400 mcg B-12, and 2500 mcg folic acid. The low-dose formula contained 200 mcg B-6, six mcg B-12, and 20 mcg folic acid. The high-dose formula lowered homocysteine more than the low-dose formula. Subjects with a lower homocysteine level at baseline were less likely to suffer another stroke, a coronary event, or death, but the supplementation had no effect on risk. However, the authors say that "further exploration of the hypothesis is warranted and longer trials in different populations with elevated total homocysteine may be necessary." (Toole, Malinow, et al., 2004)

Dr. David Spence and others involved in the VISP trial later published an analysis of the effects of the B vitamin supplements "in patients most likely to benefit from the treatment." (Spence, Bang, et al., 2005) For this analysis, they excluded people with very low or very high serum B-12 levels at baseline in order to exclude those with malabsorption and those already being treated with B-12. In the 2,155 patients considered in this analysis, there was a 21 percent reduction in the risk of stroke, coronary disease, or death in the high-dose B vitamin group. They suggest that, "in the era of folate fortification, B-12 plays a key role in vitamin therapy for total homocysteine. Higher doses of B-12 and other treatments to lower total homocysteine may be needed for some patients." (Spence, Bang, et al., 2005)

After other trials failed to find the benefits of B vitamins, Dr. Spence published an editorial entitled "Call Off the Funeral," urging researchers not to jump to the conclusion that B vitamins have no impact on cardiovascular disease without carefully evaluating the design of current trials, and especially whether studies are incorporating a sufficient amount of vitamin B-12. (Spence, 2006)

The Norwegian Vitamin trial (NORVIT) studied the effects of B vitamins in 3,749 men and women who were enrolled in the trial within seven days after suffering an MI. (Bonaa, Njolstad, et al., 2006) The patients were given 800 mcg of folic acid, 400 mcg of B-12, and 40 mg of B-6; or only the folic acid and B-12; or only the B-6; or a placebo. The primary endpoint was suffering another MI, a stroke, or sudden death due to coronary artery disease within a period of more than three years (40 months). Treatment with folic acid and B-12 lowered homocysteine but did not have a benefit on disease outcome. In the group given the relatively high dose of B-6, there was a trend toward increased risk, which the authors say "could readily be explained by chance."

The Heart Outcomes Prevention Evaluation (HOPE-2) trial involved 5,522 patients with vascular disease or diabetes who were given 2.5 mg of folic acid, 50 mg of B-6, and one mg of B-12, or who received a placebo for a period of about five years. (Lonn, Yusuf, et al., 2006) The average age of the patients at the beginning of the study was 69 years. The primary outcome measure was whether the subjects suffered an MI, a stroke, or death from cardiovascular causes. The B vitamin treatment reduced homocysteine levels but did not reduce the risk of major cardiovascular events. There were, however, fewer nonfatal strokes in the treatment group. More than 70 percent of the subjects lived in areas with mandatory folic acid fortification of food. The authors say, "This exposure probably reduced the number of patients with substantially increased homocysteine levels, the subgroup that might be most likely to benefit from B vitamin supplementation." (Lonn, Yusuf, et al., 2006)

As in other trials of patients who have suffered a stroke or MI, the subjects in the HOPE-2 trial were being given extensive medical care and were taking the medications indicated for their condition. For example, the B vitamin group used the medications shown below, among others. (Lonn, Yusuf, et al., 2006) It is reasonable to wonder whether a few B vitamins can realistically be expected to make an impact above and beyond the effects of standard medical care in such patients.

PERCENTAGE OF HOPE-2 SUBJECTS (IN B VITAMIN GROUP) TAKING THE FOLLOWING MEDICATIONS

MEDICATION	PERCENT USING
Aspirin or antiplatelet agents	78%
Beta-blockers	46%
Lipid-lowering drugs	59%
ACE inhibitors	66%

The WAFACS trial was a test of the effect of B vitamins on cardiovascular disease (CVD) in 5,442 women who were U.S. health professionals with a history of CVD or three or more coronary risk factors. Subjects were given a placebo or a B vitamin supplement containing 2.5 mg folic acid, 50 mg vitamin B-6, and one mg vitamin B-12 for a period of just over seven years. Homocysteine levels were reduced, but there was no impact on cardiovascular events. (Albert, Cook, et al., 2008)

