Original Article

Vitamin E and Risk of Type 2 Diabetes in the Women's Health Study Randomized Controlled Trial

Simin Liu,[1,2,3] I-Min Lee,[1,2] Yiqing Song,[1] Martin Van Denburgh,[1] Nancy R. Cook,[1,2] JoAnn E. Manson,[1,2] and Julie E. Buring[1,2,4,5]

We directly assessed the efficacy of vitamin E supplements for primary prevention of type 2 diabetes among apparently healthy women in the Women's Health Study randomized trial. Between 1992 and 2004, 38,716 apparently healthy U.S. women aged ≥45 years and free of diabetes, cancer, and cardiovascular disease were in two randomly assigned intervention groups and received 600 IU of vitamin E (α-tocopherol, *n* = 19,347) or placebo (*n* = 19,369) on alternate days. During a median 10-year follow-up, there were 827 cases of incident type 2 diabetes in the vitamin E group and 869 in the placebo group, a nonsignificant 5% risk reduction (relative risk [RR] 0.95 [95% CI 0.87–1.05], *P* = 0.31). There was no evidence that diabetes risk factors including age, BMI, postmenopausal hormone use, multivitamin use, physical activity, alcohol intake, and smoking status modified the effect of vitamin E on the risk of type 2 diabetes. In a sensitivity analysis taking compliance into account, women in the vitamin E group had an RR of 0.93 (95% CI 0.83–1.04) (*P* = 0.21) compared with those randomized to placebo. In this large trial with 10-year follow-up, alternate-day doses of 600 IU vitamin E provided no significant benefit for type 2 diabetes in initially healthy women. *Diabetes* 55:2856–2862, 2006

Oxidative stress due to increased production of reactive oxygen species and decreased antioxidant status have been implicated in the pathogenesis of type 2 diabetes and its complications (1–4). Experimental studies suggested that oxidative stress impaired pancreatic β-cell insulin secretion (2,5), interfered with glucose disposal in peripheral tissues (2,3), and elicited systemic inflammation (3), thereby accelerating the development and progression of type 2 diabetes. Vitamin E is a major lipid-soluble chain-breaking antioxidant with anti-inflammatory properties (6,7). In vitro studies indicated that vitamin E may improve insulin action and insulin secretion by protecting peripheral tissues and β-cells from free radical–mediated damage, leading to the hypothesis that this vitamin may help delay the development of type 2 diabetes (6–8).

In animal models, diabetes can be induced by reactive free radicals (9), and vitamin E can act as scavengers of these oxygen radicals in preventing the development of diabetes (10–12). In observational epidemiologic studies, an inverse association between serum or plasma levels of α-tocopherol and type 2 diabetes risk was observed in some (13–16), but not all, case-control and cohort studies (17,18). In a large cohort of Finnish men and women, those who self-selected for higher intake of dietary vitamin E experienced a significantly decreased incidence of type 2 diabetes (19). However, observational studies cannot fully address biases due to selection of the study population, measurement error of dietary vitamin E intake, and residual confounding from other unmeasured or imperfectly measured risk factors such as highly correlated dietary or lifestyle factors (20). Well-designed and -conducted randomized trials, the most reliable design strategy, can avoid most of the biases inherent in observational studies and help evaluate a possible causal relationship between vitamin E and risk of type 2 diabetes (20); however, there are no previous trials examining the efficacy of vitamin E supplementation in the primary prevention of type 2 diabetes thus far.

To provide direct evidence, we examined whether vitamin E supplementation decreased the incidence of type 2 diabetes in the Women's Health Study (WHS), a randomized, double-blind, placebo-controlled trial conducted over an average duration of 10.1 years.

RESEARCH DESIGN AND METHODS

The WHS was a two-by-two factorial trial evaluating the balance of risks and benefits of low-dose aspirin (100 mg every other day; Bayer Healthcare) and vitamin E (600 IU α-tocopherol every other day; Natural Source Vitamin E Association) in the primary prevention of cardiovascular disease and cancer (21,22). Originally, a third component, β-carotene, was also included. However, this component was terminated early in January 1996, after a median treatment duration of 2.1 years (23). Written informed consent was obtained from all women. The trial was approved by the institutional review board of Brigham and Women's Hospital and monitored by an external data- and safety-monitoring board.

