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


Q 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 (table). However, although mortality was not increased in 8 RCTs evaluating low dose vitamin E, high dose vitamin E was associated with increased mortality (11 RCTs) (table). 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 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 (table). However, although mortality was not increased in 8 RCTs evaluating low dose vitamin E, high dose vitamin E was associated with increased mortality (11 RCTs) (table). 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 or 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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### Table: Risk of All Cause Mortality to High Dose Vitamin E Compared with Placebo

<table>
<thead>
<tr>
<th>Number of trials (n)</th>
<th>Vitamin E dose</th>
<th>RII (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)t</td>
<td>257 (136 to 3334)</td>
</tr>
<tr>
<td><strong>RRR (CI)</strong></td>
<td></td>
<td></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; RII, 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.