

costs. However, it is our understanding that the current costs, availability, and palatability of wheat substitutes in countries where 20 ppm is the accepted threshold are not different from those of products sold in northern Europe, where 200 ppm is the recommended daily gluten intake. Therefore, we see no advantage to embracing gluten limits that may harm those populations that consume higher amounts of wheat substitutes than the Finnish population (3). The fact that the Food and Drug Administration recently defined gluten-free products as those products that contain <20 ppm gluten (4) is testimony to the validity and feasibility of this threshold. This has been a noteworthy accomplishment, as testified by national newspaper editorials, including the *Wall Street Journal* (2). To conclude, although we agree that the findings of our pilot study should be confirmed by clinical trials in a larger number of subjects, the findings of our study will contribute to the improvement in the quality of life of celiac disease patients and their families.

AF has economic interests in Alba Therapeutics, a company that conducts research on the treatment of autoimmune diseases, including type 1 diabetes and celiac disease. CC serves as a consultant for Biaglut and Schär, companies that produce gluten-free products.

Carlo Catassi
Alessio Fasano

Center for Celiac Research
20 Penn Street
University of Maryland School of Medicine
Baltimore, MD 21201
E-mail: afasano@mbrc.umaryland.edu

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Evidence-based medicine and vitamin E supplementation

Dear Sir:

In a recent editorial in the *Journal*, Traber (1) recommended vitamin E supplementation for most adults in the United States. The logic behind her recommendation was as follows. First, Wright et al (2) reported in the same issue of the *Journal* that the lowest overall risk for mortality in the 19-y follow-up of the Alpha-Tocopherol Beta-Carotene (ATBC) Study occurred at serum vitamin E concentrations of 13–14 mg/L, and Traber labels that as an optimal concentration for reducing the risk of chronic disease. Second, 75% of men in the United States have serum vitamin E concentrations of <14.6 mg/L, which suggests widespread vitamin E deficiency in her

opinion. Third, “given the dietary habits of most Americans,” “optimal” concentrations of serum vitamin E are achievable only with vitamin E supplements (1).

We believe that Traber’s recommendation for vitamin E supplementation in the general population is unjustified. Inferring cause and effect and making such broad public health recommendations for supplements on the basis of observational data violate the established principles of evidence-based medicine. In fact, her recommendations are not aligned with those based on systematic reviews of large clinical trials of vitamin E supplementation, which do not recommend vitamin E supplement use (3) and discourage the use of high-dose vitamin E supplements (4).

The risks of recommending dietary supplements on the basis of observational studies are well documented. The classic example is the divergence between the finding of an inverse association between serum concentrations of β -carotene and lung cancer risk and the finding of increased risk of lung cancer in subjects assigned β -carotene supplements in controlled clinical trials (as reviewed in reference 5). The lesson of the β -carotene example is that the unreliability of drawing strong cause-and-effect conclusions from correlation data has evolved into an important teaching example for students of epidemiology.

Recommendations for vitamin E supplementation are not supported by findings from the trial period of the ATBC Study. In subjects in the lowest quintile of plasma α -tocopherol concentration, the similar mortality in the groups with supplement intakes of 50 and 0 mg α -tocopherol ($n = 1628$ and 1610, respectively; see Table 3 in reference 2) refutes the notions that a low α -tocopherol intake—ie, 9.4 mg/d—is the specific cause of high mortality and that correction of this “deficiency” with 50 mg α -tocopherol/d would affect mortality in this high-risk quintile.

Other clinical outcomes reported from the ATBC Study show that supplementation with 50 mg vitamin E/d has divergent relations with the incidence of pneumonia and the common cold. Although vitamin E showed no overall benefit against pneumonia, the age at smoking initiation significantly modified the effect of vitamin E, so that it was harmful or beneficial, depending on this characteristic in each participant (6). The effect of vitamin E on common cold incidence was significantly modified by smoking level at baseline, age, and residential neighborhood (7). It is worth noting that, in both of these cases, smoking-related variables modified the effect of vitamin E. Although it is not reasonable to assume that the factors that modify the effect of vitamin E on respiratory infections identically modify the effect of vitamin E on cancer, coronary heart disease, or total mortality, the possibility that the effect on these latter outcomes is also modified by various factors should not be ignored. Because of this heterogeneity in the effects of vitamin E, it is possible that supplementation of a wide population may cause harm to some restricted population groups, as indicated by a recent meta-analysis (4).