Details of the study design and recruitment process have been described previously (21,22,24). In brief, between September 1992 and May 1995, a total of 65,169 female health professionals were identified throughout the U.S., who were willing and eligible to participate. Eligibility criteria included age ≥45 years; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of side effects from aspirin; no use of aspirin or nonsteroidal

From the [1]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the [2]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [3]Department of Epidemiology and Center for Human Nutrition, University of California, Los Angeles, California; the [4]Division of Aging, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the [5]Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Simin Liu, MD, ScD, Department of Epidemiology, UCLA School of Public Health, 71-254 CHS, Box 951772, 650 Charles E. Young Dr. South, Los Angeles, CA 90095-1772. E-mail: siminliu@ucla.edu.

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anti-inflammatory medications more than once a week (or willingness to forego their use); no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or β-carotene more than once a week. Eligible women were enrolled into a 3-month run-in period using placebo medications to identify likely long-term compliers to pill taking. Following the run-in period, 39,876 women remained willing, eligible, and compliant and were randomized using blocks of 16 within a 5-year age strata to vitamin E or placebo. In the present analyses, we excluded women with prevalent diabetes at baseline (n = 1,160), leaving a total of 38,716 women; 19,347 were assigned to vitamin E and 19,369 to placebo.

Each year, participants received calendar packs that contained amber capsules (vitamin E or placebo) and white pills (aspirin or placebo) on alternate days. Every 6 months for the 1st year and annually thereafter, they also received follow-up questionnaires inquiring about compliance with pill taking, potential side effects, occurrence of end points, and risk factors. Study medications and end point ascertainment were continued in blinded fashion through the scheduled end of the trial (31 March 2004). Follow-up and validation of reported end points were completed in February 2005. Morbidity and mortality follow-up were 97.2 and 99.4% complete, respectively.

Using the information provided on questionnaires, compliance, defined as taking at least two-thirds of the study capsules, was 78.9% at 5 years and 71.6% at 10 years. Averaged throughout the trial, it was 75.8% with no difference between active and placebo groups (P = 0.64). Nontrial use of individual supplements of vitamin E on ≥4 days/month ("drop-ins") was 10.0% at 5 years and 10.9% at 10 years. Averaged throughout the trial, outside use was somewhat lower in the active (8.6%) than placebo (8.9%) group (P = 0.07).

Confirmation of incident type 2 diabetes. Details regarding the ascertainment of incident type 2 diabetes in the WHS have been reported previously (25). Briefly, participants were asked annually whether and when they had been diagnosed with diabetes since baseline. In this study, screening rates for diabetes were high, with at least 85–90% of all participants reporting a recent blood glucose screening on their annual questionnaire. Using the diagnostic criteria recommended by the American Diabetes Association (ADA) (26), all self-reported cases of type 2 diabetes were confirmed by a supplemental questionnaire, which was validated by medical record review. Only confirmed cases of incident type 2 diabetes are included in this report.

We also conducted a small validation study by using three complementary approaches to assess the validity of self-reported incident cases of diabetes. Method 1 involved a telephone interview by a study physician of 473 women with self-reported diabetes who participated in a previous study (27). Method 2 used a supplemental questionnaire that contained detailed information mailed to a random sample of 147 women who self-reported diabetes. Method 3 involved contacting individual physicians for medical records of those women consenting for medical record review in method 2. Using method 1, self-reported diagnoses of type 2 diabetes were confirmed in 406 of 446 women who responded via a physician-led telephone interview (positive predictive value 91.0% [95% CI 88.4–93.7]). For method 2, among 136 responders to the supplemental questionnaire, there were 124 diabetic women who were classified using the ADA criteria (91.2% [86.4–95.9]). With method 3, among 113 women who gave permission for study investigators to contact their primary care physician, 97 physicians responded, of whom 90 provided adequate medical record information to apply the ADA criteria. Of these 90 women, 89 were confirmed to have diabetes on the basis of the combined information from the supplemental questionnaire and physician information. Thus, we believe that self-reported type 2 diabetes is valid in the WHS.

