and vitamin E supplements failed to prevent prostate cancer. Participants taking vitamin E had a small increase in prostate cancer, while participants taking only selenium were more likely to develop diabetes. These results strongly support the findings of our review.


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Antioxidants are not identical and their effects are not uniform over the population, 24 August 2009

Summary
Antioxidants are not identical and their effects are not uniform over the population
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Submitter agrees with the default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply
Dr. Harri Hemilä wrote:
There are two fundamental problems with the review by Bjelakovic and coworkers. First, the authors are combining apples and oranges. Second, the authors ignore the evidence indicating that vitamin E effect is not uniform over the population.
First, let us consider an analogy. If a researcher is interested in the effect of antibiotics on mortality caused by infections, and combines all antibiotics to a single broad category of ‘antibiotics’, and pools all ‘antibiotic trials’ together, people with basic background in clinical microbiology would consider such a project silly. Different antibiotics kill different bacteria, there is geographic and social group variation in the occurrence of pathogenic bacteria, the usage of antibiotics generates resistant strains, etc., etc. The biology of antibiotics is very complex. It is obvious that a single universal estimate for ‘antibiotic effect’ is meaningless.
Antioxidants are also a heterogeneous group. Vitamin C is water soluble, vitamin E is fat soluble, selenium is an inorganic element, beta-carotene is not an essential nutrient, etc. Moreover, in model systems small-molecule antioxidants are oxidized at different speeds. For example, activated neutrophils in plasma first oxidize vitamin C, whereas the oxidation of urate starts only after vitamin C has been consumed, and the level of vitamin E remains virtually unchanged [1]. From the point of view of biology, there is no basis to consider that all antioxidants are similar enough to justify the pooling of all trials with compounds belonging to the broad category of ‘antioxidants’. In a proper analysis, each antioxidant should be analyzed specifically.
- Response:
We thank Dr Hemilä for the comments. We agree that ‘antioxidants’ are a heterogeneous group of substances. Vitamin E and the other antioxidant supplements may have different effects in different populations. Accordingly, we have accounted for the statistical heterogeneity in our analyses. Several potentially interesting subgroup analyses may be considered, but the included trials do not report the necessary data. When performing systematic reviews, the decision to split or lump a heterogeneous group of trials may be difficult. Splitting trials into various subgroups may provide more focused answers, but will also increase the risk of spurious results. Lumping a heterogeneous group of trials provides a less focused answer, but may increase the external validity. In the present review, we decided to focus on antioxidants supplements to provide an overall picture of the potential effects. Our results provide information that may form basis for future trials and reviews.
We have analysed antioxidant supplements combined (beta-carotene; vitamin A; vitamin C; vitamin E; selenium) as well as individually.
Dr. Harri Hemilä wrote:

Bjelakovic and coworkers label vitamin A as an antioxidant. Halliwell and Gutteridge write in the latest edition of their monograph, that “vitamin A can do the same [scavenging some oxidants, as beta-carotene does] but no data exist supporting such a role in vivo?” [2 p. 177]. Of course, Halliwell and Gutteridge may be wrong, but given the depth of their familiarity with the antioxidant literature, Bjelakovic and coworkers should give explicit reference(s) to reject that statement when labelling vitamin A as an antioxidant. Most biomolecules are oxidized by hydroxyl radical, but it is not reasonable to thereby label all of them as antioxidants. Halliwell and Gutteridge suggest that the definition of “antioxidant” should require that it delays, prevents or removes oxidative damage [2 p. 80-81]. Thus, a systematic review focusing on antioxidants should consider and define what is meant by an “antioxidant”. Bjelakovic writes that “there are pros and cons in the literature about vitamin A being antioxidant”, which in my opinion is not a scientific argument to justify labelling vitamin A as an antioxidant. Furthermore, Bjelakovic and coworkers write in Discussion that “recent research revealed that vitamin A can cause oxidative damage to DNA”. Thus, there is lack of logic when claiming that vitamin A has been shown to be a pro-oxidant, but include it in the review restricted to antioxidants on the basis of conflicting opinions.

- Response:

Based on previous evidence, we have classified vitamin A as an antioxidant supplement. The potential antioxidant and pro-oxidant potentials of vitamin A are clarified in the discussion section of our review. We kindly refer the reader to this discussion. Multivitamins/multiminerals (containing vitamin A) are the most commonly used dietary supplements. What is important is the effect of vitamin A on mortality irrespective of specific biological effect.

Dr. Harri Hemilä wrote:

Analyzing trials by the specific biochemical substance that is tested would make the review much more logical. If a review focuses on, say, vitamin A and mortality, there is no need to firmly decide whether vitamin A is an antioxidant or not. The problem of defining ‘antioxidant’, and deciding whether some of them is pro-oxidant under certain condition is avoided if the substances are analyzed by the biochemical definitions. In such an approach, antioxidant and pro-oxidant concepts could be left to the Discussion section for giving plausible biological explanations for the observed effects.

