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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