



Since November 10, 2004, vitamin E has been subject to unfair attack based on a single poorly designed study, which misleadingly claimed that high-dose (≥ 400 IU per day) vitamin E supplements may increase all-cause mortality and should be avoided (Miller ER 3rd et al. "Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortal-

plements on total mortality in humans. This means that the study was not a clinical trial generating new results, but old data of prior studies were pooled and statistically re-analyzed. The researchers combined the data of a total of 135,967 participants, who were randomly assigned to take vitamin E (in amounts ranging from 16.5 to 2,000 IU daily) or a placebo for at least one year. Most of the patients were seriously ill and suffered from one or more chronic diseases, such as heart disease, diabetes, Parkinson's disease, Alzheimer's disease or kidney failure or were at high risk of developing heart disease. In addition most of the subjects were more than 60 years old.

A good meta-analysis is a useful tool but its quality directly depends on the quality of the included studies and their comparability in terms of study design and characteristics of patients. The poor comparability and the methodology used are at the heart of the problems of the meta-analysis from Miller et al—it was even criticized by independent statisticians outside the vitamin E community.

Pooling of Insignificant Data to Reach Statistical Significance

Study data, which on their own did not reach statistical significance, were pooled together to achieve a low significance. It is noteworthy that in the overall analysis, the study found no effect on mortality. Only in the dose-response analysis a significant effect on total mortality was found at intakes beyond 900 IU of sick individuals or those at high risk of disease. This result was based on eight studies using dosages of 500 IU or more. However, these studies showed no significant effect on total mortality when evaluated individually. In addition, among these was only one large study, the MRC trial ("MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomized placebo-controlled trial." *Lancet*, July 6, 2002;360(9326):23-33) with 20,536 participants, who received 660 IU of vitamin E and showed a slight but not significant increase in risk. The

Reviewing Vitamin E

Journalists love bad news and unwarrantedly discredit the safety of vitamin E.

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ity." *Ann Intern Med*. November 10, 2004; Epub ahead of print). The study reported that adults who took supplements of 400 IU/day or more were 6% more likely to die from any cause than those who did not take vitamin supplements. Thereupon several articles luridly reported, "Vitamin E increases death." However, this was not the outcome proven by the study, and it stands in total contrast to the hundreds of peer-reviewed human studies showing its safety and efficacy, which lead to the conclusion of the U.S. Institute of Medicine that vitamin E is safe at levels as high as 1500 IU per day. To date, numerous voices have emerged from the medical and nutritional community to criticize the study and corroborate the safety and health benefits of vitamin E. In fact, The Council of Responsible Nutrition (CRN), Washington, D.C., officially stated, "Vitamin E is safe and offers many health benefits. Numerous clinical studies support vitamin E's role in cardiovascular health, immune function, and antioxidant protection." But what is the real story behind the trouble? Is there cause for real concern? Or is this an alarming tempest in the teapot caused by scientists and journalists looking for publicity?

The meta-analysis of 19 clinical studies investigated a potential dose response relationship of vitamin E sup-

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other seven studies were small with 176 to a maximum 2002 participants per study.

Arbitrary Study Selection

The trial selection process was criticized as a large design flaw due to the applied exclusion criteria. The researchers claimed to have identified 36 randomized, controlled trials with follow-up longer than one year. But 12 of them were excluded because there were fewer than 10 deaths. Unfortunately, they gave no convincing explanation for this criterion. Therefore one might assume that the exclusion was done for the purpose of not jeopardizing the marginal significance of the negative results.

Combination of Differing Study Designs

The meta-analysis combined studies that were statistically incompatible due to the varying quality of design. For example, there were patients with various degrees of

medical conditions—from healthy to seriously ill; they were taking of other high-dose vitamin and mineral supplements beside vitamin E, and probably multiple prescription drugs; and there was no consideration given to the types of vitamin E used, whether natural or synthetic, and what effects they can have on the body. However, what most likely distorted the results of the study were the other high dosage supplements, especially vitamin C, beta-carotene, zinc and selenium.

Arbitrary Definition of “Low-Dose” and “High-Dose” Vitamin E

Based on this meta-analysis, there seems to be a possibility that high doses beyond 900 IU per day of vitamin E supplements are unfavorable in sick individuals or those at high risk of disease. But the researchers arbitrarily selected 400 IU as the line between “low-dose” and “high-dose.” As a consequence, the previ-

ously mentioned 900 IU dose was used to draw the conclusion that “high-dosage vitamin E (≥ 400 IU/day) showed increased risk for all-cause mortality.” It is important to know that there were only two studies at 400 IU, the HOPE study [(Yusuf S et al. “Vitamin E supplementation and cardiovascular events in high-risk patients.” “The Heart Outcomes Prevention Evaluation Study Investigators.” *N Engl J Med.*, January 20, 2000;342(3):154-60; and the AREDS study (Age-related Eye Disease Study Research Group). “A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta-carotene for age-related cataract and vision loss: AREDS report no. 9.” *Arch Ophthalmol.* October, 2001;119(10):1439-52)]. The first clearly showed no effect and the AREDS study found no significant increase on total mortality. The PPS study (Greenberg ER et al. “A clinical trial of antioxidant

vitamins to prevent colorectal adenoma." Polyp Prevention Study Group. *N Engl J Med*. July 21, 1994;331(3):141-7) was the only one using 440 IU and even showed a significant decrease in total mortality in the vitamin E group. Hence, the fast reader may get the unproven impression that 400 IU per day of vitamin E is an unfavorable dose, which is definitely not supported by the meta-analysis.

Omission of Hundreds of Clinical Studies Supporting the Safety of Vitamin E

The general health risk of too much vitamin E is low (Kappus H and Diplock AT. "Tolerance and safety of vitamin E: A toxicological position report." *Free Radic Biol Med*, 1992;13:55-74; Dietary Supplement Fact Sheet on Vitamin E. National Institutes of Health (NIH), Office of Dietary Supplements (ODS), http://ods.od.nih.gov/factsheets/VitaminE_pf.asp). And, there are literally hundreds of peer-reviewed scientific studies and references supporting the safety and health benefits of vitamin E. But the researchers of the meta-analysis neither discussed this large body of scientific evidence nor included it in their final conclusions.

The U.S. IOM has set an upper tolerable intake level for vitamin E at 1000 mg (1500 IU) per day for any form of supplementary vitamin E (U.S. Department of Agriculture (USDA), Agricultural Research Service (ARS), 2004. USDA National Nutrient Database for Standard Reference, Release 16-1. Nutrient Data Laboratory Home Page, <http://www.nal.usda.gov/fnic/food-comp>).

Appropriate Generalization of the Whole Population

Although the researchers themselves admitted the limitations of their results when they stated, "High-dosage trials (≥ 400 IU per day) were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain," they nevertheless draw a conclusion for the whole population, including younger and healthy persons.

Summary

In summary, we have to agree with John Hathcock, Ph.D., vice president, scientific and international affairs, CRN, who said, "This is an unfortunate misdirection of science in an attempt to make

something out of nothing for the sake of headlines." Clearly, before any action is taken to discourage the use of vitamin E and to confuse millions of consumers and patients, further real clinical studies are needed to prove any lack of safety. **NW**