Statistical analysis. Primary analyses were performed on an intention-to-treat basis, including all randomized women without self-reported diabetes at baseline, as randomized. All analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC), and a two-sided significance level of $\alpha = 0.05$ was used ($P \leq 0.05$).

The divergence of incidence over time between the vitamin E and placebo groups was estimated using Kaplan-Meier survival curves, and the log-rank test was computed to compare curves. We used Cox proportional hazard models to calculate the estimates of relative risks (RRs) and 95% CIs, comparing event rates in the vitamin E and placebo groups after adjustment for age and randomized assignment of aspirin and β-carotene. To test the proportionality assumption (i.e., that of nonchanging RRs over time), we included an interaction term of vitamin E with the logarithm of time in the Cox models.

Subgroup analyses were conducted to examine the effect of vitamin E on risk of type 2 diabetes according to major risk factors for type 2 diabetes at baseline, including age-groups (45–54, 55–64, and ≥65 years), BMI (calculated as weight in kilograms divided by the square of height in meters), smoking (current, past, or never), alcohol use (<1 or ≥1 drink per week), family history of diabetes (yes or no), physical activity (estimated energy expenditure from leisure activities of <1,000 or ≥1,000 kcal per week), menopausal status and hormone therapy (uncertain menopausal status, premenopausal, or postmenopausal including current, past, or never users of hormone therapy), and randomized assignment of aspirin and β-carotene. We assessed effect modification using interaction terms between subgroup indicators and vitamin E assignment, testing for trend when subgroup categories were ordinal.

To examine the effect of actual as opposed to assigned vitamin E use, we carried out a sensitivity analysis according to compliance. Women were censored if and when they stopped taking at least two-thirds of their study pills, whether active vitamin E or placebo. To assess the effect of nontrial use of individual supplements of vitamin E, we also did an additional sensitivity analysis where women were censored when they stopped taking at least two-thirds of their study pills or reported outside use of vitamin E supplements for at least 4 days per month.

RESULTS

The mean age of women at baseline was 54.6 years, and clinical characteristics were evenly distributed in the vitamin E and placebo groups (Table 1), which was expected in this very large sample through effective randomization. The average duration of follow-up from randomization to the end of the trial was 10.0 years (median 9.8 years), during which 1,696 women were diagnosed with type 2 diabetes (827 in the vitamin E group and 869 in the placebo group) (Table 2). There was no significant effect of vitamin E on the development of type 2 diabetes (RR 0.95 [95% CI 0.87–1.05], P = 0.31).

When the period of risk was subdivided by years of follow-up, no benefit was observed for any time period or duration of treatment (Table 2). There also were no effects on type 2 diabetes when excluding cases that occurred in the first 2 or 5 years of follow-up. Figure 1 shows the cumulative incidence rates of type 2 diabetes events among women in the two groups by year of follow-up. The curves were almost identical in the vitamin E and placebo groups. After 3 years of follow-up, a small reduction in the incidence curve of the vitamin E group compared with that of the placebo group was observed, but this was not statistically significant (P = 0.31 by the log-rank test). A test for proportionality of the hazard ratio over time showed no statistically significant trend over time (P = 0.72).

