Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly 1,2

Katalin G Losonczy, Tamara B Harris, and Richard J Havlik

ABSTRACT We examined vitamin E and vitamin C supplement use in relation to mortality risk and whether vitamin C enhanced the effects of vitamin E in 11,178 persons aged 67-105 y who participated in the Established Populations for Epidemiologic Studies of the Elderly in 1984-1993. Participants were asked to report all nonprescription drugs currently used, including vitamin supplements. Persons were defined as users of these supplements if they reported individual vitamin E and/or vitamin C use, not part of a multivitamin. During the follow-up period there were 3,490 deaths. Use of vitamin E reduced the risk of all-cause mortality [relative risk (RR) = 0.66; 95% CI: 0.53, 0.83] and risk of coronary disease mortality (RR = 0.53; 95% CI: 0.34, 0.84). Use of vitamin E at two points in time was also associated with reduced risk of total mortality compared with that in persons who did not use any vitamin supplements. Effects were stronger for coronary heart disease mortality (RR = 0.37; 95% CI: 0.15, 0.90). The RR for cancer mortality was 0.41 (95% CI: 0.15, 1.08). Simultaneous use of vitamins E and C was associated with a lower risk of total mortality (RR = 0.58; 95% CI: 0.42, 0.79) and coronary mortality (RR = 0.47; 95% CI: 0.25, 0.87). Adjustment for alcohol use, smoking history, aspirin use, and medical conditions did not substantially alter these findings. These findings are consistent with those for younger persons and suggest protective effects of vitamin E supplements in the elderly. Am J Clin Nutr 1996;64:190-6.

KEY WORDS Vitamin E, antioxidants, supplements, elderly persons, coronary heart disease, mortality

INTRODUCTION

Growing evidence suggests that antioxidant vitamins, especially vitamin E, metabolize free radicals and reduce the risk of disease outcomes. Free radical damage has been implicated in the causal pathway of lipid peroxidation, a major factor in atherogenesis and coronary heart disease (1-4). Vitamin E—the major lipid-soluble, chain-breaking antioxidant—has been associated with a reduction in lipid peroxidation, platelet adhesiveness, and thrombosis (2-5). Vitamin E also modulates synthesis of prostaglandins and other host defenses, which are important for immune response (6-12).

Evidence for a protective effect of vitamin E in humans includes both studies of serum measures and associations with dietary intake and supplement use. Vitamin E supplement intake was reported recently to be associated with reduced coronary artery lesion progression in a clinical trial of 156 middle-aged men (13). High serum concentrations of vitamin E as well as a higher dietary intake of vitamin E have been associated with a reduced risk of atherogenesis, coronary heart disease, and stroke (14-18). Serum concentrations of vitamin E were significantly and inversely related to angina in a case-control study of men aged 35-54 y (19). A strong inverse association was found for plasma vitamin E and ischemic heart disease in a large cross-cultural study of men (20). Antioxidants, including vitamin E, have also been associated with a reduced risk of certain cancers (21-25).

Vitamin E intake was reported to reduce the risk of coronary disease in recent large-scale prospective studies. Dietary vitamin E was reported to be significantly and inversely related to coronary mortality in 5133 men and women aged 30-69 y over 14 y (26). The Scottish Heart Study (27) found that the risk of undiagnosed coronary heart disease was significantly lower in the highest quintile of dietary vitamin E intake in 10,359 men and women aged 40-59 y. The Health Professionals Follow-up Study (28) of 39,910 men aged 40-75 y found a relative risk (RR) of 0.60 (95% CI: 0.44, 0.81) for coronary heart disease for the highest quintile of vitamin E intake, including both diet and vitamin E supplements, compared with the lowest quintile of intake. An RR of 0.59 (95% CI: 0.38, 0.91) was found for women who took vitamin E supplements for > 2 y in the Nurses’ Health Study (29) of 87,245 women aged 34-59 y. Clinical trials are underway in the Women’s Health Study and in a secondary prevention trial to examine the relationship between antioxidant supplements including vitamin E and cardiovascular disease in women.

