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Vitamin E Supplement Use and the Incidence of Cardiovascular Disease and All-Cause Mortality in the Framingham Heart Study: Does the Underlying Health Status Play a Role?

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Abstract

Background—Observational studies generally showed beneficial associations between supplemental vitamin E intake and cardiovascular disease (CVD) risk whereas intervention trials reported adverse effects of vitamin E supplements. We hypothesize that these discordant findings result from differing underlying health status of study participants in observational and intervention studies.

Objective—Determine if the relation between supplemental vitamin E intake and CVD and all-cause mortality (ACM) depends on pre-existing CVD.

Design—Proportional hazards regression to relate supplemental vitamin E intake to the 10-year incidence of CVD and ACM in 4,270 Framingham Study participants stratified by baseline CVD status.

Results—Eleven percent of participants used vitamin E supplements at baseline. In participants **with** pre-existing CVD, there were 28 (44%) and 20 (32%) incident cases of CVD and ACM in the vitamin E supplement users versus 249 (47%) and 202 (38%) in the non-users, respectively (CVD HR, 0.90; 95% CL, 0.60–1.32; ACM HR, 0.74; 95% CL, 0.46–1.17). In participants **without** pre-existing CVD, there were 51 (13%) and 47 (12%) cases of CVD and ACM in the vitamin E supplement group versus 428 (13%) and 342 (10%) in the non-vitamin E supplement group, respectively (CVD HR, 1.00; 95% CL, 0.75–1.34; ACM HR 1.20; 95% CL, 0.89–1.64).

Conclusion—CVD status has no apparent influence on the association of supplemental vitamin E intake and risk for CVD and ACM in this large, community-based study. Further research is needed to clarify the basis for the discrepant results between intervention and observational studies of supplemental vitamin E intake.

Keywords

Vitamin E supplements; health status; cardiovascular disease; all-cause mortality; Framingham Heart Study

INTRODUCTION

Several observational studies published in the 1990's suggested that higher vitamin E intake is associated with a significantly lower risk of cardiovascular disease (CVD)[1–4]. The Nurses Health Study and the Health Professionals Follow-up Study for example showed that higher vitamin E intake from supplements for more than two years significantly reduced the relative risk for coronary heart disease (CHD)[1, 2]. Results from these studies were the catalyst for randomized controlled vitamin E intervention trials. The majority of these intervention trials, however, did not support the hypothesis derived from the observational studies [5, 6]. Recently, unexpectedly, two meta-analyses of vitamin E intervention trials of CVD, cancer, and other diseases, reported an increased relative risk of all-cause mortality. Further, two individual vitamin E intervention trials reported increased risk of heart failure[7–10].

Previous observational studies of vitamin E supplement use and CVD focused on primary prevention and most excluded individuals with CVD at baseline, whereas the majority of the vitamin E intervention trials focused on secondary prevention and included individuals at high risk of CVD (e.g., patients with diabetes) or with pre-existing CVD. The meta-analyses, which are based on these intervention trials, therefore also mainly included individuals with pre-existing diseases.

Based on this major difference in design of the observational and intervention studies, we hypothesized that health effects of vitamin E supplement use vary, based on the underlying health status of individuals. Thus, the purpose of our study was to investigate both, primary and secondary prevention within an observational study. Specifically, we hypothesized that among individuals free of CVD we will observe a lower risk of CVD and all-cause mortality with vitamin E supplement use, and among individuals with pre-existing CVD, we will observe either no effect or harmful health effects.

To examine our hypothesis, we investigated the association between vitamin E supplement use and the risk of CVD and all-cause mortality in 4,270 participants of the Framingham Heart Study, stratifying our analyses by presence versus absence of prevalent CVD. In secondary analyses, we investigated the association between the vitamin E supplement dose and duration of use and the risk of CVD and all-cause mortality.

The single entity vitamin E supplement use is from here on described as "vitamin E supplement use" and does not include vitamin E from other sources such as multivitamin supplements or dietary vitamin E intake.

