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

These are
Reviewers' and editor's comments of Rejuvenation Research
Our replies
Conclusion by the editor of Rejuvenation Research

1 April 2010

-------- Original Message --------
Subject: Rejuvenation Research - Decision on Manuscript ID REJ-2010-1042
Date: Wed, 24 Mar 2010 20:32:36 -0400 (EDT)
From: aubrey@sens.org
To: harri.hemila@helsinki.fi
CC: aubrey@sens.org

24-Mar-2010
Dear Dr. Hemila,
Manuscript ID REJ-2010-1042 entitled "Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking" which you submitted to Rejuvenation Research, has been reviewed. The comments of the reviewers are included at the bottom of this letter.
The reviewers have recommended revisions to your manuscript, and I think their comments are reasonable. Therefore, I invite you to respond to the reviewers' comments and revise your manuscript. I am particularly interested in your response to reviewer 2's view that this manuscript insufficiently extends the results you have previously published in AJE.
To revise your manuscript, log into http://mc.manuscriptcentral.com/rejuvenationresearch and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.
Please note that the revision must be resubmitted by the same author who submitted the original manuscript.
You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.
When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewers.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to Rejuvenation Research, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.
Once again, thank you for submitting your manuscript to Rejuvenation Research and I look forward to receiving your revision.
Best wishes,
Dr. Aubrey de Grey
Editor-in-Chief, Rejuvenation Research
aubrey@sens.org

Reviewers' Comments to Author:

Reviewer: 1

Comments to the Author

The paper by Hemila and Kaprio suggests with their large trial of ATBC study that vitamin E may affect the life expectancy of men, especially in those have higher vitamin C intake and smoke less. The goals and objectives were crystal clear. The study designs and working effort were quite impressive. The analytic models were good and well accepted. Clearly, if true, this finding is potentially important since there are some considerable concerns about the effect of nutrients supplement on aging. The main concerns are listed as follows:

1. This study is one of the few trials that use biological age instead of time after treatment as their timeline. One good thing of this way is easy to interpret and apply. However, the bad side is the effect modification by age is mixed with the effect of primary factor. It would be better to show both time-after-treatment and age-dependent models to readers.

2. Since the authors found a protective effect of vitamin E in those followed up over 72 years old, they concluded vitamin E was However, another possible explanation is that Vitamin E supplement is just only an additive 'benefit' to already healthier individuals who can live longer, but not have therapeutic anti-oxidative effect to those vulnerable. This is partly in agreement with the positive finding in the subgroup of least smoking and more vitamin C intake that should be healthier. If it was due to an anti-oxidative effect it should be more prominent in heavy smoking group. Could the authors discuss a little bit on this?

3. Minor: Page 10, line 4-6: was restricted in/for

Reviewer: 2

Comments to the Author

This paper expands on a previous published report from The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (Am J Epidemiology, ref 31 in the submitted paper). In the published paper, the same authors reported that although vitamin E supplementation had no overall effect on mortality, they found that "age and dietary vitamin C intake had a second-order interaction with vitamin E supplementation of 50 mg/day. Among participants with a dietary vitamin C intake above the median of 90 mg/day, vitamin E increased mortality among those aged 50-62 years by 19% (95% confidence interval: 5, 35), whereas vitamin E decreased mortality among those aged 66-69 years by 41% (95% CI: -56, -21). Vitamin E had no effect on participants who had a dietary vitamin C intake below the median. Smoking quantity did not modify the effect

of vitamin E. “

In the present paper, the authors hypothesize that “if Vitamin E has an effect on total mortality in the old-age region, it may influence the life span.” This question under study seems strange, because I assume that mathematically, decreasing mortality must increase life span. This paper is limited to participants who were followed past age 65. They found no effect of vitamin E supplementation on those ages 65-71, but reduced mortality among those ages 72+. Among the 20% who had vitamin C above the median and smoked less than 1 pack/day, Vitamin E extended life by 2 years.

This paper addresses the same topic as the previous paper in AJE, using the same data, with a few differences in analysis. They give some results in terms of life expectancy rather than hazard rations and exclude the younger age group. The results are presented on somewhat differently defined subgroups with slightly different results. These results are not worthy of a second paper published on the same topic using the same population. The different subgroups and slightly different findings are more confusing than illuminating to the reader. If the authors feel that they need to correct or improve upon the subgroup analyses of the AJE paper, a letter to AJE would be more appropriate.