An important goal in modern biomedicine is specificity. The strength of the randomized trial is that the difference between the trial groups can be specifically attributed to the intervention that is being tested. However, when the intervention varies from a single antioxidant to the combinations of diverse antioxidants, and includes 11 trials in which “participants were supplemented with different mixtures of antioxidants as well as with vitamins and mineral without antioxidant properties”, we lose specificity because of the apples and oranges problem.

- Response:

We agree that specificity is an important goal. This is why we report meta-analyses of the selected five antioxidant supplements together (beta-carotene; vitamin A; vitamin C; vitamin E; selenium) as well as meta-analyses of them individually (beta-carotene; vitamin A; vitamin C; vitamin E; selenium). Our intention by also using meta-analyses of the individual supplements was to evade the critic of mixing ‘apples and pears’ or ‘apples and oranges’.

Dr. Harri Hemilä wrote:

In Table 6, Bjelakovic and coworkers calculate the specific effect of vitamin A (95% CI for the RR: 0.84 to 1.68; N=2406) and vitamin E (95% CI for the RR: 0.98 to 1.05; N=41341), but these specific effect estimates are hidden from the reader. In the Discussion, Bjelakovic and coworkers state that “beta-carotene, vitamin A, and vitamin E given singly or combined with other antioxidant supplements significantly increase mortality”, which is false and misleads those readers who skip Table 6 and only look at the Discussion. The above confidence intervals show that vitamins A and E singly do not significantly increase mortality. In the Abstract, Bjelakovic does not give the specific estimates for vitamins A and E, but gives RR estimates based on studies with scores of other antioxidants including beta-carotene, which has been known to increase mortality since the publication of the ATBC and CARET trials. A reader of the Abstract cannot figure out that the given RR-values don’t tell us anything about the specific effects of vitamins A and E. Thus, even the Abstract is misleading.

- Response:

As described in the methods section, we described our results of the overall, subgroup, and sensitivity analyses. We are surprised that Hemilä accuses us from hiding any information the information from the random-effects model analyses were clearly presented in Table 5 and the corresponding analyses from the fixed-effect analyses were presented in Table 6. Now Hemilä is especially interested in certain subgroup results. Such data may be misleading as they may not have the necessary power and precision. The data we present in our abstract are those having the best power and precision and hence represent findings with most external validity.

Second, when Bjelakovic and coworkers first published the review in JAMA, I pointed out that the effect of vitamin E on respiratory infections was heterogeneous in the large scale ATBC Study [3,4]. Vitamin E had no overall effect on the incidence of the common cold or pneumonia, but the effects were significantly modified by age and smoking [5,6]. Although heterogeneity in the effect on respiratory infections was significant in the large scale ATBC Study, there was only a trend towards significance in the CARET Study [3,4].
Finally, Bjelakovic and coworkers were ambitious when covering all antioxidants plus vitamin A trials. Such wide coverage requires intervention effect. On the effect of antioxidant supplementation is an example of the ecological fallacy. Observed for the averages for groups necessarily hold for individuals. Thus, Bjelakovic’s conclusion that treatment duration has no effect on the effect: to whom there is effect and to whom not. When there is evidence of heterogeneity, the main focus should be on trying to understand any sources of heterogeneity that are present.

Although heterogeneity in vitamin E effect on mortality does not directly imply that the effect of vitamin C and beta-carotene must be uniform; a possibility should not be ignored. In fact, we can even turn the argument around. Given the strong evidence that vitamin E effect is heterogeneous, why should we accept such a premise that the effects of other antioxidants are uniform over the population. If we assume that the effects of antioxidants are heterogeneous, further studies should try to identify and characterize the subpopulations where the antioxidants might be beneficial, rather than calculating a fictionally accurate average effect on all people.

Lack of uniformity in vitamin C effect is suggested by the interaction between vitamin E supplementation and dietary vitamin C intake. Although dietary vitamin C has a high level of correlation with other substances in fruit and vegetables, the other substances did not explain the modification of vitamin E effect in the ATBC cohort.

**- Response:**

Dr Hemilä reports some interesting subgroup analyses from a randomised trial. The data suggest a possible beneficial effect of vitamin E given in combination with vitamin C seen in certain populations. Although we cannot exclude such an effect, we are unable to analyse the question as only trial-level data were available for our meta-analyses. In our review, we have clarified that the effect of antioxidant supplementation might not be uniform across the population.

Bjelakovic and coworkers write in their Discussion that “our analyses had little trial heterogeneity. This increases the trustworthiness of our findings.” I cannot see any justification for such an argument. If there is a strong premise that the effect of, say, vitamin E should be uniform over the population, in such a case observing little heterogeneity is consistent with our expectations. However, as noted above, there is no basis for such a premise in general, and in the case of vitamin E it was firmly refuted. The level of heterogeneity is no measure of ‘trustworthiness’.