METHODS

Study Sample

The Framingham Heart Study, a prospective, population-based study on risk factors for CVD, began in 1948 enrolling 5209 men and women[11]. Participants in the original cohort are examined every two years. Details of the study design and selection criteria for the original Framingham Heart Study have been described elsewhere[12]. The Framingham Offspring Study began in 1971 with the recruitment of 5,124 men and women who were offspring and spouses of offspring of the above mentioned original Framingham Heart Study cohort. The

Framingham Offspring cohort has undergone repeat examinations at approximately three to four years intervals.

Outcomes and Eligibility

Participants were eligible for the present investigation if they attended the 20th examination of the original cohort (1986 through 1990, 1401 participants) or the 5th examination of the offspring cohort (1991 through 1995, 3799 participants). The 20th and 5th examinations were chosen in order to have a long enough follow-up for this analysis. Vitamin supplement data were routinely obtained at these examinations. Of 5,200 eligible participants, we excluded 930 participants (18%) due to missing data. Of the 930 excluded participants, 611 (65.7%) had missing data on Vitamin E use, 112 (12.0%) had missing data on covariates, and 207 (22.3%) participants had missing data on both covariates and Vitamin E use. Therefore, a total of 4,270 participants were available for the primary analyses of CVD and all-cause mortality. For the secondary analyses, among the 460 subjects taking vitamin E supplements, 50 had missing data on Vitamin E dose and 41 had missing data on Vitamin E duration. Therefore, a total of 4,220 participants were available for the dose analyses and 4,229 participants were available for the duration analyses.

We investigated the association between vitamin E supplement use, dose and duration, and two primary outcomes: incidence of CVD and all-cause mortality over a ten-year period. All participants are under continuous surveillance for the occurrence of CVD events and death. Participants are evaluated periodically at the Heart Study (every two years for original cohort and every 3–4 years for the Offspring cohort), and via health history updates in between examinations (obtained via telephone interviews). Hospitalization records and physician office visit records are obtained and reviewed by a committee of three experienced investigators. Each death is also reviewed by the same committee. As part of this review all available medical information about each death is used, including Framingham Heart Study records, hospitalization records, and when available, autopsy results. After review of each death, the panel jointly assigns an underlying cause of death, which is then coded and assigned to one of six mutually exclusive categories: coronary heart disease, stroke, other cardiovascular disease, cancer, other or unknown cause[13].

Criteria for the diagnoses of cardiovascular events have been described elsewhere[14]. Incident CVD includes coronary heart disease (recognized or unrecognized myocardial infarction, angina pectoris, coronary insufficiency, and coronary heart disease death), cerebrovascular disease (stroke or transient ischemic attack), congestive heart failure, or peripheral vascular disease (intermittent claudication). An unrecognized myocardial infarction was considered to have occurred if there was electrocardiographic evidence of significant loss of R waves or appearance of pathologic Q waves on serial tracings in the absence of a clinically recognized event[14]. Sudden death, defined as death occurring within one hour of onset of symptoms, is attributed to CHD unless another cause is apparent[13]. Informed consent was obtained from study participants and the research protocol was reviewed and approved by the institutional review board (IRB) of Boston University School of Medicine.

Assessment of Vitamin E Supplement Use, Dose and Duration

Vitamin E supplement use, dose and duration were assessed using the Harvard semi-quantitative food frequency questionnaire (FFQ)[15, 16]. The questionnaires were mailed to the participants before the examination and participants were asked to bring the completed questionnaire with them to their Heart Study examination, at which time the FFQs were reviewed by study staff together with the study participants. The FFQ contains specific questions regarding the use of multivitamin supplements and single-entity vitamin supplements including vitamin E. In addition to questions regarding use, the FFQ also inquired about

supplement dose and duration of use. FFQs were administered in the original cohort examinations 20, 21, and 22 (through 1994) and in all Offspring examinations from exam 5 on to the present.