REJ-2010-1042
Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking
submitted to Rejuvenation Research

Authors: Harri Hemilä and Jaakko Kaprio
University of Helsinki

Reviewers' Comments to Author:
Reviewer: 1
Comments to the Author
The paper by Hemila and Kaprio suggests with their large trial of ATBC study that vitamin E may affect the life expectancy of men, especially in those have higher vitamin C intake and smoke less. The goals and objectives were crystal clear. The study designs and working effort were quite impressive. The analytic models were good and well accepted. Clearly, if true, this finding is potentially important since there are some considerable concerns about the effect of nutrients supplement on aging. The main concerns are listed as follows:

1. This study is one of the few trials that use biological age instead of time after treatment as their timeline. One good thing of this way is easy to interpret and apply. However, the bad side is the effect modification by age is mixed with the effect of primary factor. It would be better to show both time-after-treatment and age-dependent models to readers.

2. Since the authors found a protective effect of vitamin E in those followed up over 72 years old, they concluded vitamin E was However, another possible explanation is that Vitamin E supplement is just only an additive 'benefit' to already healthier individuals who can live longer, but not have therapeutic anti-oxidative effect to those vulnerable. This is partly in agreement with the positive finding in the subgroup of least smoking and more vitamin C intake that should be healthier. If it was due to an anti-oxidative effect it should be more prominent in heavy smoking group. Could the authors discuss a little bit on this?

3. Minor: Page 10, line 4-6: was restricted in/for

HH+JK:
Reviewer 1 **comment 1**: "*the bad side is the effect modification by age is mixed with the effect of primary factor. It would be better to show both time-after-treatment and age-dependent models to readers.*"

This is a good comment. However, it is not easy to implement the suggestion, because the number of participants is small in the 72+ years follow-up range (small statistical power), and the resulting presentation might become confusing to the readers.

Furthermore, in our Table 1 we show the subgroup analysis by the baseline age in the 72+ years follow-up period. This subgroup analysis is quite close to analysis by the follow-up time (time of vitamin E supplementation, "time-after-treatment"). The participants who were youngest (62-65 yr at baseline) had at least 7 years follow-up (vitamin E treatment) before the age of 72 years, whereas the oldest subgroup (68-69 yr at baseline) had at most 4 years of follow-up before the age of 72 years. The confidence intervals are wide and overlapping in the three subgroups, but the oldest subgroup shows that particularly long supplementation was not needed for the benefit. The lack of benefit in the young participants (62-65 yr at baseline) might be caused by 1) statistical variation since the confidence interval is wide (overlapping substantially with the old groups), 2) lack of benefit by very long supplementation, or 3) differences in the participants. By the third

alternative we mean that randomization in the trial was over vitamin E and placebo, but there may be systematic unidentified differences between the participants who were 62-65 and 68-69 years at baseline. We cannot distinguish between these three alternative explanations in our study: the number of deaths in Table 1 is only 29 in the vitamin E participants.

Unless the editor considers that we should make additions to our analysis, we do not follow reviewer's suggestion.

Reviewer 1 **comment 2**: "*... If it was due to an anti-oxidative effect it should be more prominent in heavy smoking group. Could the authors discuss a little bit on this?* ."

This is a good comment, but we do not consider that we can propose any detailed explanations. We refer to two papers (a large review and one original study) which argue that the main/only effect of vitamin E is the antioxidant effect. Given that smoking causes oxidative stress, we would expect that vitamin E might be more beneficial for smokers. Our empirical finding (Fig. 2) however indicates that the benefit is restricted to the less smoking ATBC Study participants.

Much of the antioxidant research has been confusing. For example, the ATBC Study was initiated with the hypothesis that beta-carotene would be particularly beneficial for smokers, but beta-carotene turned out to be harmful. We have not seen a good biochemical explanation for the mechanism whereby beta-carotene caused harm, but that does not challenge the empirical finding of harm. Consequently, if we want to find out whether vitamin E has effects on people, we cannot require that there are detailed biochemical explanations for the findings.

Unless the editor considers that we should extend our discussion on this topic, we do not follow reviewer's suggestion.

Reviewer 1 **comment3.** Minor: Page 10, line 4-6: was restricted in/for
Corrected.

