Letter to the Editor

Authors' Reply: Comparison of different vitamin E forms is confounded by heterogeneity in vitamin E effects

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We appreciate the thoughts and comments on our review of the effects of *RRR*- vs all-*racemic* (all-*rac)* α-tocopherol on health outcomes.[1] Like our review, Dr Hemilä's letter emphasizes the complexity and gaps in our understanding of vitamin E in human health.

Dr Hemilä provides additional results from analyses of vitamin E studies, primarily adverse outcomes in long-time smokers participating in the Alpha-Tocopherol, Beta-Carotene (ATBC) Study.[2] In this trial, male smokers received a placebo, 50 mg of DL-α-tocopheryl acetate, 20 mg of β-carotene, or a supplement containing both DL-α-tocopheryl acetate (50 mg) and β-carotene (20 mg) daily for 5 to 8 years.[2] Contrary to the hypothesis, supplementation with β-carotene, a carotenoid with antioxidant properties, paradoxically increased lung cancer risk. In individuals other than heavy smokers or those exposed to asbestos, β-carotene consumption has demonstrated few adverse effects besides yellowing of the skin (carotenemia).[3, 4] High daily doses of β-carotene given to study participants with a high risk of lung cancer and a high oxygen environment in the lung may have led to the formation of β-carotene oxidation products, resulting in procancer effects.[5, 6] We suggest that a parallel could be drawn to explain the negative health effects of vitamin E observed in participants who were heavy smokers but not in those who smoked less frequently. Therefore, the apparent heterogeneity of the effects of the vitamin E supplement in the ATBC Study participants may not be applicable to the general, nonsmoking population.

Our review did not focus on the negative effects of vitamin E supplements but instead calls attention to the lack of progress in defining the amount of all-*rac* α-tocopherol that is "equivalent" to *RRR* α-tocopherol for meeting the requirement for this nutrient. Although we included α-tocopherol supplementation trials in our review, our primary objective was not to address which form of α-tocopherol is most beneficial to consume in supplements. Investigating, and possibly refining, the currently accepted *RRR* to all-*rac* α-tocopherol ratio of biopotency will be critical for setting intake recommendations from foods and for proper labeling on food products. We feel this is an important gap in knowledge, especially given the vast number of commonly consumed food products that are fortified with all-*rac* α-tocopherol. Dr Hemilä proposes "it would seem useful first to characterize definitively the population groups for which vitamin E supplementation may be beneficial. . ." Unfortunately, 93% of Americans do not consume the Estimated Average Requirement for vitamin E (12 mg/d).[7] Thus, unless current intake patterns change to include more α-tocopherol–containing oils, many individuals will need supplementation.

Studies using the α-tocopherol transfer protein knockout ($Ttpa^{-/-}$) mouse model to compare the effects of *RRR* vs all-*rac* α-tocopherol on the development of the central nervous system are under way in our laboratory. We hope these studies will provide insight into the efficacy of α-tocopherol sources for human-relevant health outcomes and encourage further research in this area.

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