Studies that examined the association of vitamin C and cardiovascular disease show conflicting results (22, 30-34). In

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the National Health and Nutrition Examination Survey the highest tertile of dietary vitamin C was associated with an RR of 0.66 (95% CI: 0.53, 0.82) for cardiovascular disease mortality compared with the lowest tertile of intake (35). In prospective studies of a Dutch population (36) and in a Swedish study of women (37) no relation was found between vitamin C and coronary mortality. Findings were negative for vitamin C intake after adjustment for covariates in the Health Professionals Follow-up Study (28) and the Nurses’ Health Study (29). All these studies examined the effect of vitamin C independent of vitamin E. We were unable to identify any studies that examined the effects of concurrent vitamin E and vitamin C intake despite some papers suggesting that their action may be synergistic (38, 39).

Our analyses test the hypothesis that ingestion of vitamin E supplements have a protective effect against all-cause mortality, coronary heart disease mortality, cancer mortality, and other remaining causes of mortality in an elderly population, and that use of vitamin E with C supplements may enhance this protective effect.

SUBJECTS AND METHODS

Study population

The Established Populations for Epidemiologic Studies of the Elderly (EPESE) is a study of health and disease data collected from four communities of free-living persons aged ≥65 y. Details were described elsewhere (40). Data collection began in 1982 in East Boston; Washington County, IA; and New Haven, CT. The fourth community was added in 1986 and consisted of five counties in North Carolina. Respondents were followed annually for 6 y. However, mortality data were available for an additional 2–3 y after the 6 y of data collection. In-person interviews were performed every 3 y, during which all medications and vitamin supplements were recorded and coded. The vital status of those not interviewed was ascertained by surveillance of obituaries. The National Death Index was used in New Haven, and in east Boston state mortality tapes were used. Death certificates were obtained for confirmation of death and coded by a single nosologist.

We elected to use the second in-person interview, conducted during follow-up year three, as our baseline to allow us to examine the effects of vitamin E supplement use ascertained at one point in time compared with two points in time. Our sample at baseline included 77% of the original enrolled sample: from the original sample 2643 persons were excluded because of death, 297 persons refused participation, and 68 persons were lost to follow-up. We further excluded 270 persons for whom race was unknown or who were other than white or African American. This resulted in a final study population of 11,178 persons interviewed at follow-up three, our study baseline.

Measures

Trained interviewers gathered data about medical history, height, body weight, and health habits. Details of methods used for data collection in the EPESE are described elsewhere (40). Respondents were asked whether they had taken any medicines or drugs not prescribed by a doctor in the past 2 wk. Respondents were told to include vitamins among these drugs at two of our four study sites. Interviewers requested to see the containers of all drugs reportedly taken by respondents. No further questions were asked about use of vitamin supplements, such as consistency of use, and no data on doses were recorded.

Vitamin supplements

From the list of medicines and supplements used in the 2 wk before the interview, we constructed six categories of vitamin supplement use to address our hypotheses. Categories of vitamin E and vitamin C use were restricted to persons who reported specific use of these supplements regardless of other supplements reported; although the doses were unknown, amounts in individual supplements of vitamin E tend to be ≥100 IU (29). Individual supplements of vitamin C are also likely to include higher doses than in multiple vitamins. When vitamin E is included in a multiple supplement the dose is usually ≤30 IU and for vitamin C the dose is commonly 60 mg (29). In addition, it was unknown whether multiple vitamins included vitamin E and/or vitamin C. Therefore, persons taking multivitamins without an additional supplement were considered in a separate category. The categories created were as follows: use of vitamin E alone, use of vitamin C alone, use of vitamins E and C together, use of multiple vitamin/mineral supplements, use of other supplements (folic acid, niacin, vitamin B-12, vitamin D, pyridoxine, and calcium), and no supplement use. Those not taking supplements served as the reference group for all analyses. To examine our main hypothesis, we contrasted the reference group with all those taking vitamin E supplements (combining the categories of vitamin E alone and vitamin E with vitamin C).

To examine duration of use of vitamin E in separate analyses, we constructed four categories: reported use of vitamin E at two points in time, use of vitamin E in the past only, use of vitamin E at baseline only, and no use of vitamin E supplements reported at any time. Because there were insufficient numbers of concurrent users of vitamins E and C at two points in time, we restricted this analysis to duration of vitamin E use, which was the main hypothesis of the paper.