Reviewer: 2

Comments to the Author

This paper expands on a previous published report from The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (Am J Epidemiology, ref 31 in the submitted paper). In the published paper, the same authors reported that although vitamin E supplementation had no overall effect on mortality, they found that "age and dietary vitamin C intake had a second-order interaction with vitamin E supplementation of 50 mg/day. Among participants with a dietary vitamin C intake above the median of 90 mg/day, vitamin E increased mortality among those aged 50-62 years by 19% (95% confidence interval: 5, 35), whereas vitamin E decreased mortality among those aged 66-69 years by 41% (95% CI: -56, -21). Vitamin E had no effect on participants who had a dietary vitamin C intake below the median. Smoking quantity did not modify the effect of vitamin E. "

In the present paper, the authors hypothesize that "if Vitamin E has an effect on total mortality in the old-age region, it may influence the life span." This question under study seems strange, because I assume that mathematically, decreasing mortality must increase life span. This paper is limited to participants who were followed past age 65. They found no effect of vitamin E supplementation on those ages 65-71, but reduced mortality among those ages 72+. Among the 20% who had vitamin C above the median and smoked less than 1 pack/day, Vitamin E extended life by 2 years.

This paper addresses the same topic as the previous paper in AJE, using the same data, with a few differences in analysis. They give some results in terms of life expectancy rather than hazard rations and exclude the younger age group. The results are presented on somewhat differently defined subgroups with slightly different results. These results are not worthy of a second paper published on the same topic using the same population. The different subgroups and slightly different findings are more confusing than illuminating to the reader. If the authors feel that they need to correct or improve upon the subgroup analyses of the AJE paper, a letter to AJE would be more appropriate.

HH+JK: Although we share the reviewer's general concern about duplicate and overlapping publications, we do not agree that our manuscript is an example of that problem.

First, Am J Epidemiology has a strict upper limit of 3000 words. When we initially submitted the 2009 paper to AJE, our manuscript was immediately rejected on the basis that our manuscript was over the 3000 words. We shortened the manuscript by some 400 words to get under their limit and then our manuscript was accepted for review. Thus, it is not fair criticism to argue that we could/should have included the findings and discussions of our current manuscript to the AJE-2009 manuscript, rather than writing a separate manuscript.

Second, although the reviewer is partly correct with his or her statement "I assume that mathematically, decreasing mortality must increase life span", this is a somewhat misleading presentation of the relationship between the relative risk of death and life expectancy.

In the controlled trials field, there is an important concept "NNT" (Number of people Needed to Treat to get benefit for one person), which is complementary to the relative effect. For example, if an intervention decreases the incidence of disease by 50% as a universal relative effect, there is substantial difference in the importance of such an intervention in different population groups depending on the baseline risk. Let us assume that in a "high risk" population 40% of people get the disease. 50% reduction would mean that 20% of people avoid the disease because of the intervention (NNT=5=1/0.2). In contrast, in a "low risk" population 2% might get the disease, and 50% reduction would mean that only 1% of people avoid the disease because of the intervention (NNT=100=1/0.01). In both cases the relative effect is the same (50%), but the practical importance is very different.

This analogy is important when we consider the relationship between the relative effect on mortality and the effect on life expectancy. Although reducing mortality implies that the average life expectancy is increased, the quantitative effect on life expectancy depends on the baseline mortality in the particular population. Therefore our AJE-2009 paper does not tell anything quantitative about the effect of vitamin E on life expectancy.

Furthermore, the above consideration is based on an assumption of homogeneity in the vitamin E effect among the population group. However, it is possible that the effect of vitamin E is not uniform in the age range 66+ years (baseline age limit used in AJE-2009 to form the old-age subgroup). Given the long follow-up, up to 8 years, the biological age range is wide in the ATBC participants who were 66+ at the baseline. In the current analysis, we found that the vitamin E effect starts at 70-72 years of biological age. This means that vitamin E had no effect on life expectancy among those participants who died before the age of 70 years.

In this respect the reviewer's comment "I assume that mathematically, decreasing mortality must increase life span" is valid for the averages, but reflects different issues.

Our current analysis suggests that further studies should focus on participants who are over 72 years (biological age -approach), instead of 66 years (baseline age -approach in AJE-2009). This does not mean that our previous analysis was incorrect, but the current analysis has much more accuracy to identify age-dependency, because we are not collapsing the several years follow-up period to the single point of baseline age.

