

## Replies to “BMC Medicine” reviewer comments on:

Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking

by

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### Reviewer's report

**Title:** Vitamin E may affect the life-span of men, depending on dietary vitamin C and smoking

**Version:** 1 **Date:** 8 September 2009

**Reviewer:** Armin Zittermann

### Reviewer's report:

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#### Minor Essential Revisions

**AZ:** Results are interesting. However, was it a pre-specified data analysis or was it a post-hoc analysis of your study participants. The latter would be a problematic approach. Specify in the statistics section.

**HH+JK:** In the Introduction we state: “In our previous exploratory analyses of the ATBC Study data, we found that age, smoking and dietary vitamin C intake significantly modified the vitamin E supplementation effect on the incidence of the common cold, pneumonia and tuberculosis [28-31]. This heterogeneity motivated us to test whether the effect on mortality is also heterogeneous.”

Thus, the preceding analyses focusing on respiratory infections were exploratory, but they allowed us to formulate a hypothesis that the effect of vitamin E on mortality might also be heterogeneous. This was analyzed in Ref. 32, which was pre-specified testing of hypothesis, justified by the studies on respiratory infections.

When we observed that older vitamin E participants had lower mortality rate (Ref. 32), that generated question about how the lower mortality in older age would transform to change in life-span. Thus, the question of the current manuscript is more about estimation and less about testing a hypothesis.

On the basis of reviewer's comment, we slightly modified the end of our Background, which describes the rationale of this study.

**AZ:** Are any objective compliance data of the study participants available?

**HH+JK:** In the Methods section we state: “Compliance with supplementation was high: some 90% of the participants took more than 90% of their prescribed capsules during their active participation in the trial; there were no differences in capsule consumption among the intervention groups [27].”

**AZ:** What are your recommendations with respect to your study results?

**HH+JK:** In the Discussion section we state e.g. “If these two age ranges are analyzed together, ignoring age as a potential modifier of the vitamin E effect, the early follow-up period is weighted more in standard analyses, camouflaging the beneficial effect at the older age. Given the evidence that the severity of oxidative stress increases with age

[5,6], it would seem more appropriate to analyze large antioxidant trials by biological age as in Figs. 1 and 2, and not by the time after randomization which has been customary [22-26].”

Therefore, our findings indicate that large scale prevention trials with old people should not just analyze results by the time after randomization, but also by the biological age of the participants.

In the Discussion we also write: “The dependence of vitamin E supplementation effect on vitamin C level (Fig. 2) implies that studies focusing on a single antioxidant might suggest a misleading conclusion about the potential roles of antioxidants. Furthermore, if the effect of vitamin E is conditional on high vitamin C intake, it seems possible that the combination of vitamins E and C supplementation might affect the life expectancy of men belonging to the subgroup of Fig. 2C.”

Although we are not using the word recommendation here, we are recommending that these two antioxidants should be studied together.

There are complex arguments and we cannot present them as a single sentence recommendation in the abstract.

We are not recommending vitamin E for old males. The heterogeneity we observed means that one must be cautious when extrapolating findings of vitamin E trials, irrespective of the size and methodological quality of the trials. Also, no recommendations for general use should be based on a single study.

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next?:** Accept for publication in BMC Medicine after minor essential revisions

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.