Covariates

We adjusted the models for covariates well known to be associated with all-cause mortality and coronary heart disease mortality. This included demographic factors (age, sex, race, and education), health habits, and indicators of health status. Education (number of years of school completed) and race were used as indicators of socioeconomic status known to be related to health. Health habits included alcohol use because moderate use of alcohol has been reported to be protective against cardiovascular disease (41, 42). Respondents who reported any alcohol consumption in the past month were assigned a “1” and those who reported no use were assigned a “0.” To adjust for cigarette smoking, a well-known risk factor for coronary heart disease and cancer, we compared current users and past users with never users of cigarettes. Aspirin use, reported to be associated with reduced risk of coronary heart disease mortality (43), was included among health habits. For health status, respondents were asked whether they had ever been told by a doctor that they had cancer, a stroke, diabetes, or coronary heart disease. If a participant responded “yes” at the study inception, at follow-up one, at follow-up two, or at
our baseline (follow-up three), the participant was considered to have this condition. Each condition was entered as a separate covariable in the models. Body mass index \( [\text{wt}(\text{kg})/\text{ht}(\text{m})^2] \) has been related to mortality in the elderly (44) and was based on weight at our baseline and on height reported at study inception. Because of the known relation of hypertension and cardiovascular disease we used measured blood pressure to define hypertension. Two blood pressure measures were taken at baseline. Persons whose second measured systolic blood pressure was \( \geq 160 \text{ mm Hg} \) or whose second measured diastolic blood pressure was \( \geq 90 \text{ mm Hg} \) were defined as positive for hypertension. Persons with missing data for blood pressure (< 10%) were assigned the mean value of the factor according to vitamin-supplement category.

Outcomes

All-cause mortality was based on the receipt of a death certificate. Cause-specific mortality was based on analysis of multiple causes of death by using ICD-9 (The International Classification of Diseases, 9th Revision) codes from up to 32 positions per death certificate. Coronary heart disease mortality included ICD codes 410-414; cancer mortality included ICD codes 140–172 and 174–208. Only 8% of death certificates included ICD codes for both coronary mortality and cancer mortality. Those cases were examined independently for both endpoints. Other mortality consisted of remaining causes of mortality after exclusion of coronary and cancer mortality.

Statistical methods

We pooled data from the four sites for increased statistical power. Results from site-specific analyses were generally consistent and inclusion of study site as a covariable had no effect on the results. Analysis among persons without cardiovascular disease at baseline had little effect on our findings. Hence, for increased statistical power we elected to include those persons and adjusted for this effect in the analysis. Proportional hazards (45) models were used to calculate the estimated RRs and 95% CIs associated with each category of vitamin supplement use. Models were first adjusted for baseline age and sex, then adjusted by other risk factors, including demographic factors (education and race), health habits (alcohol consumption, smoking history, and aspirin use), and indicators of health status (BMI and history of coronary disease, stroke, diabetes, cancer, and hypertension). An interaction term for vitamins E and C was examined in a separate model. To test whether disproportionate representation of African Americans among nonsupplement users may have accounted for our results, we conducted a separate analysis limited to whites only. Because the results remained consistent (data not shown), we included African Americans in our analysis.

RESULTS

There were 3490 deaths by the end of the study period. Among these there were 1101 coronary heart disease events, 761 cancer events, and 1719 "other" events.

Baseline characteristics

The mean age of all vitamin E users was 75.0 y; nonusers were 76.3 y (Table 1). About 94% of all users of vitamin E supplements were white whereas 77.6% of nonusers were white. About 3% of all vitamin E users reported a history of

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**TABLE 1**

Characteristics of the study population according to vitamin supplement use for 11178 men and women