The VITATOPS (Vitamins to Prevent Stroke) trial recruited more than 8,000 patients with recent stroke or TIA (transient ischemic attack) to test B vitamin therapy consisting of two mg folic acid, 25 mg B-6, and 500 mcg B-12 in an effort to determine whether the supplements plus "best medical and surgical management" would reduce the combined incidence of stroke, MI, and vascular death over a period of two years. Patients were recruited from 104 medical centers in 20 countries on five continents. (Hankey, Algra, et al., 2007) Results reported in 2010 indicated no significant risk reduction from the B vitamin treatment. (VITATOPS Trial Study Group, 2010)

Bottom Line

There is clear evidence that, in the general population, people with lower homocysteine levels have a lower risk of cardiovascular disease. It is known that giving B vitamins will lower homocysteine levels if they are high, and it was reasoned that lowering these levels would also lower heart disease risk in the population. Has this hypothesis been fairly tested in the clinical trials? Interventions in older people with recent cardiovascular events may not be the appropriate test for evaluating the effect of lowering homocysteine levels on the risk of cardiovascular disease in the general population.

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Benefits of Long-Chain Omega-3 Fatty Acids EPA and DHA

An abundance of evidence strongly suggests that increased intakes of long-chain omega-3 fatty acids can markedly reduce the risk of heart disease. The omega-3 fatty acids believed to be largely responsible for these effects include EPA and DHA (eicosapentaenoic acid and docosahexaenoic acid). These are polyunsaturated fatty acids (PUFA) with numerous double bonds.

These "good fats" are naturally present in some types of fish and in other marine organisms such as algae, and they are also readily available in purified form in dietary supplements. Most Americans eat fish less than once a week or not at all, and average per capita consumption is only about five ounces per week. (National Oceanic and Atmospheric Administration, 2008; Smith, Barraj, et al., 2009) Consequently, Americans have very low intakes of the marine long-chain omega-3 fatty acids EPA and DHA (also referred to as n-3 fatty acids).

According to the late Dr. William E. Connor of the Oregon Health Sciences University, an internationally recognized expert on omega-3 fatty acids and health, hundreds of experimental and clinical studies have provided strong evidence that omega-3 fatty acids may help prevent heart disease through a number of different mechanisms. Several studies indicate that eating fish once or twice a week can reduce deaths from coronary artery disease by about 50 percent. "The most important finding is of a reduction in sudden death from ventricular fibrillation and tachycardia." Omega-3 fatty acids also reduce the tendency to thrombosis (formation of blood clots), and thus help prevent myocardial infarction (MI). EPA and DHA also have several actions that inhibit the development of atherosclerosis. While these fatty acids do not lower plasma cholesterol levels, they do have a substantial triglyceride-lowering effect and also raise levels of HDL ("good" cholesterol). Connor concluded that omega-3 fatty acids "are natural food substances that prevent coronary artery disease and sudden death." He emphasized that these fatty acids "have immense public health significance for the control of the current coronary epidemic." (Connor, 2001)

WHAT ARE OMEGA-3 AND OMEGA-6 FATTY ACIDS?

The term "omega-3" or "n-3" indicates that the first double bond is located at the third carbon from the end of the fatty acid chain. The long-chain omega-3s from marine sources are EPA and DHA, with 20 and 22 carbons and with five or six double bonds. These are the focus of this chapter. There are also plant sources of omega-3 fatty acids with 18 carbons and three double bonds.

Structure of Omega-3 Fatty Acids

Docosahexaenoic acid (DHA)
22 carbons and six double bonds

Eicosapentaenoic acid (EPA)
20 carbons and five double bonds

Alpha-linolenic acid (ALA)
18 carbons and three double bonds

Omega-6 fatty acids are polyunsaturated fatty acids that have the first double bond at the sixth carbon from the end of the fatty acid chain, like linoleic acid, which has 18 carbons and two double bonds. These are the types of fats present in some of the most commonly used vegetable oils such as corn oil, safflower oil, and sunflower oil.

