Plasma tocopherols and the risk of cognitive impairment

Dear Sir:

In a recent issue of the Journal, Ravaglia et al (1) reported that higher plasma concentrations of some forms of vitamin E were associated with a higher risk of cognitive impairment in an elderly Italian cohort. The population-based study, which aimed to investigate epidemiologic and risk factors for cognitive impairment, was properly designed and carried out, and the results obtained are interesting. However, several issues in this article, which could profoundly affect the interpretation of the data obtained, need clarification.

The first such issue is the unit of expression for plasma tocopherols and their oxidation products. Plasma (or serum) tocopherol concentration has been reported as μg, mg, μmol, or mmol per mL or L of plasma, with or without adjustment for per unit of lipid, triglyceride, or cholesterol (or all 3). Nagaya et al (2) compared various indexes for vitamin E status in health subjects and concluded that the ratio of vitamin E to total triglyceride plus total cholesterol is the simplest and most appropriate index for serum vitamin E status when serum fatty acid composition is not analyzed. On the basis of the data obtained from routine analysis, Ford et al (3) reported that ratios of vitamin E to cholesterol can be used to better define the vitamin E status of patients with disease states or disorders that are likely to increase LDL-cholesterol concentrations, such as cholestasis. They also reported that measurement of serum fatty acid composition is not analyzed. On the basis of the data obtained from routine analysis, Ford et al (3) reported that ratios of vitamin E to cholesterol can be used to better define the vitamin E status of patients with disease states or disorders that are likely to increase LDL-cholesterol concentrations, such as cholestasis. They also reported that measurement of serum fatty acid composition is not analyzed. On the basis of the data obtained from routine analysis, Ford et al (3) reported that ratios of vitamin E to cholesterol can be used to better define the vitamin E status of patients with disease states or disorders that are likely to increase LDL-cholesterol concentrations, such as cholestasis. They also reported that measurement of serum fatty acid composition is not analyzed. On the basis of the data obtained from routine analysis, Ford et al (3) reported that ratios of vitamin E to cholesterol can be used to better define the vitamin E status of patients with disease states or disorders that are likely to increase LDL-cholesterol concentrations, such as cholestasis. They also reported that measurement of serum fatty acid composition is not analyzed. On the basis of the data obtained from routine analysis, Ford et al (3) reported that ratios of vitamin E to cholesterol can be used to better define the vitamin E status of patients with disease states or disorders that are likely to increase LDL-cholesterol concentrations, such as cholestasis. They also reported that measurement of serum fatty acid composition is not analyzed.

Because serum cholesterol is significantly lower in subjects with dementia, it is not surprising that the plasma concentrations of some tocopherols as well as α-tocopheryl quinone and 5-nitro-γ-tocopherol in these persons are significantly higher than those in the other 2 groups when the data are adjusted for cholesterol. As is shown in Table 1 here, when data are expressed in mmol/L, the mean concentrations of tocopherols, α-tocopheryl quinone, and 5-nitro-γ-tocopherol (the values are obtained by multiplying cholesterol-adjusted tocopherol concentrations by the cholesterol concentrations of respective groups) in the plasma are similar among the 3 subject groups.

Another issue that needs clarification is the concentrations of α-tocopheryl quinone and 5-nitro-γ-tocopherol. α-Tocopherol is well recognized as the dominant form of plasma vitamin E. In addition, the plasma or tissue concentrations of α-tocopheryl quinone

<table>
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<th>Table 1</th>
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<td>Mean concentrations of tocopherols and their oxidation products in the plasma of persons with normal cognition, mild cognitive impairment, or dementia</td>
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<tr>
<td>Normal cognition</td>
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<tr>
<td>α-Tocopherol</td>
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<tr>
<td>β-Tocopherol</td>
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<td>γ-Tocopherol</td>
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<td>δ-Tocopherol</td>
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<tr>
<td>α-Tocopheryl quinine</td>
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<td>5-Nitro-γ-tocopherol</td>
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(4, 5) and 5-nitro-γ-tocopherol (6, 7) reported by others are only a small fraction of α-tocopherol or are not detectable. Thus, the higher plasma concentration of α-tocopheryl quinone than of α-tocopherol and the high plasma concentration of 5-nitro-γ-tocopherol reported by Ravaglia et al are a surprise. It is not clear how the plasma concentrations of α-tocopheryl quinone and 5-nitro-γ-tocopherol were measured and whether their values are presented on the same basis as the values of α-tocopherol.

