Vitamin E Does Not Reduce Cognitive Decline in Healthy Elderly Women

Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166:2462–8.

Study Overview

Objective. To determine if long-term supplementation with vitamin E impacts cognitive function in older women.

Design. Substudy of the Women's Health Study (WHS), a randomized, placebo-controlled study.

Setting and participants. The WHS was originally designed to evaluate the effect of low-dose aspirin (100 mg every other day) and vitamin E supplementation (600 IU every other day) on cardiovascular and cancer outcomes compared with placebo [1]. 39,876 participants were enrolled, and eligibility criteria included age ≥ 45 years; no history of coronary artery disease, cancer, cerebrovascular disease, or other major chronic illness; and not actively using aspirin or vitamin E. For this substudy, active WHS participants aged ≥ 65 years were recruited (3184 from the vitamin E group, 3193 from the placebo group).

Intervention. Participants were evaluated at baseline (1998), in 2000, and in 2002 via a telephone interview consisting of 5 tests that measured general cognition (the Telephone Interview of Cognitive Status [TICS]), verbal memory (immediate and delayed recalls of the East Boston Memory test and delayed recall of the TICS 10-word list), and category fluency (animal naming in 1 min).

Main outcome measures. The primary outcome was a global composite score averaging performance on all cognitive tests. The secondary outcome was a composite score averaging performance on measures of verbal memory.

Main results. There was no difference in global cognitive score between the 2 groups after 4 years (mean difference in score, 0.00 [95% confidence interval {CI}, –0.04 to 0.04]). The mean difference in the rate of cognitive decline over the 4-year trial between the 2 groups was also not significant (0.02 [95% CI, –0.01 to 0.05]; $P = 0.16$). In secondary analyses, the effect of vitamin E supplementation was significantly modified by dietary vitamin E intake and physical activity. Among women with a dietary intake of vitamin E below the median (< 6.1 mg/day), the mean difference in rate of cognitive decline on the global summary score between the vitamin E and placebo groups was 0.05 (95% CI, 0.01–0.09), whereas in women with a dietary intake of vitamin E above the median (≥ 6.1 mg/day), the mean difference in rate of decline was –0.01 (95% CI, –0.06 to 0.03). Similar differences were seen when the results were stratified by physical activity. In individuals who exercised less than 1 time a week, the mean difference in the rate of cognitive decline between the vitamin E and placebo groups was 0.06 (95% CI, 0.03–0.10), while in women who exercised 1 or more times a week, the mean difference in cognitive decline was –0.04 (95% CI,–0.09 to 0.01).

Conclusion. Vitamin E supplementation did not provide cognitive benefits in healthy, older women after 4 years of follow-up.

(continued on page 77)

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(continued from page 73)

Commentary

Oxidative damage through lipid peroxidation in the brain is thought to play a major role in the development of dementia [2]. Animal studies have suggested that antioxidants, such as vitamin E, may reduce neuronal damage associated with oxidative stress and thus potentially prevent dementia. Observational studies have proposed that vitamin E supplementation may be associated with a lower risk of developing Alzheimer's disease and cognitive decline [3]; however; prior clinical trials have not found vitamin E to be protective [4]. These earlier trials were limited by either small sample size or relatively short duration.

This study by Kang et al contributes importantly to the data from these earlier studies because of its relatively large size (n = 6377) and long duration (10 years of treatment, 4 years of follow-up). As a substudy of the WHS, the study by Kang et al was designed to assess the effects of vitamin E on cognitive decline. Cognitive decline was chosen as an outcome because it is highly correlated to the risk of Alzheimer's disease. Overall, the study results were null and demonstrated no cognitive benefit with vitamin E supplementation. However, results suggested that women who were compliant with treatment, had low dietary vitamin E, were physically active, or who did not have diabetes may have received some cognitive benefits of vitamin E, but these were secondary analyses and may be chance findings.

There are several weaknesses to the study. First, the dose of vitamin E was 600 IU every other day, which was considerably less than doses evaluated in observational studies and animal models. Second, observational studies typically evaluated vitamin E content associated with foods, which is predominately γ-tocopherol as opposed to α-tocopherol found in vitamin preparations [5]. It is unclear if different forms of vitamin E might have different benefits. Although the duration of the trial was modest (4 years), this still may not be enough time to reduce the rate of cognitive decline. Additionally, some research has suggested that for vitamin E to have the most benefit, it must be initiated at much younger ages, long before any oxidative damage occurs in the brain. Finally, compliance was good but not perfect, with 25% of participants not taking their assigned medication.

Despite these limitations, the study supports prior randomized trials that have not found a clinical benefit of vitamin E on cognitive decline. In reviewing the totality of the evidence, vitamin E does not appear to be neuroprotective against dementia. It is clinically important to note that in the overall WHS, there were no differences in the number of cardiovascular events or cancer diagnoses between the intervention and control groups. In fact, there was an unexpected and largely unexplained increased risk of congestive heart failure in vitamin E users.

Applications for Clinical Practice

Despite suggested benefit of vitamin E in earlier observational studies, this randomized controlled trial supports previous clinical trials that do not demonstrate that vitamin E supplementation is efficacious at reducing cognitive decline. Because of the lack of clinical benefit of vitamin E in decreasing the risk of cardiovascular disease, cancer, and cognitive decline as well as the possibility of toxicities, providers should not be routinely recommending vitamin E to their patients.

—Review by Harvey J. Murff, MD, MPH

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