In the U.S., intakes of omega-6 fatty acids are about 10 times as high as intakes of omega-3 fatty acids. The average intake for omega-6 fatty acids in adults is nine to 17 grams per day, while the average intake for omega-3 fatty acids is only one to two grams per day. Further, most of the omega-3 intake is in the form of ALA, not in the form of EPA and DHA. Average intake of EPA in adults is less than 0.01 gram per day, and average intake of DHA is also less than 0.1 gram per day. (Institute of Medicine, 2002)

RECOMMENDATIONS OF AN ILSI WORKSHOP

A workshop sponsored by the International Life Sciences Institute of North America (ILSI) in 2008 evaluated the evidence on the benefits of increased consumption of EPA and DHA and recommended a combined intake of 250 to 500 mg per day to reduce the risk of heart disease. (Harris, Mozaffarian, et al., 2009) Some of the key findings of the workshop are summarized below.

Heart disease is a complex condition that may develop over years but eventually results in an acute attack. The build-up of plaque in the arteries is a long, slow process that may begin in youth and continue to old age. The plaque may remain stable for years, but when it ruptures it may cause clots, blockage, and ventricular arrhythmia, which is usually fatal. Numerous studies have demonstrated that people with higher intakes or higher blood levels of EPA and DHA have a lower risk of death—including sudden death—from heart attacks. The impact of EPA and DHA may be primarily in preventing or alleviating the arrhythmia.

Findings from the ILSI workshop included the estimate that "cardiac mortality is reduced about 35 percent by modest EPA+DHA consumption (about 250-500 mg/d), an effect at least as great, for example, as that of statin therapy." (Harris, Mozaffarian, et al., 2009) Several European groups have published recommendations for EPA+DHA intake, and these tend to be at the upper end of this range—around 500 mg per day.

...modest EPA+DHA consumption markedly reduces the risk of cardiac death. The quality, strength, and concordance of this evidence are remarkable, meeting and indeed generally exceeding those for any other dietary factor...

Higher intakes of EPA and DHA have favorable effects on other factors related to cardiovascular risk, including blood pressure, heart rate, and triglyceride levels. The potential benefit of ALA on cardiovascular risk is less well established. According to the ILSI workshop, ALA "should not be considered as a replacement for EPA+DHA in reducing risk of cardiac death or other CVD [cardiovascular disease]."

The participants in the ILSI workshop concluded that the evidence "indicates that modest EPA+DHA consumption markedly reduces the risk of cardiac death. The quality, strength, and concordance of this evidence are remarkable, meeting and indeed generally exceeding those for any other dietary factor" implicated in reducing heart disease risk, including the evidence relating to saturated fat, dietary cholesterol, salt, and dietary fiber. (Harris, Mozaffarian, et al., 2009)

In infancy, the brain and retina contain large amounts of DHA and of arachidonic acid (AA). These fatty acids accumulate in the central nervous system during fetal development and throughout infancy and early childhood. Adequate levels of omega-3 fatty acids have been shown to be related to visual function, possibly cognitive development, and language or communication ability. Regulations currently permit DHA to be added to infant formula in the U.S. at a level up to 0.35 percent. The ILSI workshop suggested that this maximum permitted level may actually be the minimum level necessary for a benefit.

Cognitive decline is widespread in the aging population and can lead to dementia, defined as loss of cognitive function that is sufficiently severe to interfere with everyday function. DHA is concentrated in some of the most metabolically active areas of the brain, and animal studies have shown that DHA levels in the brain decrease with aging. The decrease is associated with decreases in antioxidant enzymes, fluidity of synaptic membranes, oxidation of lipid membranes, and ischemic damage. Some epidemiologic studies have shown a decreased risk of dementia in people who ate fish once or twice a week, and more studies are underway. The evidence regarding cognitive decline is described as "promising but limited."

An Omega-3 Index has been developed, which is a measure of the amounts of EPA+DHA in red cell membranes as a percentage of total red cell fatty acids. EPA and DHA affect basic cellular function through their effects on and in membranes. "This marker has been validated against dietary intake and has been shown to correlate strongly with reduced risk for mortality from CHD." An Omega-3 Index of less than 4 percent is associated with a high risk of sudden cardiac death, while an Omega-3 Index of 8 percent indicates a strong cardioprotective effect. (Harris, Mozaffarian, et al., 2009)

EPIDEMIOLOGY SHOWS BENEFITS OF FISH AND OMEGA-3 CONSUMPTION

For many years, scientists were puzzled by the fact that heart disease among Greenland Eskimos was extremely rare despite their consumption of a high-fat, high-cholesterol diet. Research revealed that the Eskimos were protected by diets largely based on seals, whales, and fish, all of which provide high intakes of omega-3 polyunsaturated fatty acids, especially EPA and DHA. (Bang & Dyerberg, 1973)

Later epidemiological studies in many countries, including the United States, demonstrated that even people who eat moderate amounts of fish get some degree of protection against heart disease.