The question regarding vitamin E supplement use was as follows: “Not counting multiple vitamins, do you take any of the following preparations?:” “Vitamin E?”, “Yes? No?”, “If yes, how many years, what dose per day?”. The response categories for duration of vitamin E supplement intake were as follows: “0–1 year”, “2–4 years”, “5–9 years”, “10+ years”, and “don’t know”. The response categories for dose of intake per day were as follows: less than 100 IU, 100–250 IU, 300–500 IU, 600 IU or more, and “don’t know”. Participants who responded “yes” to Vitamin E supplement use but did not provide dose and or duration information were set to missing in the dose and duration analyses, respectively, but were included in the supplement use yes/no analysis.

Statistical Analyses

Primary Analyses—We used Cox proportional-hazards regression models to examine the association of supplemental vitamin E intake with the incidence of CVD and all-cause mortality. For analysis of each of these two primary outcomes, we defined three groups of ‘at risk’ participants and performed separate regression analyses: a) participants with pre-existing CVD (“CVD participants”), b) “participants without pre-existing CVD”, and c) all participants combined (“all participants”).

We tested all models for interactions between vitamin E supplement use and sex, age, and cohort. All interactions were tested by including an interaction term which was the product of the variable of interest (vitamin E use) and the predictor. Sex and cohort were treated as dichotomous variables; age was treated as a continuous variable. No significant interactions were identified. All analyses were therefore conducted pooling both sexes, all age groups, and both cohorts. We also tested for interactions between supplement use and pre-existing CVD. Although we did not observe a statistically significant interaction, we present results by baseline CVD status because of our a priori hypothesis.

For each outcome, and for each ‘at risk’ group, we estimated the hazard ratios for CVD and all-cause mortality in participants taking vitamin E supplements as compared to participants not taking vitamin E supplements (who served as referent). The proportion hazards assumptions were tested and met for each of the Cox proportional-hazards regression models generated.

All Cox models were adjusted for age, sex, systolic blood pressure, treatment for hypertension, smoking, ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, body mass index (BMI), and type 2 diabetes mellitus (all defined at the baseline examinations). The ‘all participants’ group was additionally adjusted for ‘existing CVD on or before baseline exam date’ because that group included participants both with and without pre-existing CVD. Age, systolic blood pressure, ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, and BMI were treated as continuous variables; sex, diabetes, blood pressure treatment, current smoking, and CVD status were treated as dichotomous variables. These covariates were included because they were found to be predictive of CVD and all-cause mortality in prior Framingham Heart Study studies[17]. We also investigated anti-cholesterol treatment, aspirin use, and multivitamin supplement intake as potential confounders in all models. Anti-cholesterol treatment included resins and fibrates for examination 20, and additionally statins and niacins for examination 5 (offspring cohort).

Secondary analyses: We used Cox proportional-hazards regression models to examine the association of the supplemental vitamin E dose and duration intake with the incidence of CVD

and all-cause mortality. These models paralleled all of the above described analyses conducted for the primary analyses (separate regression analyses for all three groups of 'at risk' participants ("CVD participants", "participants without pre-existing CVD" and "all participants"). All models were controlled for the same covariates as the primary models and all the same interaction tests were conducted. In the interaction analyses, the categories for duration of vitamin E supplement intake and dose were treated as categorical variables (as listed in Table 1).

RESULTS

By the end of the 10 year follow-up period, 756 of the 4,270 participants experienced a CVD event (17.7%) and 611 participants had died of any cause (14.3%). In the "all participants" group, for CVD incidence and ACM, there were 79 (17%) and 67 (15%) cases in the vitamin E supplement group vs 677 (18%) and 544 (14%) in the non-vitamin E supplement group, respectively.