There was no evidence that any of the prespecified diabetes risk factors considered, except family history of diabetes, modified the effect of vitamin E on type 2 diabetes (Table 3). A marginally significant reduction in risk of type 2 diabetes among women assigned to vitamin E was observed among those without a family history of diabetes (RR 0.88 [95% CI 0.78–1.00]) but not among those with a family history (1.05 [0.91–1.21]), where the interaction was marginally significant (P = 0.07). In addition, neither treatment with aspirin nor treatment with β-carotene significantly modified the effect of vitamin E on type 2 diabetes. Similar associations between vitamin E supplementation and the occurrence of type 2 diabetes persisted in multivariate analysis adjusting for age, aspirin assignment, β-carotene assignment, BMI, smoking status, alcohol intake, physical activity, history of high cholesterol or hypertension, use of multivitamins, menopausal status and hormone therapy use, and family history of diabetes. Since compliance diminished over time, we performed a sensitivity analysis that censored noncompliant women at the time they stopped taking at least two-thirds of their study pills during the preceding year. In this analysis, there also was no significant benefit of vitamin E (0.93 [0.83–1.04], P = 0.21). In a separate analysis where women were censored at the time they stopped taking at least two-

TABLE 1
Baseline characteristics of women according to vitamin E and placebo groups, WHS

Characteristic	Vitamin E	Placebo	Total	*P* value
n	19,347	19,369	38,716	
Age (years)	54.6 ± 7.0	54.6 ± 7.0	54.6 ± 7.0	0.89
45–54	11,730 ± 60.6	11,743 ± 60.6	23,473 ± 60.6	0.92
55–64	5,666 ± 29.3	5,651 ± 29.2	11,317 ± 29.2	
≥65	1,951 ± 10.1	1,975 ± 10.2	3,926 ± 10.1	
Smoking status				
Current	2,515 (13.0)	2,562 (13.2)	5,077 (13.1)	0.52
Past	6,971 (36.1)	6,877 (35.5)	13,848 (35.8)	
Never	9,842 (50.9)	9,913 (51.2)	19,755 (51.1)	
Alcohol Intake				
Never/rarely	8,644 (44.7)	8,523 (44.0)	17,167 (44.4)	0.18
At least once a month	10,696 (55.3)	10,843 (56.0)	21,539 (55.6)	
Multivitamin use				
Yes	7,599 (39.3)	7,465 (38.5)	15,064 (38.9)	0.14
No	11,748 (60.7)	11,904 (61.5)	23,652 (61.1)	
BMI (kg/m^2)	25.9 ± 4.98	25.9 ± 4.95	25.9 ± 4.96	0.94
<25	9,784 ± 51.7	9,871 ± 52.0	19,655 ± 51.8	0.70
25 to <30	5,887 ± 31.1	5,826 ± 30.7	11,713 ± 30.9	
≥30	3,271 ± 17.3	3,292 ± 17.3	6,563 ± 17.3	
Physical activity (kcal/week)	979 ± 1,245	973 ± 1,212	976 ± 1,229	0.66
≤1,000	12,626 ± 66.1	12,566 ± 65.7	25,192 ± 65.9	0.34
>1,000	6,470 ± 33.9	6,573 ± 34.3	13,043 ± 34.1	
Menopausal status and HT use				
Premenopausal	5,349 (27.7)	5,408 (28.0)	10,757 (27.9)	0.96
Uncertain	3,455 (17.9)	3,471 (18.0)	6,926 (17.9)	
Postmenopausal, current HT use	5,845 (30.3)	5,841 (30.2)	11,686 (30.3)	
Postmenopausal, past HT use	1,319 (6.83)	1,308 (6.77)	2,627 (6.80)	
Postmenopausal, never used HT	3,331 (17.3)	3,290 (17.0)	6,621 (17.2)	
Hypertension*				
Yes	4,738 (24.5)	4,852 (25.1)	9,590 (24.8)	0.20
No	14,607 (75.5)	14,510 (74.9)	29,117 (75.2)	
Hyperlipidemia†				
Yes	5,565 (28.8)	5,643 (29.2)	11,208 (29.0)	0.41
No	13,776 (71.2)	13,716 (70.9)	27,492 (71.0)	
Family history of diabetes‡				
Yes	4,801 (24.8)	4,820 (24.9)	9,621 (24.8)	0.87
No	14,546 (75.2)	14,549 (75.1)	29,095 (75.2)	

Data are means ± SD or *n* (%). *Hypertension was defined as a self-reported systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or physician-diagnosed hypertension. †Hyperlipidemia was defined as a self-reported total cholesterol ≥240 mg/dl or physician-diagnosed high cholesterol. ‡Family history of diabetes was defined as self-reported diabetes in a first-degree relative. HT, hormone therapy.

thirds of their study pills or started to use outside vitamin E supplements on ≥4 days per month, findings were similarly nonsignificant.

