Review: high dose vitamin E supplementation is associated with increased all cause mortality


Does vitamin E supplementation increase all cause mortality? Does a dose-response relation exist between vitamin E and all cause mortality?

**METHODS**

- **Data sources:** Medline (1966 to August 2004), Cochrane Central Register of Controlled Trials, bibliographies of relevant studies and reviews, and personal files of the investigators.
- **Study selection and assessment:** randomised controlled trials (RCTs) that compared vitamin E supplementation (alone or combined with other vitamins or minerals) with a control or placebo group in men or non-pregnant women. Study duration and follow up were >1 year, and ≥10 deaths occurred.
- **Outcomes:** all cause mortality.

**MAIN RESULTS**

19 RCTs (n = 135 967, mean age range 47–84 y) met the selection criteria. 9 RCTs evaluated vitamin E alone, and 10 combined vitamin E with other vitamins or minerals. 16 RCTs were placebo controlled. Vitamin E dose varied between 16.5 and 2000 IU/d. Overall, vitamin E supplementation did not affect all cause mortality (alone or combined with other vitamins or minerals). However, mortality was not increased in 8 RCTs evaluating low dose vitamin E, high dose vitamin E was associated with increased mortality (11 RCTs). A dose-response analysis showed that all cause mortality increased as vitamin E dose increased to >150 IU/d. The effect of vitamin E did not change after adjustment for differences in sex, mean age, or mean follow up. The association of high dose vitamin E and mortality was stronger after adjustment for simultaneous use of other vitamins and minerals (pooled relative risk 1.06, 95% CI 1.01 to 1.11; risk difference 63 per 10 000 persons, CI 6 to 119).

**CONCLUSIONS**

High dose (>400 IU/d) vitamin E supplementation is associated with increased risk of all cause mortality. A dose-response relation exists between vitamin E doses >150 IU/d and mortality.

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**A modified version of this abstract appears in ACP Journal Club.**

## Commentary

At least 22% of older adults in the US take a vitamin E supplement, often at high doses. The meta-analysis by Miller et al provides evidence that such high doses of vitamin E are harmful. However, in the trials analysed, high dose vitamin E was often used in patients with chronic illness, so the effect of concomitant medication may have influenced the findings. Similarly, studies of low dose vitamin E were often done in malnourished populations, making it difficult to extrapolate the findings of increased mortality at higher doses to the general population.

Many of the trials used vitamin E in addition to other supplements, such as β-carotene. Although Miller et al controlled for the possible effects of other supplements, the higher mortality rate among those using high dose vitamin E may have been influenced by the combined effect of nutritional status, other medications, and concurrent administration of other vitamin supplements. None of the studies analysed seemed to differentiate between natural and synthetic sources of vitamin E, which could be a confounding variable.

Despite these limitations, the results of this review are important to nurses working with patients with chronic illnesses, public health nurses, and those working in primary care. Based on these findings, it may be prudent to advise patients, especially those with chronic illness, to avoid high dose vitamin E supplementation because the risk of harm may outweigh any perceived benefit. Further study is needed to determine the effects of individual vitamin supplements on various populations. Intuitively, vitamins are often assumed to be safe—this study suggests that, as with prescribed medications, more is not necessarily better, or indeed safe.

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**High dose (≥400 IU/d), low dose (<400 IU/d), and all doses of vitamin E supplementation v placebo or no vitamin E for all cause mortality**

<table>
<thead>
<tr>
<th>Number of trials (n)</th>
<th>Vitamin E dose</th>
<th>RRI (95% CI)</th>
<th>Risk difference (per 10 000 persons) (CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (135 967)</td>
<td>High and low</td>
<td>1% (−2 to 4)</td>
<td>10 (−18 to 38)</td>
<td>Not significant</td>
</tr>
<tr>
<td>11 (40 950)</td>
<td>High</td>
<td>4% (1 to 7)</td>
<td>39 (3 to 74)†</td>
<td>257 (136 to 3334)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>RRR (CI)</strong></td>
<td></td>
<td><strong>NNT</strong></td>
</tr>
<tr>
<td>8 (95 017)</td>
<td>Low</td>
<td>2% (−1 to 4)</td>
<td>−16 (−41 to 10)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Abbreviations defined in glossary; RRI, RRR, NNH NNT, and CI calculated from data in article. Follow up ranged from 1.4 to 8.2 years. A dose-response regression model was used.

†Favours placebo or no vitamin E.