These results highlight the misconception that supplementing to correct “deficiencies” of a single micronutrient is an inaccurate interpretation of the relation between nutritional markers and the risk of chronic disease in epidemiologic studies. Most blood concentrations of micronutrients, including antioxidants, are collinear. High concentrations of antioxidants reflect an antiatherogenic diet (lower in fat and saturated fat and higher in fruit, vegetables, nuts, whole grains, and low-fat dairy), which also has beneficial effects on traditional cardiovascular disease risk factors, including blood pressure, lipid concentrations, and glucose metabolism. Supplementing with vitamin E has no effect on traditional cardiovascular disease risk factors and does not lower the risk of chronic disease by other proposed mechanisms, such as by reducing oxidative stress.



Traber (1) argued that 93% of men and 96% of women in the United States do not consume the recommended amount of vitamin E. However, the current US recommendation for vitamin E is based on peroxide-dependent erythrocyte hemolysis, a surrogate endpoint that has not been validated against any clinically relevant outcome (8, 9). Furthermore, according to the current nutritional recommendations, there is no evidence that, among free-living persons, dietary vitamin E intake may meaningfully correlate with plasma α -tocopherol concentrations (8). We are not aware of any reasonable evidence indicating that 93% of men and 96% of women in the United States may suffer any harmful effect on health because of their "low" vitamin E intake.

In our opinion, the attitude toward vitamin E supplementation should be based on randomized controlled trials, which have not shown a benefit in preventing or treating chronic diseases, and not on observational studies, which are highly susceptible to biases that may remain even after statistical adjustment for confounders (5, 10). Although it is possible that some population groups may benefit from vitamin E supplementation, the evidence is so equivocal that it is inappropriate to make the sweeping recommendation for vitamin E supplementation in the United States that Traber makes. Implying health benefits of supplementation in the general population is contrary to the evidence; moreover, it puts people at risk if excess use occurs and will benefit only the industry that produces, promotes, and protects the continued sale of supplement products.

Neither author had a personal or financial conflict of interest with respect to the study by Wright et al or the editorial by Traber.

Harri Hemilä

Department of Public Health, POB 41
University of Helsinki
Helsinki FIN-00014
Finland
E-mail: harri.hemila@helsinki.fi

Edgar R Miller III

Johns Hopkins University School of Medicine
Baltimore, MD 21205

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Reply to H Hemilä and ER Miller III

Dear Sir:

We appreciate the earlier editorial by Traber (1) and the current comments from Hemilä and Miller. In our study, we found that higher prerandomization serum concentrations of α -tocopherol were associated with significantly lower total and cause-specific mortality in men participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (2). Only 10% of participants reported vitamin E supplement use before randomization, and the exclusion of these men from our analyses did not alter the observed relations. This indicates that pretrial serum vitamin E concentrations in the ATBC Study population were achieved primarily through dietary intakes and other host factors known to affect circulating vitamin E concentrations (eg, age, body mass index, and serum cholesterol) and not through vitamin E supplement use. It is important to note that neither the use of supplemental vitamin E before the trial nor the trial intervention itself (50 mg *all-rac*- α -tocopheryl acetate) was the focus of our report.

As Traber (1) pointed out in her editorial, we observed the lowest overall mortality at serum α -tocopherol concentrations of \approx 13 mg/L (14 mg/L for cardiovascular disease mortality; see Figure 2 in reference 2). It should be emphasized that mortality did not diminish further at higher concentrations: relative mortality estimates drifted back toward unity (relative risk = 1) as blood concentrations rose beyond 13–14 mg/L. The precise vitamin E intake required to achieve this "optimum" serum concentration cannot be inferred from our study, however. Even though men in the fourth quintile of serum vitamin E (ie, 12.2–13.5 mg/L) consumed an average of 13.3 mg α -tocopherol/d (see Table 1 in reference 2), that mean value reflected a wide range of intakes (5.7–29.3 mg/d) within the specific serum quintile. This finding highlights the multifactorial determinants of serum α -tocopherol concentrations, including dietary intake, absorption, lipoprotein concentrations, blood transport, tissue uptake, oxidative stress load, and the genotypic variants that likely affect these specific contributory phenotypes. Carefully controlled feeding studies can help shed light on the amounts of vitamin E that need to be ingested to achieve particular blood concentrations. In this regard, however, studies have made clear that a range of serum concentrations can result from any single daily dietary intake and, conversely, that a range of intakes can lead to a single target blood or tissue concentration. Finally, it should be reemphasized that any "optimal" serum α -tocopherol value that we observed with respect to overall mortality among Finnish male smokers may not be applicable in other groups, including nonsmokers, women, and ethnically diverse populations. This question should be addressed in other studies.