DISCUSSION

In this large, double-blind, placebo-controlled, primary-prevention trial in 38,716 initially healthy women, vitamin E supplementation at a dose of 600 IU every other day for 10 years was not associated with a significant reduction in the risk of type 2 diabetes. A modest and marginally significant protective effect on type 2 diabetes was observed among women without family history of diabetes; however, this subgroup finding may have emerged by chance due to multiple comparison and needs to be confirmed in future investigations.

Several previous trials of healthy persons have shown that high intake of vitamin E supplementation can decrease lipid peroxidation (28–30) and proinflammatory markers (31) and improve glucose disposal (32), supporting the role of vitamin E as a potent antioxidant in primary prevention of type 2 diabetes. Also, three prospective studies (14–16) have consistently reported an RR of 0.12–0.61 in comparisons of groups with the lowest and highest categories of serum or plasma levels of α-tocopherol. However, evidence from observational studies may be limited because of potential biases due to residual confounding, measurement errors, and statistical uncertainty due to highly correlated dietary or lifestyle factors. The net effect from such biases can be as large as the postulated benefit and thereby disrupt a true small to moderate effect that cannot be detected in observational settings (20).

Some small and short-term randomized trials, most designed to examine the effect of vitamin E supplementation on diabetes-related phenotypes (e.g., glycemic control, insulin sensitivity) among patients with type 2 diabetes, have been conducted to directly test the efficacy of vitamin E in the secondary prevention of type 2 diabetes (32–38). Of them, five randomized placebo-controlled trials with a sample size from 15 to 57 participants found that vitamin E supplementation with dosages from 600 to 1,600 IU reduced oxidative stress and improved glycemic con-

TABLE 2
RRs and 95% CIs for type 2 diabetes according to vitamin E and placebo groups, WHS

Follow-up interval (years)	Vitamin E (n = 19,347)	Placebo (n = 19,369)	RR (95% CI)*	P value
End of study	827	869	0.95 (0.87–1.05)	0.31
1–2	91	87	1.05 (0.78–1.41)	0.76
3–4	151	183	0.83 (0.67–1.03)	0.08
5–6	176	197	0.89 (0.73–1.09)	0.27
7–8	166	163	1.02 (0.82–1.26)	0.87
9–10	215	209	1.03 (0.85–1.24)	0.78
11–12	28	30	0.94 (0.56–1.57)	0.80
0–5 follow-up years	418	467	0.90 (0.79–1.02)	0.10
≥6 follow-up years	409	402	1.02 (0.89–1.17)	0.81
Excluding first 2 years	736	782	0.94 (0.85–1.04)	0.24
Excluding first 5 years	496	504	0.98 (0.87–1.11)	0.79
Compliance analyses†	539	581	0.93 (0.83–1.04)	0.21
Compliance analyses‡	499	525	0.95 (0.84–1.07)	0.36

*Adjusted for age and randomized assignment of aspirin and β-carotene. †Sensitivity analysis; censored when patient stopped reporting taking at least two-thirds of vitamin E or placebo pills. ‡Censored when patient stopped reporting taking at least two-thirds of vitamin E or placebo pills or if they were taking four out-of-trial vitamin E pills per month.

trol among diabetic patients during a period of 4–16 weeks (32,35–38).