In the Physicians Health Study, researchers identified 94 men "in whom sudden death was the first manifestation of cardiovascular disease." These men were matched with 184 controls, and blood levels of long chain omega-3 fatty acids (also called n-3 fatty acids) were assessed. Men with low blood levels of omega-3 fatty acids were three to five times more likely to suffer sudden death from heart disease than men with higher blood levels of omega-3 fatty acids. The researchers suggest that omega-3 fatty acids may protect against death from heart disease by decreasing the heart's tendency to arrhythmia. (Albert, Campos, et al., 2002)

In the Nurses Health Study, fish consumption was found to be associated with a lower risk of coronary heart disease (CHD) and a lower rate of all-cause mortality during 16 years of follow-up. The protective effect was stronger for fatal CHD than for nonfatal myocardial infarction (MI). The protective association with omega-3 fatty acid intake was similar to that for fish intake. "This finding is consistent with the hypothesis that omega-3 fatty acids are the active agent primarily responsible for the apparent protective effect of fish." (Hu, Bronner, et al., 2002)

An earlier report from the Nurses Health Study found that fish consumption lowered the risk of stroke. The researchers found that the "risk of thrombotic infarction [stroke] was significantly reduced by 48 percent among women who ate fish 2 to 4 times per week." (Iso, Rexrode, et al., 2001)

Among the Inuit of northern Quebec, the traditional diet is very high in long-chain omega-3 fatty acids from fish, whales, and seals, and the Inuit have traditionally had low rates of heart disease. In modern times, the Inuit diet may be shifting away from traditional patterns, but the Inuit still have a very low rate of heart disease, and the researchers attribute this protective effect to a diet rich in omega-3 fatty acids. Average consumption of marine products in this population was 131 grams per day (about 4.8 ounces). This corresponds to an intake of about 2 grams of EPA and DHA per day. (Dewailly, Blanchet, et al., 2001)

In the Netherlands, people over the age of 65 were followed for 17 years and the relationship between fish consumption and heart disease was evaluated. About 60 percent of this elderly cohort ate fish and 40 percent did not. Those who ate fish had a significantly lower rate of mortality from heart disease. (Kromhout, Feskens, et al., 1995)

In a case-control study of 334 people with primary cardiac arrest and 493 controls, researchers in the Cardiovascular Health Research Unit at the University of Washington found seafood consumption to be protective. People who ate even one fatty fish or seafood meal per week had a 50 percent reduced risk of cardiac arrest compared to people who ate none. People with higher levels of omega-3 fatty acids in their red blood cell membranes (five percent compared to three percent) had a 70 percent lower risk of cardiac arrest. The researchers suggested that an increase in membrane levels of omega-3 fatty acids in some way lowers the subjects' vulnerability to arrhythmia or ventricular fibrillation. (Siscovick, Raghunathan, et al., 1995)

In the Physicians Health Study, researchers from Brigham and Women's Hospital and Harvard Medical School found that doctors who consumed fish at least once a week had half the risk of sudden cardiac death compared to doctors who ate fish less than once a month. The researchers noted that there are about 250,000 sudden cardiac deaths every year in the United States, and over half of these occur in people with no history of heart disease. Therefore, the public health impact of any intervention that could reduce that risk would be substantial. (Albert, Hennekens, et al., 1998)

In the Cardiovascular Health Study, plasma omega-3 levels were measured in 179 adults who had a fatal or nonfatal MI compared to 179 controls. The plasma samples were drawn about two years before the events. Higher plasma levels of EPA+DHA were associated with a lower risk of fatal MI. "The association of n-3 polyunsaturated fatty acids with fatal ischemic heart disease, but not with nonfatal myocardial infarction, is consistent with possible antiarrhythmic effects of these fatty acids." (Lemaitre, King, et al., 2003)

