

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.

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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.

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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 ≈ 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