Potential harm of vitamin E supplementation

Dear Sir:

In their recent Journal review of the safety of vitamins E and C, Hathcock et al (1) stated, "At present, the evidence is not convincing that vitamin E supplementation up to the UL [ie, the tolerable upper intake level, or 1000 mg/d] increases the risk of death due to CVD [cardiovascular disease] or other causes." However, to focus only on the effect on mortality is a very narrow view of safety.

A recent double-blind, placebo-controlled trial in 652 Dutch persons aged $\geq$ 60 y found greater severity of respiratory infections among participants supplemented with 200 mg vitamin E/d than among those not given vitamin E (3). During respiratory episodes, the presence of fever ($P = 0.009$) and the restriction of activity ($P = 0.02$) were more common, the number of symptoms was higher ($P = 0.03$), and the total illness duration was longer ($P = 0.02$) among the vitamin E–supplemented participants than among those who received no vitamin E. These findings directly point out that some population groups may be harmed by vitamin E supplementation. Thus, when assessing the safety of vitamin E, it is not reasonable to focus only on mortality when there is evidence of aggravation of a disease that is very common.

A further problem in the review by Hathcock et al is their implicit assumption that the population is homogeneous with respect to the potential harmful effects of vitamin E. In the Alpha-Tocopherol Beta-Carotene (ATBC) Study cohort, the effect of vitamin E on the risk of pneumonia was significantly modified by the age of smoking initiation ($P = 0.0007$) (4). Vitamin E was beneficial to participants who initiated smoking at later ages [relative risk (RR) of pneumonia = 0.65; 95% CI: 0.49, 0.86] but harmful, although not significantly so, to those who initiated smoking at earlier ages (RR = 1.14; 95% CI: 0.98, 1.32). In the ATBC Study, the vitamin E dose was 50 mg/d, which is substantially less than the UL of 1000 mg/d. Thus, the lack of adverse effects in one population group—in this case, those less exposed to cigarette smoking—cannot be directly extrapolated to all people, eg, those who initiated smoking at early ages.

Although there is evidence that, for short-term supplementation, vitamin E in doses of ≤1 g/d does not cause adverse effects in a large proportion of the general population (1, 2), data from trials by Graat et al (3) and Hemilä et al (4) indicate that much lower doses, eg, 50–200 mg/d of vitamin E, may be harmful to some population groups. The harm associated with such low doses should not be extrapolated directly outside of the particular groups of trial participants, but, at the same time, these 2 trials should not be disregarded in statements that there is no evidence of potential harm from vitamin E supplementation (1).

The current US nutritional recommendations consider that clinical trials of doses above the UL (ie, 1000 mg/d) should not be discouraged (2), which seems to be a justified conclusion, given that participants in controlled trials are carefully selected and followed. However, the lack of benefit in several large controlled trials (5, 6) and the evidence of harm found in some groups (3, 4) provide a sound basis for discouraging large-dose vitamin E self-supplementation in the general population, until subpopulations that might benefit from supplementation are characterized properly.

The author had no conflicts of interest with the study by Hathcock et al.

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Reply to H Hemilä

Dear Sir:

Two significant issues were raised by Hemilä—that our review (1) focused only on mortality as a measure of safety, and that substantial evidence indicates an increase in respiratory infections among some population groups at vitamin E intakes in the range of 50–200 mg/d.

Notwithstanding Hemilä's interpretation, our review did not focus on mortality alone as a safety outcome; rather, the sentence he quotes is taken from our section on specific studies dealing with this single aspect of safety. Our conclusions were based on clinical trials that individually evaluated the effects of vitamin E on ischemic heart disease, cancer, type 2 diabetes, Alzheimer disease, Parkinson's disease, or age-related macular degeneration. All of these trials included standard monitoring for potential adverse effects as assessed by standard clinical chemistries, hematologic indicators, and clinical examination. Our review noted the presence or absence of any indications of adverse effects.

With regard to the effect of vitamin E on risk of infection, we note that, although the trial of Graat et al (2) involved a large cohort and a 2×2 factorial treatment design, we consider the health assessment by self-evaluation to be a limiting factor. In contrast, we consider the professional evaluation in the trials by Meydani et al (3, 4) to be much more reliable and to justify greater confidence in the possibility that supplementation with 200 IU vitamin E/d protects against upper respiratory tract infections, particularly the common cold, in elderly nursing home residents (4). Other differences in dosage and subjects may have contributed to the different outcomes in the studies by Graat et al (2) and Meydani et al (4).

Our review was intended to be a safety evaluation based exclusively on clinical trial data. We did not encourage large-dose vitamin E self-supplementation in the ordinary population, only the apparent relative safety of vitamin E up to 1600 IU/d (equivalent to 1073 mg *RRR*-α-tocopherol). What is more important, we did state (in agreement with Hemilä), "The UL is not intended to apply to the most sensitive persons in sensitive subpopulations… but, instead, to apply to the healthy general population…." We did not review, and our conclusions do not assume, a homogenous population.

JNH is employed by a vitamin and dietary supplement trade association. AD is a consultant to a dietary supplement trade association and other associations. KK is employed by a vitamin manufacturer. None of the other authors had any personal or financial conflicts of interest.

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