Baseline Characteristics

The characteristics of the study participants at the baseline examination of interest are shown in Table 1 for all participants and according to use of vitamin E supplements. Eleven percent of participants took single vitamin E supplements (460 of 4,270). Most characteristics were similar for participants taking vitamin E supplements versus those not taking vitamin E supplements. Compared to the participants who were not taking vitamin E supplements, the ones taking them were slightly but significantly older (by 1.1 years; $p=0.04$). Women comprised a greater proportion of participants taking vitamin E supplements than those not taking supplements (62% vs 53%; $p<0.001$). Participants in the users group had significantly higher BMI ($p=0.01$), although the difference is only 0.6 kg/m^2. Participants taking vitamin E supplements were also significantly more likely to take multivitamins than participants not using vitamin E supplements (63% vs 22%; $p<0.001$).

At study baseline, more than one-half of the participants who took vitamin E supplements had taken them for four years or less (30% for up to one year and 22% for 2–4 years), and 25% had taken them for ten or more years. The most commonly consumed dose was 300–500 IU. Of the Offspring cohort participants at exam 5 who took vitamin E supplements, 68.2% still took Vitamin E supplements at exam 6 (three to four years later). Of the original cohort participants at exam 20 who took vitamin E supplements, 57.6% still took vitamin E supplements at exam 21 (two years later).

Vitamin E supplement use and CVD and all-cause mortality

The incidence and hazard ratios for CVD and all-cause mortality associated with vitamin E supplement intake for the overall sample and according to prevalent CVD status at the baseline examination are shown in Table 2. No statistically significant associations between vitamin E supplement intake and CVD and all-cause mortality were observed in any of the three 'at risk' groups evaluated (all participants, individuals without and with pre-existing CVD).

In all models, age, diabetes, and treatment for blood pressure were significant positive predictors of CVD and all-cause mortality. Sex, systolic blood pressure (SBP), smoking, ratio of total cholesterol to HDL cholesterol, and BMI were significant predictors in some but not all of the models: Male sex, SBP, smoking, and ratio of total cholesterol to HDL cholesterol were positively associated and BMI was inversely associated with CVD and all-cause mortality. For reasons of consistency, all of the above mentioned covariates were included in all multivariate models. Hazard ratios and confidence limits did not change significantly when

aspirin use, anti-cholesterol treatment, or multivitamin use were included in all models (data not shown), and were therefore not included as covariates in the final models.

Dose and duration of vitamin E supplement use and CVD and all-cause mortality

In secondary analyses, we investigated the associations between dose and duration of use of vitamin E supplements and CVD and all-cause mortality for all three participant groups. Among the 460 participants taking vitamin E supplements, 410 were available for the dose analyses and 419 for the duration analyses. No statistically significant associations were observed in any of the analyses for CVD or all-cause mortality (data shown as Supplemental Table 1). We also investigated aspirin use, anti-cholesterol treatment, and multivitamin use as potential confounders in all dose and duration multivariate models. Adding these covariates to the models did not change the results.

DISCUSSION

We investigated the relations between supplemental vitamin E intake and risk of cardiovascular disease and all-cause mortality in the Framingham Heart Study, a large community-based observational study. Observational studies on vitamin E have generally investigated primary prevention, whereas intervention trials mainly focused on secondary prevention. The purpose of our study was to investigate both, primary and secondary prevention within an observational study, a novel systematic approach that has not been reported in the literature before. We conducted the analyses separately in participants who were free of overt CVD and in participants who had CVD at baseline.

Whether vitamin E supplement intake is beneficial or without any effect in the prevention of CVD has been vividly discussed in the scientific literature over the past decades. The discussion around vitamin E has gained special momentum over the course of the last three years when several studies were published reporting adverse effects of vitamin E supplementation, an effect that has not been reported before. These reports came from two meta-analyses of vitamin E intervention trials which reported increased risk of all-cause mortality[7, 8] and from two individual studies, the HOPE and GISSI studies[9, 10], which reported increased risk of heart failure. Bjelakovic et al. conducted a meta-analysis on randomized trials of antioxidant supplement intake and reported significantly increased mortality with vitamin E supplement intake. Miller et al. conducted a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality and reported a statistically significant relationship between vitamin E dosage and all-cause mortality with increased risk of high dose intake. The report by Miller et al., however, has been repeatedly questioned due to several limitations it had. The majority of trials included were secondary prevention trials, thus participants already had chronic diseases and therefore may have had a higher risk of mortality. It therefore is not applicable to a population free of chronic disease. Further, it combined trials that used synthetic and natural vitamin E which have different bioavailability[18]. The report also did not assess the adherence of study participants to vitamin E supplement intake[18] and the reported effect size of vitamin E treatment was quite small.