Traber correctly highlights the possibility that dietary recommendations based on preventing overt deficiency symptoms—peroxide-dependent erythrocyte hemolysis, in the case of vitamin E—may



differ from recommendations based on the prevention of chronic disease or death. As she notes, the Recommended Dietary Allowance (RDA) for vitamin E is 15 mg α -tocopherol/d for men and women >18 y old, and this amount is based on experiments conducted almost a half-century ago in men who were experimentally vitamin E depleted (3). Overt vitamin E deficiency is extremely rare in the United States, despite the fact that most US men and women are not meeting the dietary recommendation for vitamin E. Again, additional research aimed at clarifying the optimal serum concentrations of vitamin E for chronic disease prevention in multiple populations, as well as the amount of dietary vitamin E required to achieve those concentrations, will be informative. As more data accumulate, the RDAs for vitamin E may need to be reevaluated with respect to important public health endpoints such as chronic disease risk and mortality and not only in relation to the avoidance of deficiency states.

We agree with Hemilä and Miller that populationwide vitamin E supplementation is not warranted at this time, according to the available research. This body of evidence includes both a demonstrated lack of efficacy for overall mortality in several supplementation trials and the elevated mortality suggested—but not universally accepted (4)—by a recent meta-analysis for high-dose vitamin E supplementation (5). We explicitly state in our report, “Because supplemental vitamin E has not been shown to reduce mortality in randomized trials, efforts to improve vitamin E status through dietary means (eg, through increasing consumption of foods rich in vitamin E, including nuts, seeds, whole grains, and dark-green leafy vegetables) may be warranted, particularly if future prospective studies show similar serum mortality associations in diverse populations, including nonsmokers” (2). Although, as Traber suggests, vitamin E-rich food sources have traditionally been of limited popularity in the American diet, we support dietary modification rather than supplementation at this time.

Results from well-designed prospective cohort studies have made, and will continue to make, substantial contributions to our knowledge regarding micronutrient-disease relations, even when the research findings appear to contradict those from controlled trials. A case in point is the diametric opposition of the conclusions of the original ATBC Study findings for β -carotene and lung cancer (6) to the findings from most case-control and cohort studies available at the time (7). We must remain cognizant of the fact that observational studies and clinical trials often address different questions. For example, trials typically test the efficacy of single-nutrient supplements, at various dosages and administered over several years, whereas observational studies examine the associations between habitual dietary intake (or serum concentrations) of nutrients that are derived primarily from foods, which contain many other, potentially anticarcinogenic substances. Whereas it is true that observational studies are susceptible to confounding and measurement error and that trials are typically free from such biases, we believe that recommendations regarding supplement use should be based on the totality of evidence provided by basic experimental and epidemiologic studies, as well as by randomized controlled trials.

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Margaret E Wright

Department of Pathology (MC 847)
College of Medicine
University of Illinois at Chicago
840 South Wood Street, Room 130
Chicago, IL 60612
E-mail: mewright@uic.edu

*Karla A Lawson
Stephanie J Weinstein
Demetrius Albanes*

Nutritional Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Bethesda, MD

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Reply to H Hemilä and ER Miller III

Dear Sir:

My recent editorial in the Journal (1) emphasized the difficulty in setting the daily α -tocopherol requirement and was not intended as advocacy for high-dose vitamin E supplementation. Evidence-based medicine is not based only on randomized clinical trials (RCTs) and meta-analyses but also takes into account all relevant evidence. The scientific evidence that vitamin E is essential for human health is overwhelming. α -Tocopherol insufficiency results in a sensory neuropathy, which has been documented in patients with ataxia and vitamin E deficiency (AVED). Symptoms are secondary to a genetic defect in the hepatic α -tocopherol transfer protein (α -TTP) (2). The plasma α -tocopherol concentrations of persons with AVED are one-tenth of normal, and their nerves become α -tocopherol-depleted before symptom onset (3); α -tocopherol supplements reverse or halt symptom progression (2). Thus, the nervous system is vulnerable to inadequate α -tocopherol status.

Hemilä and Miller refer to peroxide-dependent erythrocyte hemolysis as “a surrogate endpoint that has not been validated against any clinically relevant outcome.” However, more than 30 y ago, this test was used clinically to show that children with cystic fibrosis were vitamin E deficient (4). These children absorbed vitamin E poorly and thus had low plasma α -tocopherol concentrations, anemia, and increased erythrocyte turnover—symptoms that were reversed by α -tocopherol supplements (4). The Food and Nutrition Board (FNB) used peroxide-dependent erythrocyte hemolysis data to set the current recommended dietary allowance (RDA)—15 mg



α -tocopherol (5)—which is lower than the “current US recommendation for vitamin E” cited by Hemilä and Miller. The US RDA uses the daily value (DV), which is defined from the 1968 FNB recommendation (also based on erythrocyte hemolysis) of 30 IU (30 mg *dl*- α -tocopheryl acetate); %DV is used on food labels.