KEY CLINICAL TRIALS

Numerous studies have specifically investigated the benefits of long-chain omega-3 fatty acids given as nutritional supplements. One large intervention trial studied more than 11,000 men who had survived an MI. It examined the effects of supplements of omega-3 fatty acids or vitamin E in protecting against later events, including nonfatal MI, stroke, or death. The patients followed Mediterranean dietary habits (considered beneficial for heart health) and continued to receive appropriate medical treatment with pharmaceutical preparations during the study. The omega-3 group was given one gram of combined EPA and DHA per day, and the vitamin E group was given 300 mg per day. No effect of supplemental vitamin E was observed, but the omega-3 supplement "significantly decreased, over 3.5 years, the rate of death, non-fatal myocardial infarction, and stroke." The decrease in risk was 10 to 15 percent. This study is known as the GISSI trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). (GISSI, 1999)

In a later variation of the GISSI trial—the GISSI-HF trial—almost 3,500 patients with chronic heart failure and an equal number of controls were recruited and were given one gram daily of EPA+DHA or a placebo for about four years. In the treatment group, there was a small but significant decrease in the number of patients who died or were admitted to the hospital. The authors conclude, "A simple and safe treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care." (Tavazzi, Maggioni, et al., 2008)

In a Japanese trial (JELIS), more than 18,000 patients with high cholesterol levels were recruited and were given 1800 mg of EPA daily along with a statin, or the statin only (controls), for a period of five years. The endpoint was any major coronary events, including sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or bypass. The EPA group had 19 percent fewer coronary events than the controls. Angina and non-fatal coronary events were also lower in the EPA group. There was no difference in the rates of sudden cardiac death. (Yokoyama, Origasa, et al., 2007)

In a study of 2,033 men who had recovered from heart attacks, researchers advised one group of men to eat more fish, but allowed them to take fish oil supplements instead of fish if they preferred. Two other groups were advised to decrease total fat consumption or to increase fiber intake. Over a two-year period, the fish and fish oil group had a 29 percent reduction in risk of death compared with the groups not advised to eat fish. The authors indicated that the fish and fish oils may have reduced mortality through their favorable effects on clotting mechanisms, platelet aggregation, and ventricular fibrillation. (Burr, Fehily, et al., 1989).

In postmenopausal women, supplementation with four g of EPA and DHA (2.4 g EPA plus 1.6 g DHA) reduced triglyceride levels by 26 percent. Reductions were similar in women using hormone replace therapy (HRT) and in those not using HRT. The researchers suggest that "this approach could potentially reduce the risk of coronary heart disease by 27 percent in postmenopausal women." (Stark, Park, et al., 2000)

COST-EFFECTIVENESS OF OMEGA-3 SUPPLEMENTATION

An analysis of the cost-effectiveness of omega-3 supplementation for secondary prevention, based on the results of clinical trials in subjects who had already experienced an MI or had otherwise been diagnosed with cardiovascular disease, concluded that "omega-3 supplements are likely to improve health and lower total costs." The authors suggest that "omega-3 supplementation should be considered an important and cost-effective option for prevention of secondary cardiovascular events." (Schmier, Rachman, et al., 2006)

HOW DO OMEGA-3 FATTY ACIDS PROTECT AGAINST CARDIOVASCULAR DISEASE?

Omega-3 fatty acids have been shown to impact several key risk factors related to heart disease. Dr. Alexander Leaf and coworkers at the Harvard Medical School and Massachusetts General Hospital in Boston have examined the effects of omega-3 fatty acids in preventing arrhythmia in heart cells and have suggested that omega-3s may prevent sudden cardiac death through this mechanism. (Leaf, 2007)

Long-chain omega-3 fatty acids can have an impact on the risk of atherosclerosis through numerous mechanisms. They not only lower triglycerides, but also decrease platelet aggregation, favor dilation of the blood vessels, and decrease the tendency to thrombosis. In a review article, Dr. Artemis Simopoulos of the Center for Genetics, Nutrition and Health lists 17 separate mechanisms by which omega-3 fatty acids may have these physiological effects. In clinical trials, beneficial effects have been attributed primarily to reducing arrhythmias and reducing thrombosis in the vessels. (Simopoulos, 1999)

WHAT OTHER BENEFITS DO OMEGA-3 FATTY ACIDS HAVE?