Bjelakovic and coworkers state in their Discussion that “adoption of the random-effects model in meta-analysis permits extension of inferences to a broader population of studies than the fixed-effect model does”, which is incorrect. If there is heterogeneity, we do not know to whom the calculated overall estimate applies, and this problem does not disappear by using the random-effects model. In the random-effects model the confidence interval is wider, but that does not help us to understand what are the characteristics that modify the effect: to whom there is effect and to whom not. When there is evidence of heterogeneity, the main focus should be on trying to understand any sources of heterogeneity that are present.

**- Response:**

In systematic reviews, different sources of intertrial heterogeneity may exist including clinical, methodological, and statistical heterogeneity. In our review, we found little evidence of intertrial heterogeneity in our meta-analyses. In our meta-regression analyses, the risk of bias and the type of antioxidant supplement were the only significant predictors of intertrial heterogeneity. In the trials with a low risk of bias, the antioxidant supplements significantly increased mortality (RR 1.05, 95% CI 1.02 to 1.08).

We have discussed differences between random-effects and fixed-effect models of meta-analysis in the section Discussion. Bjelakovic and coworkers also conclude that the effect of antioxidants is uniform over the duration of supplementation: “we found no significant effect of treatment duration on our results” (Discussion). Our analysis of the individual-level data of the ATBC study refuted also this conclusion. In young participants who had high dietary vitamin C intake, vitamin E supplementation had no effect over the first 3.3 years, but thereafter increased mortality by 38% [7]. Adding the two different vitamin E effects significantly improved the Cox model (P=0.007). Correlation of treatment effect with the average duration of supplementation at the trial level is too crude a method to examine the time dependency of supplementation effects. In epidemiology, ‘ecological fallacy’ means thinking that relationships observed for the averages for groups necessarily hold for individuals. Thus, Bjelakovic’s conclusion that treatment duration has no effect on the effect of antioxidant supplementation is an example of the ecological fallacy.

**- Response:**

We found a number of trials assessing similar intervention regimens to the one assessed in the ATBC trial. Based on our meta-regression analyses stratified by the intervention regimen, the duration of supplementation was not a predictor of the estimated intervention effect.

Finally, Bjelakovic and coworkers were ambitious when covering all antioxidants plus vitamin A trials. Such wide coverage requires lots of work and easily leads to errors in the extraction of data, and to the lack of time to read the papers and learn the context of the
in October, 2008 over a disproportionally high incidence in prostate cancer in participants in the trial who were taking vitamin E.  

References:

**Contributors**

*Goran Bjelakovic, Christian Gluud, Lise Lotte Gluud, Rosa Simonetti, Dimitrinka Nikolova.*

**WHAT’S NEW**

Last assessed as up-to-date: 16 January 2012.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>16 January 2012</td>
<td>New citation required but conclusions have not changed</td>
<td>Compared to our previous review (<em>Bjelakovic 2008</em>), the number of included trials in the present review is expanded with 11 new trials (16.4%) adding another 64, 157 participants (27.6%). Moreover, we have obtained updated results of longer follow-up in two large-scale randomised trials (<em>SIT 2006; SUVIMAX 2010Low</em>). In spite of the addition of the 11 new trials and updated follow-up results of two of the included trials, our results remained largely the same.</td>
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<tr>
<td>16 January 2012</td>
<td>New search has been performed</td>
<td>We have now updated the review, published in 2008 (<em>Bjelakovic 2008</em>). The searches were extended to February 2011.</td>
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**HISTORY**


Review first published: Issue 2, 2008
Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

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Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2012.

Review content assessed as up-to-date: 16 January 2012.


ABSTRACT

Background

Our systematic review has demonstrated that antioxidant supplements may increase mortality. We have now updated this review.

Objectives

To assess the beneficial and harmful effects of antioxidant supplements for prevention of mortality in adults.

Search methods

We searched The Cochrane Library, MEDLINE, EMBASE, LILACS, the Science Citation Index Expanded, and Conference Proceedings Citation Index-Science to February 2011. We scanned bibliographies of relevant publications and asked pharmaceutical companies for additional trials.

Selection criteria

We included all primary and secondary prevention randomised clinical trials on antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus placebo or no intervention.

Data collection and analysis

Three authors extracted data. Random-effects and fixed-effect model meta-analyses were conducted. Risk of bias was considered in order to minimise the risk of systematic errors. Trial sequential analyses were conducted to minimise the risk of random errors. Random-effects model meta-regression analyses were performed to assess sources of intertrial heterogeneity.

Main results

Seventy-eight randomised trials with 296,707 participants were included. Fifty-six trials including 244,056 participants had low risk of bias. Twenty-six trials included 215,900 healthy participants. Fifty-two trials included 80,807 participants with various diseases in a stable phase. The mean age was 63 years (range 18 to 103 years). The mean proportion of women was 46%. Of the 78 trials, 46 used the parallel-group design, 30 the factorial design, and 2 the cross-over design. All antioxidants were administered orally, either alone...