

Can vitamin supplements prevent cognitive decline and dementia in old age?^{1,2}

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Cognitive impairment and dementia are common occurrences in old age. Their effects on families and patients are irreversible, debilitating, and costly. Interventions that can prevent and effectively treat these conditions are sorely lacking. Because the risk factors for cognitive decline are multivariate, several possible strategies for prevention, including antiinflammatory therapy and the use of antioxidant supplements, could potentially be effective. A growing body of evidence supports the notion that oxidation and inflammation are part of the physiologic substrate underlying progression toward dementia. It follows that antioxidant supplementation might be effective. Considerable effort, so far with mixed results, has gone into evaluating the effects of vitamin supplements on the risk of dementia and on the progression of dementia (1–3). Two large observational cohort studies found lower risks of Alzheimer dementia in persons who had a high dietary intake of vitamin E or C than in persons who had a low intake, but the studies did not evaluate combined supplementation (2, 4). A trial in patients with Alzheimer dementia of vitamin E (2000 IU/d) and selegiline reported modest benefits from vitamin E supplementation in an analysis adjusted for baseline cognitive status, but an intention-to-treat analysis showed no benefit on the progression of dementia (5). This trial has prompted many clinicians to prescribe high-dose vitamin E therapy to dementia patients, perhaps with the view that such treatment is unlikely to do harm and may do some good in patients for whom there may be little else to do.

An important question is addressed in the article by Grodstein et al (6) in this issue of the *Journal*: whether vitamin E and vitamin C affect various cognitive domains differently. Changes in some cognitive domains may be early indicators of dementia, whereas other changes are not predictive of dementia. The ability to identify these precursors and to treat them effectively may greatly enhance our ability to prevent or even reverse progression toward dementia. The benefits for cognitive status of vitamin E and C supplements—together and separately—offered in this report are modest. However, there is a pattern of results that is encouraging. Verbal fluency scores were consistently higher in the subjects taking vitamins E and C or vitamin E alone but were lower in those taking vitamin C alone. Early changes in verbal fluency have been noted in several studies as being helpful in predicting the development of dementia. The word-list recall tests (delayed recall of a 10-word list and delayed recall of the East Boston Memory Test) in the Nurse's Health Study battery specifically evaluate short-term verbal memory. Because memory impairment is thought to be a predictor of Alzheimer dementia and is an essential criterion for diagnosing Alzheimer dementia, this is an important issue. Overall, the short-term verbal-memory test scores were consistently higher in the women who took combined


vitamin E and C supplements than in those who took either vitamin alone. Assuming a greater benefit from longer supplement use, longer duration of use should be associated with better cognitive status. Surprisingly, among those who had taken supplements for ≥ 10 y, the delayed recall scores on the East Boston Memory Test were higher for the women who took only vitamin C than for those who took vitamins E and C or vitamin E alone. No information on any dose-response relation is offered, so the implications for recommended doses are unclear.

Inflammation and oxidation are an important part of current investigations into the causes, treatment, and prevention of cognitive impairment and dementia. Elevations in C-reactive protein and corticosteroids may be reduced by supplementation with vitamins E and C (7, 8). Other work suggests that very high amounts of vitamin E alone may actually increase oxidation and that the combination of vitamins E and C may reduce the oxidative properties of high-dose α -tocopherol. Most work has focused on supplementation with vitamin E, for which the primary variant is α -tocopherol, but dietary vitamin E is primarily γ -tocopherol. Some authors have suggested that γ -tocopherol may have stronger antioxidant properties than does α -tocopherol. α -Tocopherol supplementation may actually reduce γ -tocopherol concentrations (9). γ -Tocopherol may inhibit cyclooxygenase activity and may be a more effective antioxidant and antiinflammatory agent than is α -tocopherol (10).

What are the implications of these findings for further study, for lifestyle modifications, or for treatment of elderly patients? Because the Nurse's Health Study is an observational cohort study, residual confounding cannot be ruled out. Nurses who take supplements, particularly specific single supplements such as a combination of vitamins E and C, are inevitably different in a myriad of often-unmeasured ways from women who are not nurses and who do not take supplements. Even extensive adjustments and sophisticated statistical modeling cannot completely account for this. The modest benefits reported in this study could be a result of residual confounding by lifestyle and sociodemographic differences. The inconsistency in these results with regard to duration of use and the types of cognitive function that are affected indicate that this study does not provide definitive evidence that vitamin E or C supplementation is a preventive treatment for cognitive decline. Taken alone, these results do not

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strongly support a recommendation for supplementation. The lack of information about any dose-response relation is also limiting. However, the specific effects of these supplements on memory tests, combined with the evidence from other research, provide encouraging signs that supplementation with vitamins E and C may be helpful in preventing cognitive impairment. No large-scale human studies to date have specifically addressed the influence of tocopherol variants on cognitive outcomes. If high doses of α -tocopherol actually do deplete γ -tocopherol, vitamin E supplementation (which is mainly α -tocopherol) may not prevent cognitive decline. Although there is an absence of reports of adverse effects of vitamin E supplementation in dementia patients receiving high doses, the effect of such treatment on patients whose disease is more severe may be different from the effects that may occur at early stages. High doses of vitamin E are also associated with some adverse effects, such as bleeding, that should be taken into account in any risk-benefit analysis. There is enough evidence at this point to warrant randomized trials to examine the effects of tocopherol variants alone and in combination with vitamin C in relation to cognitive outcomes. 

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