While there is an abundance of research on the cardiovascular benefits of omega-3 fatty acids, it should also be recalled that these substances are critical to many physiological functions. Maternal levels of omega-3 fatty acids during pregnancy determine the levels present in the developing infant. The long-chain omega-3 fatty acid DHA is particularly critical in supporting infant growth and development, and DHA levels in newborns are correlated with birth weight, birth length, and head circumference. It has been suggested that women and their infants may benefit if the mother is supplemented with DHA during pregnancy. The ratio of omega-3 to omega-6 fatty acids in the total diet is also important, and many scientists believe current diets in the United States are too low in omega-3 fatty acids, compared to the relatively high intakes of omega-6 fatty acids. (Hornstra, 2000)

Long-chain omega-3 fatty acids are present in breast milk and have been related to improved visual acuity and cognitive function in infants. (Birch, Garfield, et al., 2000) In many countries, including the United States, omega-3 fatty acids are added to infant formula.

In older adults, low blood levels of omega-3 fatty acids have been linked to cognitive impairment and dementia. (Conquer, Tierney, et al., 2000)

COST OF 500 to 600 mg OMEGA-3 EPA AND DHA

Long-chain omega-3 fatty acids are naturally found in fish, especially in fatty fish such as salmon, but also occur in smaller amounts in other types of fish

and seafood. These nutrients (EPA and DHA) are also available in dietary supplements. The following table shows relative costs, based on the amount of fish or supplements needed to provide roughly 500 or 600 mg of long-chain omega-3 fatty acids. The amount of omega-3 in fresh salmon is based on data provided on the website of the National Fisheries Institute, while the amounts in other products are based on information provided in nutrition labeling. Costs are based on prices in supermarkets or drug stores in the upper Midwest early in 2012.

COST OF 500 TO 600 mg EPA AND DHA

PRODUCT	COST
Brand A fish oil capsules, two capsules providing 600 mg EPA and DHA	$ 0.26
Brand B fish oil capsules, two capsules providing 600 mg EPA and DHA	$ 0.40
Canned red salmon, one ounce providing about 500 mg EPA and DHA	$ 0.53
Fresh salmon, one ounce providing about 600 mg EPA and DHA	$ 0.56
Canned tuna, eight ounces providing about 500 mg EPA and DHA	$ 3.27

Bottom Line

An abundance of scientific evidence suggests that most American diets are very low in long-chain omega-3 fatty acids EPA and DHA and that increasing intakes could potentially reduce the risk of cardiovascular disease. Eating more fish is an excellent way to increase the consumption of omega-3 fatty acids, but only a few varieties of fish are rich in these compounds. Another way to increase consumption is to use a dietary supplement providing these critical nutrients.

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Benefits of Increased Fiber Intake

Diets that are naturally high in fiber are those that contain generous amounts of whole grains, fruits, and vegetables. The Food and Drug Administration (FDA) has concluded that diets low in fat and naturally high in *dietary fiber* are associated with a reduced risk of cancer and has permitted a "health claim" that can appear in labeling for foods that are good sources of dietary fiber. (FDA, 1993a) Dietary fiber consists of the bulky, non-digestible components of plant foods, such as the cellulose in plant cell walls. An example of a claim permitted under this regulation is:

> "Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a disease associated with many factors."

FDA has also concluded that diets low in fat and naturally high in *soluble fiber* are associated with a reduced risk of heart disease. (FDA, 1993b) Soluble fiber has been shown to lower LDL cholesterol ("bad cholesterol"), and this is the mechanism by which it is believed to lower heart disease. Based on these effects, FDA permits "health claims" on the labels of foods that are good sources of naturally occurring soluble fiber. An example of a claim permitted under this regulation is:

> "Development of heart disease depends on many factors. Eating a diet low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber may lower blood cholesterol levels and reduce your risk of heart disease."

In addition, FDA permits health claims for some specific soluble fibers that have been shown to lower LDL cholesterol, and these claims are permitted for foods and dietary supplements to which these soluble fiber ingredients have been added. These include soluble fibers from oats, barley, or psyllium. (FDA, 1997)

POSITION OF THE ACADEMY OF NUTRITION AND DIETETICS

The Academy of Nutrition and Dietetics (formerly the American Dietetic Association) urges people to "consume adequate amounts of dietary fiber from a variety of plant foods." (Slavin, 2008) A position paper issued in 2008 describes the benefits of fiber, as summarized in the following section.