<table>
<thead>
<tr>
<th></th>
<th>All E(^1)</th>
<th>E and C(^2)</th>
<th>E alone(^3)</th>
<th>C alone(^3)</th>
<th>Multiple(^4)</th>
<th>Other(^3)</th>
<th>None(^3)</th>
<th>E at two points(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>75.0 ± 5.4(^*)</td>
<td>75.1 ± 5.6</td>
<td>74.9 ± 5.2</td>
<td>76.3 ± 6.3</td>
<td>77.2 ± 6.5</td>
<td>78.2 ± 6.2</td>
<td>76.3 ± 6.4</td>
<td>75.4 ± 5.5</td>
</tr>
<tr>
<td>Men (%)</td>
<td>33.8</td>
<td>31.6</td>
<td>36.8</td>
<td>31.3</td>
<td>27.3</td>
<td>32.7</td>
<td>36.2</td>
<td>37.2</td>
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<tr>
<td>Women (%)</td>
<td>66.3</td>
<td>68.5</td>
<td>63.2</td>
<td>68.7</td>
<td>72.7</td>
<td>67.3</td>
<td>63.8</td>
<td>62.8</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>White</td>
<td>94.4</td>
<td>95.1</td>
<td>93.4</td>
<td>93.3</td>
<td>95.2</td>
<td>87.6</td>
<td>77.6</td>
<td>96.7</td>
</tr>
<tr>
<td>African American</td>
<td>5.6</td>
<td>4.9</td>
<td>6.6</td>
<td>6.7</td>
<td>4.8</td>
<td>12.5</td>
<td>22.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Education (y)</td>
<td>10.6 ± 3.2</td>
<td>10.9 ± 2.9</td>
<td>10.1 ± 3.6</td>
<td>10.3 ± 3.7</td>
<td>9.6 ± 3.5</td>
<td>9.5 ± 4.0</td>
<td>9.1 ± 3.7</td>
<td>10.2 ± 3.4</td>
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<tr>
<td>Alcohol use (%)</td>
<td>38.8</td>
<td>38.0</td>
<td>39.7</td>
<td>34.9</td>
<td>34.8</td>
<td>32.7</td>
<td>29.7</td>
<td>43.0</td>
</tr>
<tr>
<td>Cigarette use (%)</td>
<td></td>
<td></td>
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<tr>
<td>Current</td>
<td>11.3</td>
<td>10.3</td>
<td>12.5</td>
<td>6.7</td>
<td>11.3</td>
<td>9.3</td>
<td>12.4</td>
<td>15.7</td>
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<td>Past</td>
<td>23.4</td>
<td>21.7</td>
<td>25.7</td>
<td>24.2</td>
<td>21.5</td>
<td>23.7</td>
<td>23.1</td>
<td>17.4</td>
</tr>
<tr>
<td>Never</td>
<td>60.9</td>
<td>64.1</td>
<td>56.6</td>
<td>64.6</td>
<td>62.4</td>
<td>63.0</td>
<td>54.5</td>
<td>61.2</td>
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<tr>
<td>Missing data</td>
<td>4.4</td>
<td>3.8</td>
<td>5.2</td>
<td>4.6</td>
<td>4.9</td>
<td>3.9</td>
<td>10.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>28.8</td>
<td>25.0</td>
<td>33.8</td>
<td>26.8</td>
<td>29.0</td>
<td>20.6</td>
<td>14.7</td>
<td>32.2</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.7 ± 4.2</td>
<td>25.0 ± 4.0</td>
<td>23.5 ± 4.4</td>
<td>25.1 ± 4.2</td>
<td>24.7 ± 4.5</td>
<td>24.5 ± 4.7</td>
<td>25.8 ± 4.5</td>
<td>25.5 ± 3.9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21.9</td>
<td>20.6</td>
<td>23.5</td>
<td>20.3</td>
<td>23.1</td>
<td>16.0</td>
<td>22.5</td>
<td>21.5</td>
</tr>
<tr>
<td>Medical history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
<td>2.7</td>
<td>2.2</td>
<td>4.8</td>
<td>7.3</td>
<td>7.0</td>
<td>6.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart disease</td>
<td>9.7</td>
<td>9.2</td>
<td>10.3</td>
<td>11.2</td>
<td>11.8</td>
<td>12.5</td>
<td>11.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.3</td>
<td>9.2</td>
<td>11.8</td>
<td>11.5</td>
<td>12.3</td>
<td>15.6</td>
<td>17.1</td>
<td>12.4</td>
</tr>
<tr>
<td>Cancer</td>
<td>13.4</td>
<td>15.2</td>
<td>11.8</td>
<td>15.1</td>
<td>14.8</td>
<td>12.5</td>
<td>12.1</td>
<td>13.2</td>
</tr>
</tbody>
</table>

\(^1\) Vitamin E supplement use at baseline regardless of vitamin C supplement use.

\(^2\) Multiple vitamin/mineral supplement use.

