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:** 2 September 2009
Reviewer: Balz Frei

Reviewer's report:
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BF: The ATBC study was not designed to look at an aging population, nor the effect of aging on mortality with vitamin E supplementation. The subset of subjects used in this analysis was not recruited at any particular age, nor provided vitamin E supplements for any fixed amount of time. It is noted by the authors that median follow-up time was 3.4 years; however, it is obvious from the data that some subjects were on these supplements for 7-8 years, while others for much shorter times. Without any clarification of how long these older subjects were taking vitamin E, it is difficult to ascribe a treatment effect on lifespan.

HH+JK: These comments are scientifically unsound:

"not designed to look at an aging population, nor the effect of aging on mortality with vitamin E supplementation"

HH+JK: Large-scale trials generate large amounts of data. It would be waste of money and resources to ignore the data that is not directly focused on the primary hypothesis of the trial. Therefore, various aspects of the large trial data are usually analyzed and they lead to the publication of dozens of studies that are not linked to the primary hypothesis.

In their popular book on epidemiology, Rothman and Greenland state that "… a large health survey of cohort study may collect data pertinent to many possible associations, including diet and cancer, or exercise and heart disease, and perhaps many other topics. A researcher could legitimately deny interest in any joint hypothesis regarding all of these topics, instead wanting to focus on those few (or even one) pertinent to his or her specialty. in such situations, multiple-inference procedures as outline above are irrelevant, inappropriate, and wasteful of information" (Rothman and Greenland, Modern Epidemiology, 2nd ed, 1998 p 228).

Following such reasoning, we can legitimately ask whether there is difference between vitamin E and no-vitamin E groups in the life-span.

The reviewer does not formulate any argument challenging the validity of our analysis to look at the aging population of the ATBC participants through the Kaplan-Meier curve over biological age.

BF: "not recruited at any particular age"

HH+JK: “Particular age” is an ambiguous concept in the context. The participants of the ATBC Study were 50 to 69 years at randomization and we could say that there is no “particular age” but a wide age range at recruitment.
In the current manuscript, we are interested in the effect of vitamin E at the age region over 65 and we can restrict to a follow-up period that corresponds to that “particular age” at the follow-up.

BF: “nor provided vitamin E supplements for any fixed amount of time.”

HH+JK: This comment is not limited to our current study.
It is also valid for the whole ATBC Study. The longest follow-up periods were up to 8 years. The shortest follow-up periods were only a few days.
All, or close to all, large-scale trials have a wide range of follow-up periods, because it is logistically impossible to have a fixed follow-up period lasting for several years. In small trials with a few dozen people it is often possible to follow all participants for a fixed time of a week or so.
In contrast, it is not possible to follow tens of thousands of people for 8 years, because there are always people who drop out for various reasons. Furthermore, for the logistics of a large trial it is usually practical to have a wide spread of starting times with an exact day of trial closure, which leads to a spread of planned follow-up times.
We have never before read a comment suggesting that the ATBC Study and other large-scale vitamin E trials should be ignored because the intervention duration is not “a fixed amount of time”.

BF: “Without any clarification of how long these older subjects were taking vitamin E, it is difficult to ascribe a treatment effect on lifespan.”

HH+JK: When we compare randomized groups so that the only difference between the groups is that one is administered vitamin E and the other is not, we can ascribe the difference in the outcome value to the vitamin E administration. This conclusion is not dependent on “how long the subjects were taking vitamin E”.
It is possible that the duration of supplementation modifies the effect of vitamin E, but that is no counterargument to the average difference we observed between the vitamin E and no-vitamin E participants.

BF: Although the authors suggest that vitamin E supplementation increased plasma #-tocopherol levels by 50%, this does not specifically refer to the subjects analyzed in this study, but the plasma concentration for a subset of the entire ATBC cohort.

HH+JK: Not relevant. Although it is possible that a fixed dose of vitamin E increases plasma vitamin E level differently in younger and older people, this is not crucial for our findings.
If the findings of a trial are negative, one can speculate that the doses were simply too low. Therefore the measurement of change in plasma vitamin E level is important to show that the plasma level actually increased with supplementation (so that the doses were not “too low”).
On the other hand, when there is a significant difference between two groups, the observed difference cannot be explained by “too low doses”. Therefore this comment does not challenge the validity of our findings, i.e. the significant difference between the survival curves of vitamin E and no-vitamin E participants.

BF: Furthermore, no data is provided for cause of death for this subset of individuals.

If vitamin E is increasing lifespan due to decreased oxidative stress and modulation of chronic disease, this divergence should be noted in some cause of death related to oxidative stress. Ideally, oxidative stress markers (F2-isoprostanes) would be measured in plasma of these subjects, in combination with plasma vitamins C and E, to substantiate the authors' conclusions.

HH+JK: Not relevant. Halliwell and Gutteridge list in their book that oxidative stress has been associated with well over 100 diseases (Free Radicals in Biology and Medicine 4th ed. 2007 p 489). Therefore it is not possible to pick a few diseases and argue that they are a specific measure of oxidative stress.

Furthermore, with increasing age, multiple disease processes are present, and “the cause of death” data do not capture them adequately. Hence, in older individuals death data would not be very informative.

In our manuscript we refer to Traber and Atkinson’s recent extensive 12-page review about the biochemical role of vitamin E (Ref. 36). They conclude that the biological effects caused by vitamin E are explained purely by the antioxidant effect (“antioxidant, nothing more” is stated even in their title). If we consider that their arguments are valid, that means that the effect of vitamin E on humans are explained specifically by the effects against oxidative stress.
The reviewer does not challenge the validity of Ref. 36 or our argumentation based on that reference.

Oxidative stress markers can be easily measured in small trials with a dozen participants, but not so easily in a large trial with tens of thousands participants. F2 isoprostanes were discovered in the early 1990s, after the initiation of the ATBC Study.
Furthermore, the interpretation of changes in F2-isoprostane levels would not be obvious. If the F2-isoprostane levels are not changed in the vitamin E participants, there are two possibilities: 1) either Traber-Atkinson’s conclusions are wrong and the effect of vitamin E on life-span is caused by non-antioxidant effects, or 2) Traber-Atkinson’s conclusions are correct and vitamin E functions as an antioxidant in other processes, without affecting the F2-isoprostane levels.
If F2-isoprostane levels are changed in the vitamin E participants, that does not prove that vitamin E cannot have non-antioxidant effects at the same time.
In this respect we cannot draw any unambiguous conclusions from the F2-isoprostane levels, whatever they might be. They cannot refute or prove that the effect on vitamin E on the life-span is caused by the antioxidant effect.
We consider that Traber and Atkinson’s extensive review is sound, which means that with the current state of knowledge, the biological effects of vitamin E can be explained by the antioxidant effect.

Which journal?: Not appropriate for BMC Medicine: an article of only archival interest, but might be suited to BMC Public Health

What next?: Reject because scientifically unsound

HH+JK: As shown above, the reviewer has not pointed out any problem in our study that would make it scientifically unsound.

Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.