Hemilä and Miller stated, “Most blood concentrations of micronutrients, including antioxidants, are collinear.” This statement is incorrect with respect to vitamin E. An appreciation of the complex pharmacokinetics of α -tocopherol is essential to understanding its disposition and human vitamin E status. High plasma α -tocopherol concentrations may reflect high α -tocopherol intakes. However, hyperlipidemia also elevates plasma α -tocopherol, because α -tocopherol concentrations are collinear with circulating lipids. In normolipidemic subjects, low plasma α -tocopherol concentrations reflect inadequate vitamin E intakes. When inadequate amounts of α -tocopherol are consumed, plasma concentrations are maintained by α -TTP, whereas peripheral tissue α -tocopherol depletion occurs (3). To assess vitamin E status, one should measure plasma α -tocopherol and lipid concentrations and, ideally, tissue α -tocopherol concentrations.

α -Tocopherol is not found in most high-antioxidant foods, such as fruit and vegetables. Low-fat diets decrease α -tocopherol intakes because the fat-soluble vitamin is largely present in high-fat foods. Therefore, substantial changes in the kinds of foods Americans eat are needed for them to obtain 15 mg α -tocopherol/d from dietary sources, such as seeds, nuts, spinach, and safflower oil.

What is the downside to consuming a less-than-optimal α -tocopherol intake? It is difficult to determine, because it takes decades for symptoms of suboptimal vitamin E status to become readily apparent. It took ≈ 40 y for symptoms to be detectable in a patient with chronic fat malabsorption and α -tocopherol deficiency (7). Such a delay in the first appearance of symptoms shows the fallacy of concluding, after an observation of only a relatively short time (eg, 5 y), that there is no harm to inadequate vitamin E intakes.

The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study provides an interesting contrast. Analysis of baseline serum α -tocopherol concentrations in ≈ 29 000 men, nearly one-half of whom are now dead, showed a significant correlation between high serum α -tocopherol status and lower chronic disease mortality (8), which suggested that long-term dietary habits that provide higher α -tocopherol intakes are beneficial. In contrast, supplementation for only 5–8 y with 50 mg *all-rac*- α -tocopheryl acetate (22 mg 2-*R*- α -tocopherol or ≈ 1.5 times the RDA) showed no such relation (8). Given that clinical symptoms take decades to appear in humans with various chronic diseases, the effects of correcting suboptimal vitamin E intakes cannot be assessed by using RCTs that last only years, rather than decades. Therefore, the suggestion by Hemilä and Miller to carry out RCTs seems impractical, if not unethical, given the potential for inadequate α -tocopherol intakes in the “placebo” group to deplete tissue, especially nervous system tissue, of α -tocopherol.

Hemilä and Miller contend that high-dose α -tocopherol is dangerous, but they specify no mechanism for any adverse effect. Miller et al (9), in a meta-analysis analyzing the relation between dose and mortality, found a benefit of $\approx 4\%$ when vitamin E supplements were provided in the range of dietary requirements. This outcome contradicts their widely publicized claim of vitamin E supplement harm, a claim that was criticized in many letters to the editor in the journal that published the report of Miller et al (see the July 2005 issue of *Annals of Internal Medicine*). A systematic review sponsored by the National Institutes of Health concluded that the evidence was insufficient to prove the “presence or absence of benefits” for vitamin E supplements (usually ≥ 400 IU) for the prevention of cancer or chronic disease (10). The Cache County Study found that vitamin E

supplements had “no effect” on mortality, but their conclusion was based on a combination of outcomes “[in which] increased mortality was observed in subjects with severe cardiovascular disease and a possible protective effect in those without” (11). This latter finding is of interest because the Women’s Health Study, a primary prevention trial with vitamin E supplements (600 IU every other day for 10 y) in ≈ 40 000 healthy women, concluded that vitamin E had no effect on the occurrence of heart disease or cancer (12). However, in subgroup analysis, vitamin E supplements decreased cardiac mortality by 49% in women >65 y old—ie, those who are at greater risk of heart disease than are younger women (12). Taken together, these studies suggest that, in healthy persons, a generous α -tocopherol intake for a prolonged period is beneficial, not harmful. Thus, intakes in the range of the RDA—15 mg α -tocopherol/d—obtained from a healthy diet, from a multivitamin, or as an α -tocopherol supplement, appear to me to be a prudent public health recommendation.

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Maret G Traber

Linus Pauling Institute
Oregon State University
Corvallis, OR 97331-6512
E-mail: maret.traber@oregonstate.edu

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