\(^3\) Vitamin E supplement use at both baseline and study inception 3 y earlier.

\(^*\) ± SD.
stroke, 9.7% reported a history of heart disease, and 10.3% reported a history of diabetes. Among nonusers of supplements, 6.1% reported a history of stroke, 11.2% reported a history of heart disease, and 17.1% reported a history of diabetes. About 30% consumed alcohol in the past month and 14.7% used aspirin. Forty-three percent of persons who reported vitamin E supplement use at two points in time used alcohol, 32.2% used aspirin, and 1.7% reported a history of stroke. Among concurrent users of vitamins E and C, 64.1% never smoked cigarettes, 20.6% reported a history of hypertension, and 9.2% reported a history of heart disease. Of vitamin E supplement users alone, 56.6% never smoked, 23.5% reported a history of hypertension, and 10.3% reported a history of heart disease.

**Vitamin supplement use and mortality**

For all users of vitamin E supplements at baseline the RR of all-cause mortality was 0.66 (95% CI: 0.53, 0.83) compared with nonusers of supplements (Table 2) after adjustment for age and sex. Results were consistent when we used the study inception as the baseline, which added 3 y to the length of follow-up (data not shown). All those using vitamin E supplements showed a reduced risk of coronary heart disease mortality (RR = 0.53; 95% CI: 0.34, 0.84) compared with nonusers of any supplements. When we examined cancer mortality, the RR was 0.77 (95% CI: 0.49, 1.20) for users of vitamin E in relation to the reference group. The RR for all other causes of mortality was 0.67 (95% CI: 0.49, 0.93).

Use of vitamin E supplements at two points in time was associated with reduced risk of all-cause mortality (RR = 0.66; 95% CI: 0.45, 0.95) and coronary heart disease mortality (RR = 0.37; 95% CI: 0.15, 0.90) when compared with persons who did not use any vitamin supplements after adjustment for age and sex (Table 2). Adjustment for all covariates had little effect on the estimates of RR although CIs widened slightly (Table 3). The RR of cancer mortality was 0.41 when adjusted for age and sex or when adjusted for all covariates; however, CIs included 1.0 (Tables 2 and 3). The risk of the other remaining causes of mortality was not associated with duration of vitamin E supplement use.

Among users of vitamin E, users of both vitamin E and C had a lower risk of all-cause mortality (RR = 0.58; 95% CI: 0.42, 0.79) than all vitamin E users combined. Vitamin E use without vitamin C was associated with a 20% reduction in risk of death compared with nonusers (Table 2). There was no decrease in mortality risk for users of vitamin C alone, users of multiple vitamin/mineral supplements, or users of other supplements compared with nonusers.

Those using both vitamins E and C had a lower risk of coronary heart disease mortality (RR = 0.47; 95% CI: 0.25, 0.87) than nonusers, and vitamin E alone also showed an RR of 0.64 (95% CI: 0.33, 1.24). Similar magnitudes of risk were seen for cancer mortality and all other causes of mortality; however, CIs tended to include 1.0. When we further adjusted for health-related covariates, the results were slightly attenuated but remained consistent (Table 3). Despite these findings, no significant interaction could be shown for vitamins E and C for any of the four outcomes: all-cause, coronary heart disease mortality, cancer mortality, or all other causes of mortality.

**DISCUSSION**

We found independent protective effects of vitamin E supplements for all-cause mortality (RR = 0.73; 95% CI: 0.58, 0.91) after adjustment for demographic factors, health habits, and medical history compared with nonusers of vitamin supplements. We found the same effect for coronary heart disease mortality (RR = 0.59; 95% CI: 0.37, 0.93) after adjustment for all covariates. Vitamin C supplement use alone did not reduce the risk of mortality. Simultaneous use of vitamin E and vitamin C appeared to lower risk but was consistent with risks from use of vitamin E alone because no significant interaction could be shown. The greatest benefit in the risk of coronary heart disease mortality was found for users of vitamin E at two points in time. These findings are consistent with those of the Health Professionals Follow-up Study (28), a somewhat

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**TABLE 2**

Age- and sex-adjusted relative risk (RR) and 95% CIs of death according to vitamin supplement use for 11178 men and women