The two individual studies which reported adverse effect of vitamin E, were conducted in patients with pre-existing cardiovascular disease or diabetes, and the majority of intervention trials included in both meta-analyses were also conducted in patients with various pre-existing chronic diseases or risk factors thereof. Observational studies conducted in the 1990ies, on the other hand, have never reported adverse effects with supplemental vitamin E intake and the majority has observed beneficial effects. Observational studies are generally conducted in participants without overt chronic diseases.

Based on this background, we hypothesized that a possible reason for the discordance between observational studies (no effect or protective effect) and the recently published studies reporting adverse effects is the underlying health status of their study participants. However, there are other differences in design between intervention studies and observational studies of vitamin E supplements and CVD. A major difference is the greater susceptibility of observational studies to bias. Other differences include the usual duration of exposure of vitamin E supplements, which tends to be longer in observational studies.

The underlying rationale for our hypothesis was based on recent data, albeit limited, suggesting that high vitamin E intake may affect drug metabolism[19–21]. It has been reported that high alpha-tocopherol (the most biologically active form of vitamin E and almost exclusively used in vitamin E intervention trials) intake may adversely affect drug metabolism by up-regulating CYP3A, the major enzyme involved in the metabolism of a majority of therapeutic agents. This up-regulation could therefore lead to a faster metabolizing of therapeutic agents and thus decrease their efficacies[19–21]. Given that individuals with pre-existing chronic diseases are more likely to be on medications for their conditions, vitamin E supplement use could therefore potentially diminish the effect of these medications, leading to a higher incidence of CVD or all-cause mortality in these individuals compared to individuals not taking medications.

Our analyses did not support this hypothesis. We did not observe any evidence of increased risk of CVD or all-cause mortality with supplemental vitamin E intake in individuals with pre-existing CVD, nor did we see any evidence of decreased risk in individuals without chronic disease in the Framingham Heart Study. However, given the width of the confidence intervals for all-cause mortality in participants without pre-existing disease, we cannot rule out an elevated risk among supplement users. Likewise, for we cannot rule out a possible protective association with all-cause mortality among those with pre-existing CVD. These relatively wide confidence intervals are a consequence of the relatively small number of participants taking vitamin E supplements.

Other potential limitations of our study was its observational design, limiting causal inference and increasing the likelihood of confounding relative to intervention trials, and the possible lack of generalizability of our findings from this cohort that is predominantly Caucasian. The strength of the present study includes the large community-based cohort of men and women, and the well-characterized CVD endpoints.

Although our results are inconsistent with our hypothesis of a differential effect of vitamin E supplementation among those with and without pre-existing disease, the above mentioned limitations prevent us from drawing any definitive conclusions about the benefit or harm of supplemental vitamin E intake from this study. Therefore, discrepancy between the results from observational studies and from the recent clinical and meta-analyses studies reporting adverse effects has not been resolved and the basis of this difference is not clear yet. Further systematic exploration of this intriguing hypothesis in other populations is warranted in order to find out if study participants' underlying health statuses may be the reason for the discrepancy.

