

Author's response to reviews

Title: Vitamin E supplementation and pneumonia risk in males who initiated smoking at an early age: effect modification by body weight and dietary vitamin C

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Author's response to reviews: see over

Vitamin E supplementation and pneumonia risk in males who initiated smoking at an early age: effect modification by body weight and dietary vitamin C

By Harri Hemilä and Jaakko Kaprio 7 Nov 2008

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Reply to reviewer's comments of 26 Oct 2008

Dear Sirs,

Thank you very much for the new reviewer comment that we received 2 Nov 2008. Please, find here our reply.

Yours,
Harri Hemilä
Jaakko Kaprio

Reviewers comment:

Discretionary Revisions:

... My other point about the number at risk in each group may not have been clear, but had to do with any differences in the follow-up time. The figures for cumulative hazard go to month 8, which is two months after the median follow-up time in this study. It might be informative to know how many participants were still in follow-up in each group at the points where the divergence of curves becomes most marked. This could be done by including the number at risk (and cumulative events per group, if desired) for each group under the survival curves. This would be a most important if there was differential loss to follow-up by group for some reason.

Reply:

HH+JK:

STATA gives the possibility to add the number at risk to the survival curves. We have tested it earlier but we found that the figure becomes very complex when two series of digits are added below each time point.

We agree with the reviewer that the issue deserves some kind of inclusion in our paper, but the addition of "number at risk" does not seem the optimal way to address this issue.

Fig 1A. In the <60 kg group, the number of participants in the vitamin E and no-vitamin E groups:

	Start	Remaining at 6-years
E:	228	114 (50%)
No-E:	240	126 (52%)

Thus, there is little difference in the follow-up between these two groups over the 6 year period. ($P=0.64$ in Fisher's exact test for the comparison of 114/228 and 126/240). Evidently, the difference is even smaller in the 3-5 year follow-up range when the "*divergence of curves becomes most marked*" the second time. The first divergence is within the first year of the follow-up.

Fig 1B. In the ≥ 100 kg group, the number of participants in the vitamin E and no-vitamin E groups:

	Start	Remaining at 6-years
E:	311	146 (47%)
No-E:	302	162 (54%)

Thus, in this case there is greater difference between the two groups over the 6 year period. However, even this difference is explained by chance alone ($P=0.10$ in Fisher's exact test for the comparison of 146/311 and 162/302).

Furthermore, within 6 years there were 11 cases of pneumonia in the vitamin E group, but only 1 case in the no-vitamin E group, with a difference of 10 cases (11-1) between the groups. These cases are excluded from further follow-up (i.e. at 6 years). Moreover, if vitamin E increases the risk of pneumonia in Fig 1B, it seems probable that vitamin E causes other harms too. In the 6-year follow-up period, there were 36 deaths in the vitamin E group, but only 28 deaths in the no-vitamin E group (excluding participants who had pneumonia before 6 years). This difference is 8 people (36-28).

Thus, the difference in the occurrence of pneumonia (10 cases) and in mortality (8 deaths) explains much of the difference in the number of participants that are remaining after 6 years (16 [=162-146]). Of course, we should not expect that the groups are exactly equal, because the day of entrance to the trial varied over a few years and it gives a random component to the follow-up periods (the day the trial was closed was the same for all). As noted above, the difference between proportions 146/311 and 162/302 is itself fully explained by random variation ($P=0.10$).

Our cases of pneumonia are collected from the national Hospital Discharge Register, and our mortality data from the National Death Registry. Therefore there cannot be substantially "*differential loss to follow-up by group*" because the data bases cover practically all hospital stays and deaths in Finland.

Our figures go to 7.2 years (not months), which is only 1.2 years (20%) over the median of 6.0 years. Furthermore, the latest shown pneumonia case is at 6.70 years in Fig. 1A and at 6.54 years in Fig 1B. These are at most 0.7 years (12%) later than the median follow-up of 6 years. The log rank test and the proportional hazard regression model both take into account the number of participants remaining at follow-up, and therefore the weight of follow-up after 6 years is very small in those methods. The great majority of pneumonia cases occurred before the median follow-up.

In this revised version we describe the number of participants at 6-years of follow-up as follows in the Fig 1 legend:

“... The survival curves are cut at 7.2 years because the number of participants declines abruptly thereafter. At 6-years of follow-up there were remaining 114 and 126 participants in A), and 146 and 162 participants in B), in the vitamin E and the no-vitamin E groups, respectively.”

We consider that this addresses the question of whether there are considerable differences between the groups in the follow-up. If you consider that this short addition is not adequate for readers, we are of course ready for more extensive descriptions.