Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality  

CRD summary
This review assessed the dose-response relationship between vitamin E supplementation and mortality, and found that doses greater than or equal to 400 IU per day may have increased all-cause mortality. The lack of a quality assessment and the clinical differences across the included studies weaken the evidence presented.

Authors' objectives
To determine the dose-response relationship between vitamin E supplementation and total mortality.

Searching
MEDLINE (from inception to August 2004) and the Cochrane Controlled Trials Register were searched; the search terms were given. In addition, the reference lists of retrieved articles and reviews and meta-analyses were checked and the investigators' files were searched. No language restrictions were imposed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up of at least 1 year were eligible for inclusion. The included studies followed up participants from 1.4 to 8.2 years on average.

Specific interventions included in the review
Studies of vitamin E supplementation alone, or in combination with other vitamins or minerals, for the duration of at least 1 year were eligible for inclusion. The vitamin E dosage ranged from 16.5 to 2000 international units per day (IU/per day), with a median dose of 400 IU/day. Most of the included studies were placebo-controlled. More than half of the studies evaluated vitamin E combined with other vitamins or minerals such as vitamin C and beta-carotene. Further details were given.

Participants included in the review
Studies of men or non-pregnant women were eligible for inclusion. Most of the studies included participants who were at high-risk for a chronic disease, most frequently coronary heart disease. The mean age ranged from 47 to 84 years, where reported.

Outcomes assessed in the review
Studies that evaluated all-cause mortality and reported at least 10 deaths were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Three reviewers independently extracted the data and any disagreements were resolved by consensus.

Methods of synthesis
How were the studies combined?
A hierarchical logistic regression model was used to determine the association between vitamin E supplementation and all-cause mortality. A quadratic-linear spline model was used to determine a dose-response relationship (using greater than or equal to 400 IU/day as high dosage). The results of the logistic regression model were transformed to give risk differences and risk ratios with corresponding confidence intervals (CIs) for ease of interpretation.

**How were differences between studies investigated?**
Sensitivity analyses were performed by repeating the analyses using different knot values (100, 200, 300, 400 or 500 IU/day vitamin E). Additional analyses were performed on those who had received vitamin E only, and the effect of adding the following variables was assessed: gender distribution, mean age, use of other vitamins or minerals combined with vitamin E, and the average duration of follow-up.

**Results of the review**
Nineteen RCTs (n=135,967) were included in the review.

When all of the trial results were analysed together, vitamin E supplementation did not affect all-cause mortality. However, in 9 of the 11 trials testing high-dosage vitamin E (greater than 400 IU/day), a significantly increased risk for all-cause mortality in comparisons of vitamin E versus control was observed. The pooled all-cause mortality risk difference in the high-dosage vitamin E trials was 39 additional deaths per 10,000 persons. For the low-dosage trials, there were no statistically significant risk differences between the participants receiving vitamin E and those receiving placebo. Overall, the meta-analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk at dosages greater than 150 IU/day.

**Authors' conclusions**
High-dose (greater than or equal to 400 IU/day) vitamin E supplements may increase all-cause mortality and should be avoided.

**CRD commentary**
The review addressed a clear research question and the inclusion criteria appeared appropriate. Two relevant databases were searched and attempts were made to identify unpublished studies. The methods used to select studies for inclusion were not reported, although the authors stated that trial investigators were contacted to confirm eligibility if needed. Methods were used to reduce reviewer error and bias in the data extraction process and, where necessary, further details were obtained from the trial investigators. It was unclear whether the quality of the included studies was assessed, thus it is difficult for the reader to establish the validity of the included studies on which the conclusions are based.

Available details of the included studies indicated that there were clinical differences across these studies. Most of the studies were performed in patients with chronic disease and more than half of the included studies evaluated vitamin E combined with other vitamins and minerals. The authors acknowledged that the generalisability of the findings to healthy adults is uncertain. In addition, they highlighted that the high-dosage trials had small sample sizes and a precise estimation of the threshold at which the risk increases was difficult. The apparent absence of a quality assessment and clinical differences across the studies weaken the evidence presented.

**Implications of the review for practice and research**
Practice: The authors stated that high-dose vitamin E supplementation should be discouraged until evidence of efficacy is demonstrated from well-conducted trials.

Research: The authors stated that further research is needed to determine the effects of low-dosage vitamin E supplementation in western populations.

**Bibliographic details**
supplementation may increase all-cause mortality. Annals of Internal Medicine 2005; 142(1): 37-46

**PubMedID**
15537682

**Original Paper URL**
http://www.annals.org/cgi/content/full/142/1/37

**Other publications of related interest**

These additional published commentaries may also be of interest. Simon JA. Review: high-dose vitamin E supplementation is associated with increased all-cause mortality. ACP J Club 2005;143:1. Mariano C. Review: high dose vitamin E supplementation is associated with increased all cause mortality. Evid Based Nurs 2005;8:82.

**Indexing Status**
Subject indexing assigned by NLM

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.