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Table 1

Baseline characteristics of study participants by vitamin E supplement use at baseline and dose and duration data of vitamin E supplement intake

Characteristics	All participants n=4270	Participants taking vitamin E supplements* n=460 (11%)	Participants not taking vitamin E supplements n=3810 (89%)	P-value**
Age, mean (SD)	59.5 (12.5)	60.5 (11.4)	59.4 (12.6)	0.04
range, y	26–95	31–92	26–95	-
Women, n, (%)	2299 (54%)	284 (62%)	2015 (53%)	<0.001
Diabetes mellitus Type 2, n, (%)	347 (8%)	29 (6%)	318 (8%)	0.13
Blood pressure, mean (SD), mmHg,				
Systolic	130.9 (21.3)	130.6 (20.6)	130.9 (21.4)	0.76
Diastolic	75.0 (10.2)	74.3 (10.0)	75.1 (10.2)	0.11
Current cigarette smoking§, n (%)	736 (17%)	75 (16%)	661 (17%)	0.57
Body mass index, mean (SD), kg/m^2	27.2 (4.9)	26.7 (4.9)	27.3 (4.9)	0.01
Total cholesterol/HDL cholesterol, mean (SD)	4.6 (1.6)	4.6 (1.7)	4.6 (1.6)	0.92
Hypertension†, n, (%)	1879 (44%)	204 (44%)	1675 (44%)	0.87
CVD at baseline‡, n, (%)	594 (14%)	63 (14%)	531 (14%)	0.89
Multivitamins consumed, n (%)	1124 (26%)	280 (63%)	844 (22%)	<0.001
Vitamin E dose¶, n, (%)				
Less than 100 IU	-	27 (6%)	-	
100–250 IU	-	71 (15%)	-	
300–500 IU	-	255 (55%)	-	
600 or more IU	-	57 (12%)	-	
unknown	-	50 (12%)	-	
Vitamin E duration¶, n, (%)				
0–1 year	-	139 (30%)	-	
2–4 years	-	101 (22%)	-	
5–9 years	-	65 (14%)	-	
10+ years	-	114 (25%)	-	
unknown	-	41 (9%)	-	

[*] Refers to single vitamin E supplement intake, not including vitamin E from multivitamins.

[**] P-values for comparison of characteristics between participants taking vitamin E supplements and participants not taking vitamin E supplements: two sample independent t-tests were conducted for the continuous variables and chi-square tests were conducted for the dichotomous variables.

Abbreviations: HDL, high-density lipoprotein; CVD, cardiovascular disease; IU, International Unit.

[§] within the last year;

[†] Hypertension was defined as systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg or use of blood-pressure lowering medications.

[‡] CVD was defined as any of the following: coronary heart disease (myocardial infarction, angina pectoris, coronary insufficiency, death from CHD (sudden and not sudden), other CVD deaths, cerebrovascular events (atherothrombotic infarction, transient ischemic attack, cerebral embolism), intermittent claudication, and congestive heart failure.

[¶] dose and duration data was available on 410 and 419 participants of the 460 participants, respectively.

Table 2

Incidence and Hazard Ratios of CVD and all-cause mortality associated with vitamin E supplement intake according to health status at baseline examination

	Participants taking vitamin E supplements no. of events/no. at risk (%)	Participants not taking vitamin E supplements no. of events/no. at risk (%)	Hazard Ratio (95% Confidence Limit)*	p-value
CVD				
CVD participants	28/63 (44%)	249/531 (47%)	0.90 (0.60–1.32)	0.58
Participants without pre-existing CVD	51/397 (13%)	428/3279 (13%)	1.00 (0.75–1.34)	0.99
All participants	79/460 (17%)	677/3810 (18%)	0.94 (0.75–1.19)	0.63
All-cause mortality				
CVD participants	20/63 (32%)	202/531 (38%)	0.74 (0.46–1.17)	0.20
Participants without pre-existing CVD	47/397 (12%)	342/3279 (10%)	1.20 (0.89–1.64)	0.24
All participants	67/460 (15%)	544/3810 (14%)	1.01 (0.78–1.30)	0.95

* Multivariate Cox Proportional Hazard model adjusted for age, sex, diabetes mellitus type 2, systolic blood pressure, blood pressure treatment, current smoking, total cholesterol/HDL ratio, body mass index. The “all participants” analyses were additionally adjusted for CVD at baseline. CVD participants n=594; Participants without pre-existing disease n=3,676; All participants n=4,270.