The comparison of different vitamin E forms is confounded by the heterogeneity in vitamin E effects

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This is a comment on:

Effects of dietary RRR α-tocopherol vs all-racemic α-tocopherol on health outcomes
Katherine M Ranard John W Erdman, Jr
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To find out whether RRR α-tocopherol and all-racemic α-tocopherol might differ in their effects on health outcomes, Ranard and Erdman reviewed studies about these two forms of vitamin E.[1] They concluded from the published studies that α-tocopherol might be only of benefit to some restricted populations.[1, p.149] However, they did not fully discuss the evidence indicating that vitamin E supplementation may also be harmful for certain population groups. In our analyses of the Alpha-Tocopherol, Beta-Carotene (ATBC) Study of Finnish male smokers, we found that vitamin E (dl-α-tocopheryl acetate) had no effects for the majority of subjects. However, vitamin E was beneficial for certain categories of participants and harmful for others.

There was significant variation in the effects of vitamin E supplementation on the incidence of the common cold, which depended on the age and level of smoking.[2] For example, in participants aged ≥72 years, vitamin E decreased the risk of colds by 29% (95% CI 9-46%) for participants who smoked <15 cigarettes per day, but increased the risk of colds by 42% (95% CI 18-70%) in those participants who smoked ≥15 cigarettes a day.[2] These confidence intervals are incompatible. Harm from vitamin E supplementation was also reported by Graat et al.[3] in their study on respiratory infections in the elderly, yet that trial was not mentioned by Ranard and Erdman.[1]

The effect of vitamin E on the incidence of pneumonia was also found to be heterogeneous in the ATBC Study. The age of smoking initiation and the level of current smoking modified the effect of the vitamin.[4] Subsequent analyses provided even stronger evidence that the effect of vitamin E on pneumonia risk was heterogeneous; some participants benefited from the vitamin, some were adversely affected, whereas the majority of participants had no demonstrable effects.[5,6] The effect of vitamin E ranged from a 69% (95% CI 43-83%) decrease in pneumonia risk to a 210% (95% CI 40-560%) increase in risk.[6] The effect of vitamin E supplementation on tuberculosis risk was also heterogeneous.[7]

Because the effects of vitamin E on respiratory infections appeared to be heterogeneous, we examined whether its effects on total mortality might also be heterogeneous. The effects of vitamin E were modified by age and dietary vitamin C intake.[8] Among ATBC participants with a vitamin C intake above the median, vitamin E increased mortality by 19% (95% CI 5-35%) among those aged 50–62 years, but decreased mortality by 41% (95% CI: 21-56%) among those aged 66–69 years. Vitamin E had no effect on participants who had vitamin C intake below the median.[8] Consistently with the benefits for the older males, vitamin E increased their life-span.[9]

The numerical estimates of vitamin E effect described above are not as important as the strong evidence of heterogeneity between certain population groups. It seems plausible that the biochemical mechanisms that cause harm and benefit may be different. Therefore, the ratio of efficacy of different vitamin E forms may vary accordingly. In addition, the mechanisms that explain the effects on different specific health outcome may also vary, leading to further possible variation in the ratio of efficacy of different vitamin E forms. At this stage it does not seem feasible to search for a universal ratio of efficacy of RRR α-tocopherol vs. all-racemic α-tocopherol.[1] Instead, it would seem more useful first to characterize definitively the population groups for which vitamin E supplementation may be beneficial and only thereafter compare the efficacy of different vitamin E forms in those groups.

References

1.Ranard KM, Erdman JW. Effects of dietary RRR α-tocopherol vs all-racemic α-tocopherol on health outcomes. Nutr Rev. 2018;76(3):141-153.
https://doi.org/10.1093/nutrit/nux067

2. Hemilä H, Virtamo J, Albanes D, Kaprio J. The effect of vitamin E on common cold incidence is modified by age, smoking and residential neighborhood. J Am Coll Nutr. 2006;25(4):332-339.
http://dx.doi.org/10.1080/07315724.2006.10719543

3. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. JAMA. 2002;288(6):715-21.
https://doi.org/10.1001/jama.288.6.715

4. Hemilä H, Virtamo J, Albanes D, Kaprio J. Vitamin E and beta-carotene supplementation and hospital-treated pneumonia incidence in male smokers. Chest 2004;125:557-565.
http://dx.doi.org/10.1378/chest.125.2.557

5. Hemilä H, Kaprio J. Subgroup analysis of large trials can guide further research: a case study of vitamin E and pneumonia. Clin Epidemiol 2011;3(1):51-59.
https://doi.org/10.2147/CLEP.S16114

6. Hemilä H. Vitamin E and the risk of pneumonia: using the I^2-statistic to quantify heterogeneity within a controlled trial. Br J Nutr 2016;116:1530-1536.
https://doi.org/10.1017/S0007114516003408

7. Hemilä H, Kaprio J. Vitamin E supplementation may transiently increase tuberculosis risk in males who smoke heavily and have high dietary vitamin C intake [Discussion: 2009;101(1):145-147]. Br J Nutr. 2008;100(4):896-902.
http://dx.doi.org/10.1017/S0007114508923709
https://doi.org/10.1017/S0007114508994423

8. Hemilä H, Kaprio J. Modification of the effect of vitamin E supplementation on the mortality of male smokers by age and dietary vitamin C. Am J Epidemiol 2009;169:946-953.
http://dx.doi.org/10.1093/aje/kwn413

9. Hemilä H, Kaprio J. Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking. Age Ageing. 2011;40(2):215-220.
http://dx.doi.org/10.1093/ageing/afq178