The reviewer states "*few differences in analysis*."
On the basis of our comments above, we do not consider that this is valid criticism.

The reviewer also states "*slightly different findings are more confusing than illuminating to the reader*".

As noted above, the relative effect on mortality does not tell anything about the quantitative effect on life expectancy (which depends on baseline mortality).

Neither does the relative effect on mortality tell anything about the dependence of vitamin E effect on biological age (effect seems to start at 70-72 years on the basis of our current manuscript, but that cannot be inferred from our AJE-2009).

We also pay attention to the problem that - even if there would be substantial effect on the mortality in the extreme old age group - such a phenomenon can be hidden within the much greater number of participants falling to the younger age range: "The number of deaths in the 65 to 71 year age range (n=1227) is substantially greater than in the ages over 72 years (n=218). 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." This problem cannot be seen in our AJE-2009 analysis and it is not a self-evident consequence of our AJE-2009 paper.

Therefore we consider that the findings in our current manuscript are not "slightly" different, but they give an important additional understanding on the relationship between vitamin E supplementation and mortality compared with the AJE-2009 paper.

Third, reviewer writes "*If the authors feel that they need to correct or improve upon the subgroup analyses of the AJE paper, a letter to AJE would be more appropriate.*"

We disagree on this suggestion for several reasons. The maximum length in AJE: "Letter to the Editor, 500–600 words". It is not possible to describe the methods of our new analysis and discuss the findings in such a short report, even if the editors might be willing to publish an addition to the regular paper (we suspect that they consider that the "letter" forum is not for such a purpose).

Furthermore, AJE is a good forum for reporting overall heterogeneity in the effects of vitamin E supplementation. However, when there is strong evidence that vitamin E has an effect at the late part of the life span, this type of finding may be even more interesting to biologically oriented gerontologists than to epidemiologically and statistically oriented public health researchers.

We are not correcting errors. Our statistical approach is different in this manuscript, based on the biological age. However, this does not mean that the AJE-2009 was technically incorrect.

Finally, at the end of our abstract we state that ”This is the first study to strongly indicate that protection against oxidative stress can increase the life expectancy of some initially healthy population groups.”

Animal studies are essentially always analyzed by biological age. Observational studies with elderly people often plot the prevalence or incidence of diseases by the biological age. However, the large controlled trials on vitamin E have not been analyzed previously by baseline age, and we are not aware that this approach would have been used in trials on other fields either. In this respect our approach has methodological novelty, although we do not think it is a main issue whether this is the first study analyzing a trial by the biological age. Reviewer 1 stated: “This study is one of the few trials that use biological age instead of time after treatment as their timeline.” which supports our view that this approach has much novelty. And it is this approach which allows us to draw the above conclusion. Our AJE-2009 paper does not (cannot) make any quantitative statement on life expectancy.

Reviewer 2 does not give any examples showing that analysis by biological age would be a common practice, which would undermine the novelty of our approach. Neither does reviewer 2 point any counterargument to our conclusion (above), which requires this approach. Our paper illustrates that data can be used to answer different study questions, which require different design and statistical approaches. Conceptually and substantially our paper provides novelty not included in our AJE-2009 paper.

-------- Original Message --------

Subject: Rejuvenation Research - Decision on Manuscript ID REJ-2010-1042.R1
Date: Wed, 31 Mar 2010 17:11:58 -0400 (EDT)
From: aubrey@sens.org
To: harri.hemila@helsinki.fi
CC: aubrey@sens.org

31-Mar-2010

Dear Dr. Hemila,

I am writing in connection with manuscript # REJ-2010-1042.R1 entitled "Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking" which you submitted to Rejuvenation Research.

Rejuvenation Research is currently receiving a sharply elevated number of submitted manuscripts, only a minority of which we can publish. I have carefully read and considered your replies to the reviewers of your original submission, especially reviewer 2, and while I essentially agree with the substance of most of your points, I'm afraid I do not feel that they add up to an argument that this manuscript constitutes a "minimum publishable unit" over and above your 2009 paper in AJE - at least, not publishable in a journal as prominent as RR. Thus, I'm afraid I cannot accept your manuscript for publication.

Thank you for considering Rejuvenation Research for the publication of your research. I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

Best wishes,

Dr. Aubrey de Grey
Editor-in-Chief, Rejuvenation Research
aubrey@sens.org