<table>
<thead>
<tr>
<th>Vitamin supplement use in three independent models</th>
<th>All-cause mortality (n = 3490)</th>
<th>Coronary disease mortality (n = 1101)</th>
<th>Cancer mortality (n = 761)</th>
<th>Other mortality (n = 1719)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>RR (95% CI)</td>
<td>Number of events</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All users of E&lt;sup&gt;1&lt;/sup&gt;</td>
<td>76</td>
<td>0.66 (0.53, 0.83)</td>
<td>19</td>
<td>0.53 (0.34, 0.84)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both E and C</td>
<td>40</td>
<td>0.58 (0.42, 0.79)</td>
<td>10</td>
<td>0.47 (0.25, 0.87)</td>
</tr>
<tr>
<td>E alone</td>
<td>36</td>
<td>0.80 (0.57, 1.11)</td>
<td>9</td>
<td>0.64 (0.33, 1.24)</td>
</tr>
<tr>
<td>C alone</td>
<td>154</td>
<td>1.04 (0.89, 1.23)</td>
<td>46</td>
<td>1.00 (0.74, 1.34)</td>
</tr>
<tr>
<td>Vitamin/mineral</td>
<td>302</td>
<td>1.04 (0.93, 1.18)</td>
<td>105</td>
<td>1.14 (0.93, 1.40)</td>
</tr>
<tr>
<td>Other</td>
<td>106</td>
<td>1.16 (0.96, 1.41)</td>
<td>33</td>
<td>1.14 (0.80, 1.61)</td>
</tr>
<tr>
<td>None (referent)</td>
<td>2852</td>
<td>1.00</td>
<td>898</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E at 2 points&lt;sup&gt;2&lt;/sup&gt;</td>
<td>28</td>
<td>0.66 (0.45, 0.95)</td>
<td>5</td>
<td>0.37 (0.15, 0.90)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Report of vitamin E supplement use at study baseline regardless of vitamin C supplement use compared with no vitamin supplement use.  
<sup>2</sup> Report of vitamin E supplement use at both baseline and study inception 3 y earlier compared with no vitamin supplement use.
TABLE 3
Multivariant relative risk (RR) and 95% CIs of death according to vitamin supplement use for 11,178 men and women

| Vitamin supplement use in three independent models | All cause mortality  
\( (n = 3490) \) | Coronary disease mortality  
\( (n = 1101) \) | Cancer mortality  
\( (n = 761) \) | Other mortality  
\( (n = 1719) \) |
<table>
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<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All users of E (^2)</td>
<td>0.73 (0.58–0.91)</td>
<td>0.59 (0.37–0.93)</td>
<td>0.78 (0.50–1.23)</td>
<td>0.74 (0.53–1.02)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both E and C</td>
<td>0.63 (0.46–0.86)</td>
<td>0.52 (0.28–0.97)</td>
<td>0.77 (0.43–1.37)</td>
<td>0.61 (0.39–0.96)</td>
</tr>
<tr>
<td>E alone</td>
<td>0.87 (0.63–1.22)</td>
<td>0.69 (0.36–1.34)</td>
<td>0.81 (0.40–1.63)</td>
<td>0.93 (0.59–1.47)</td>
</tr>
<tr>
<td>C alone</td>
<td>1.09 (0.93–1.28)</td>
<td>0.99 (0.74–1.33)</td>
<td>0.88 (0.61–1.28)</td>
<td>1.19 (0.95–1.49)</td>
</tr>
<tr>
<td>Vitamin/mineral</td>
<td>1.03 (0.91–1.16)</td>
<td>1.11 (0.91–1.36)</td>
<td>1.06 (0.82–1.37)</td>
<td>1.02 (0.85–1.21)</td>
</tr>
<tr>
<td>Other</td>
<td>1.17 (0.96–1.42)</td>
<td>1.13 (0.80–1.61)</td>
<td>0.76 (0.44–1.28)</td>
<td>1.33 (1.03–1.72)</td>
</tr>
<tr>
<td>None (referent)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E at two time points (^3)</td>
<td>0.71 (0.49–1.03)</td>
<td>0.40 (0.17–0.96)</td>
<td>0.41 (0.15–1.10)</td>
<td>0.99 (0.63–1.56)</td>
</tr>
</tbody>
</table>

\(^1\) Relative risk adjusted for age, sex, race, education, alcohol use, smoking history, aspirin use, coronary heart disease, stroke, diabetes, cancer, hypertension, and body mass index.