Adequate Intakes (AIs) for fiber were established by the Institute of Medicine in 2002, and these are based on the amounts of total fiber believed to protect against heart disease and also to reduce the risk of diabetes. Recommended levels of fiber intake may also help support regularity (avoid constipation), protect against diverticular disease, reduce blood glucose and lipid levels, and contribute to satiety.

An AI of total fiber is suggested to be about 14 grams per 1,000 Kilocalories in the diet, which works out to about 25 grams per day for women and about 38 grams per day for men. Usual fiber intakes in the U.S. are much lower than this—about 15 grams per day.

"Based on current data, dietary fiber intake from whole foods or supplements may lower blood pressure, improve serum lipid levels, and reduce indicators of inflammation. Benefits may occur with intakes of 12 to 33 g fiber per day from whole foods or up to 42.5 g fiber per day from supplements." (Slavin, 2008)

"Many fiber sources, including cereal bran, psyllium seed husk, methylcellulose, and a mixed high-fiber diet, increase stool weight, thereby promoting normal laxation [regularity]." Also, there is some evidence that higher fiber intakes from foods or supplements may also have some benefit in weight loss. They may increase satiety and slow the rate of energy and nutrient absorption, leading to lower blood glucose and lipid levels following a meal.

The position statement concludes: "Many of the diseases of public health significance—obesity, cardiovascular disease, and type 2 diabetes—as well as the less prevalent but no less significant diseases of colonic diverticulosis and constipation can be prevented or treated by increasing the amounts and varieties of fiber-containing foods." (Slavin, 2008)

Bottom Line

American diets are typically low in dietary fiber and soluble fiber, food components that are associated with a variety of health benefits, including potentially helping protect against some cancers and cardiovascular disease. Increasing fiber intake through dietary improvement would be very beneficial, and fiber supplements may be of benefit to people whose diets remain low in these critical compounds.

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ABOUT THE COUNCIL FOR RESPONSIBLE NUTRITION

The Council for Responsible Nutrition (CRN), founded in 1973, is based in Washington, D.C., and is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN member companies produce a large portion of the dietary supplements marketed in the United States and globally. The companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. They also market products through natural food stores and mainstream direct selling companies. In addition to complying with a host of Federal and state regulations governing dietary supplements, the manufacturer and supplier members also agree to adhere to voluntary guidelines for manufacturing and marketing and agree to comply with CRN's Code of Ethics. CRN has approximately 100 member companies, including voting and associate members.

CRN's mission is to sustain and enhance a climate for its member companies to responsibly develop, manufacture and market dietary supplements and nutritional ingredients. CRN provides its member companies with expertise and action in the areas of scientific and regulatory affairs, government affairs, media outreach and communications, and international affairs. CRN takes a leadership role to advocate for public policy based on sound science that permits consumers to have access to a wide variety of high quality, safe and beneficial dietary supplements.

CRN's scientific and regulatory staff includes recognized experts in nutrition and a practitioner of integrative medicine. John Hathcock, Ph.D., Senior Vice President, Scientific & International Affairs, has decades of experience in evaluating the safety of nutrients and other dietary ingredients, having been a professor at Iowa State University and a senior scientist at the Food and Drug Administration before joining CRN in 1995. Douglas "Duffy" MacKay, N.D., Vice President, Scientific & Regulatory Affairs, is a licensed Naturopathic Doctor who has served as a medical consultant to companies in the dietary supplement industry and who also has hands-on experience as a practitioner of integrative medicine. Taylor Wallace, Ph.D., FACN, Senior Director, Scientific & Regulatory Affairs, earned his graduate degrees from The Ohio State University, was formerly with the International Life Sciences Institute, and is an active author and reviewer of articles relating to nutrition. Members of the CRN science staff, as well as Andrew Shao, Ph.D., former Senior Vice President, Scientific & Regulatory Affairs, reviewed this paper and provided valuable assistance and commentary.

Additional information about CRN is available on the website at www.crnusa.org.

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