The importance of plasma tocopherols in relation to other characteristics of the subjects studied is another concern. In addition to serum cholesterol, several of the characteristics of subjects, including age, sex, years of education, Mini-Mental State Examination score, current smoking, stroke, body mass index, and sedentary lifestyle, are significantly associated with cognitive status or dementia (see Table 1 in Ravaglia et al). Moreover, the concentrations of some tocopherols and their oxidation products are significantly associated with cognitive status or dementia only when the data are adjusted for cholesterol. It is not clear why Ravaglia et al singled out plasma tocopherols and their oxidation products, rather than other characteristics of subjects, as predictors for the risk of cognitive impairment.

Reports dealing with the association between the intake or status of a nutrient or dietary component and the risk of chronic diseases often command high attention. Readers and the scientific community as a whole can benefit from a thorough evaluation and cautious interpretation of data obtained through investigations.

The author had no personal or financial conflict of interest.

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**REFERENCES**


**Reply to CK Chow**

Dear Sir:

We thank Dr Chow for his comments on our study (1). Several methods have been suggested and used to adjust serum vitamin E status for serum lipids (2), but the issue has not been standardized. In preliminary analyses, we tested several possible approaches—the ratios of vitamin E to cholesterol, to triglycerides, or to cholesterol plus triglycerides—but the results did not differ significantly. Therefore, we chose the adjustment that made it easier to compare our data with the data of the studies we referenced. The fact that significant associations were found only after adjustment for cholesterol values was clearly pointed out in the discussion as a major limitation of the study. However, the plasma concentration of vitamin E varies with the amount of concurrent lipids, and lipid standardization is needed to estimate the biological status of vitamin E (3).

We entirely agree that, because of their cross-sectional design, data on prevalent dementia cannot establish whether serum vitamin E status affects cognitive function or whether cognitive function, via altered dietary habits and blood lipid carriers, affects serum vitamin E status. However, to better clarify this issue, our investigation also provided longitudinal data, which are less likely to be biased by the effect of cognitive function on nutritional status at baseline.

The table provided by Chow does not seem to take into account the fact that we provided absolute plasma concentrations of vitamin E metabolites as supplemental data (see E-Table 1 under “Supplemental data” online at http://www.ajcn.org/cgi/content/full/87/5/1306/DC1). In particular, absolute concentrations of plasma tocopherols were reported in μmol/L, but plasma α-tocopheryl-quinone and 5-nitro-γ-tocopherol were reported in nmol/L, which means that values must be multiplied by 0.001 to be expressed in μmol/L. Therefore, contrary to the statement of Chow statement and in full agreement with previous literature (4), the plasma α-tocopheryl-quinone and 5-nitro-γ-tocopherol concentrations in our cohort were much lower than the corresponding concentrations of α-tocopherol. Finally, our results did not by any means exclude the possibility that variables other than serum vitamin E status may be related to the risk of cognitive impairment. Indeed, this possibility is the reason that we included sociodemographic features, lifestyle habits, cardiovascular risk factors, and previous cognitive status in the analyses as possible confounders.

Neither of the authors had a personal or financial conflict of interest.

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**REFERENCES**


**“Adherence bias” in nutritional epidemiology**

Dear Sir:

In 1980, the Coronary Drug Project (CDP) Research Group published data to warn against the practice of analyzing randomized trial treatment group data by adherence status for evidence of the efficacy of the treatment (1). Using data from the trial’s placebo group (Table 1), they found that participants taking <80% of the per-protocol placebo dose (nonadherers) had a 5-y total mortality rate nearly 90% higher than that of participants taking ≥80% of the dose (adherers), a differential that could not be explained by the potential confounding variables (≈20) examined. Whereas this story is of obvious relevance to the clinical trialist, it is also a cautionary tale for the nutritional epidemiologist. In any sample of persons enumerated as part of a cohort study, there will be a percentage of persons who would be nonadherers were they participants in a randomized trial. Their presence could lead to substantial confounding if nonadherer status is associated with the exposure of interest.

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**REFERENCES**