\(^2\) Report of vitamin E supplement use at study baseline regardless of vitamin C supplement use compared with no vitamin supplement use.

\(^3\) Report of vitamin E supplement use at both baseline and study inception 3 y earlier compared with no supplement use.

younger cohort, which found an inverse relation between vitamin E intake and coronary heart disease, but did not find a lower risk of coronary disease associated with vitamin C intake after adjustment for other risk factors.

Use of multiple vitamin/mineral supplements was not associated with risk of mortality. This is consistent with results of a prospective study of a nationally representative sample of 10,758 men and women aged 25–74 y in which no protection against mortality was found for vitamin/mineral supplement users compared with nonusers (46). In that study no differentiation was made among types of vitamin supplement used. Although multiple vitamin/mineral supplements may contain some vitamin E, the concentrations may not be high enough to be protective for all-cause and coronary heart disease mortality.

Limitations of our data prevent us from fully examining the relation of vitamin E with reduced mortality risk. Information about dietary intake of vitamin E was not collected. Several studies (16, 26, 27) have shown dietary vitamin E to be protective; however, more consistent beneficial effects have been reported with supplements. Again, we do not regard this to be a major problem because the dose of vitamin E derived from supplements is much higher than that from vitamin E obtainable by diet alone. A more important limitation may be that because no dietary data were available, we could not account for other possible beneficial effects of nutritional habits of vitamin E supplement users that could contribute to reduced risk of mortality, eg, lower fat intake or greater consumption of whole grains or fruits and vegetables containing β-carotene. However, when dietary fat and carotene intakes as well as physical activity were adjusted for in other large-scale prospective studies (28, 29), dietary intake and physical activity had little effect on the reduced risk associated with high vitamin E intake.

Information was not available about the dose of vitamin supplements or about how consistently vitamin supplements were used. It is possible that vitamin supplement use was underreported because some subjects may not have considered vitamins when asked about medications used. However, were a “true” causal relation to exist, misclassification of vitamin E use, dose, and consistency of vitamin E supplement use would tend to reduce the apparent strength of our findings. Lastly, we could not examine the duration of vitamin E supplement use without vitamin C because of a limited number of persons who reported use of vitamin E and vitamin C supplements at two points in time.

It is plausible that our results are due to confounding by other factors associated with vitamin supplement use, such as practice of better health habits and access to better health care by users compared with nonusers. Although users of vitamins E and C tended to have more years of education than did multiple vitamin/mineral supplement users and nonusers of any vitamin supplements, adjustment for education, a measure of socioeconomic status, did not affect the relation between vitamin supplement use and mortality. Furthermore, we adjusted the models for several health conditions known to be fairly well measured from self-report (47, 48), as well as for aspirin use. Our findings were significant even after these adjustments. To examine the possibility that persons with diagnosed coronary disease at baseline changed their health habits, including vitamin supplement use, we excluded persons who reported coronary disease at baseline. The results again remained consistent (data not shown). Furthermore, vitamin C use was also associated with higher education and better access to medical care and was not associated with a protective effect for mortality.

A plausible mechanism for lower coronary mortality among vitamin E users could be that the etiology of cardiovascular disease includes oxidation of LDL cholesterol, increased platelet adhesiveness, and arterial stiffness (1–4). By stabilizing the free radicals implicated in these causal factors, vitamin E could reduce the initiation or severity of coronary disease (2–5). Vitamin C in turn has a sparing effect on vitamin E (38). The same mechanism may explain our results for all-cause mortality because that group includes a large portion of cardiovascular and associated mortalities. The lower RR for cancer mortality in relation to vitamin E and vitamin C use may be explained by a reduction of free radical damage to DNA, a possible initiator of cancer. Also, these antioxidant vitamins have been associated with beneficial effects on immune func-
tion (8—12). This may also contribute to lower all-cause mortality by reducing disease or disease severity that may have lead to death.

The results of our analyses are consistent with the hypothesis that use of the antioxidant supplements, vitamin E along with vitamin C, may reduce the risk of all-cause and coronary heart disease mortality. Further research using prospective data and trials in the elderly is warranted.

REFERENCES