To date, no randomized trials, however, have directly assessed the efficacy of vitamin E supplements in the primary prevention of type 2 diabetes. Because of its large sample size, long follow-up period, high rates of compliance, and a large number of diabetes outcomes, the WHS had high statistical power to detect a modest-to-moderate intervention effect. Our finding of a lack of benefit from vitamin E appears to be congruent with previous data from the Physicians' Health Study, showing a lack of efficacy of β-carotene supplementation for the primary prevention of type 2 diabetes (39). Similarly, β-carotene was thought to exert a protective effect against the development of type 2

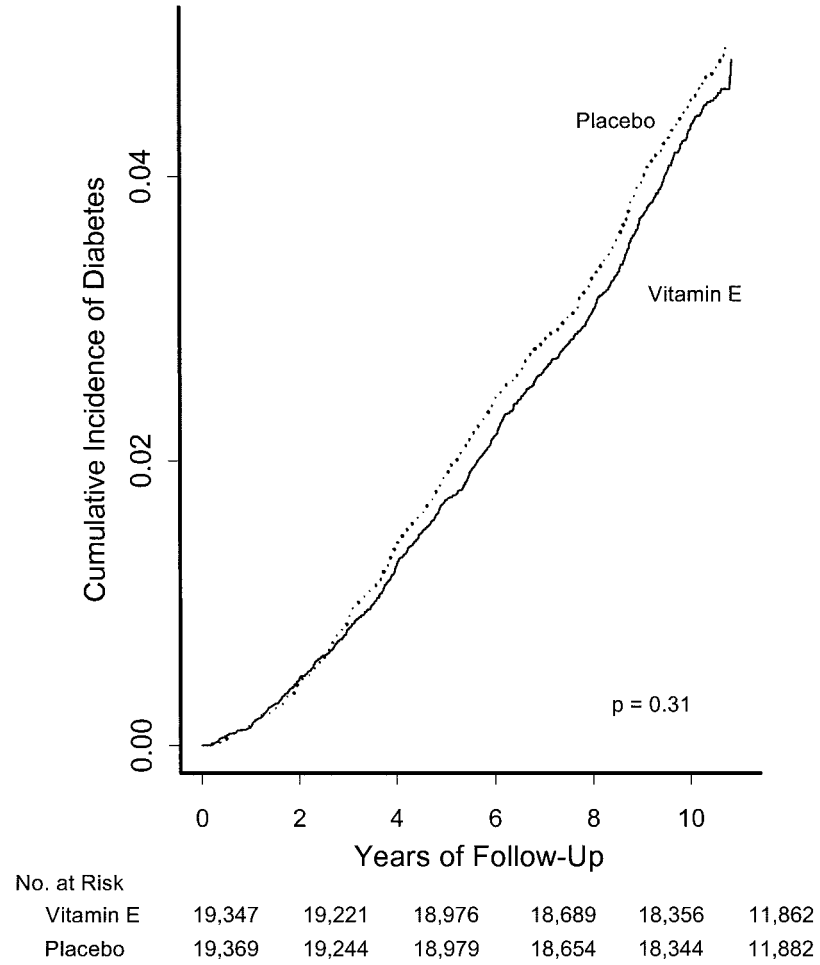

FIG. 1. Cumulative incidence rates of type 2 diabetes according to vitamin E or placebo groups.

TABLE 3
RRs and 95% CIs for type 2 diabetes comparing vitamin E and placebo groups, according to baseline characteristics, WHS

Group	*n*	Vitamin E (*n*)	Placebo (*n*)	RR (95% CI)*	*P* value	Multivariate adjusted RR (95% CI)†	*P* value
Age (years)							
45–54	23,473	465	483	0.96 (0.85–1.09)	0.56	0.98 (0.86–1.11)	0.72
55–64	11,317	283	311	0.91 (0.77–1.07)	0.23	0.90 (0.76–1.06)	0.20
≥65	3,926	79	75	1.06 (0.78–1.46)	0.71	1.06 (0.77–1.46)	0.72
Smoking status							
Current	5,077	121	134	0.91 (0.72–1.17)	0.47	0.91 (0.71–1.18)	0.47
Past	13,848	293	299	0.97 (0.83–1.14)	0.74	0.97 (0.83–1.15)	0.76
Never	19,755	413	435	0.95 (0.83–1.09)	0.47	0.95 (0.83–1.09)	0.48
Alcohol intake							
Never/rarely	17,167	519	516	0.99 (0.88–1.12)	0.89	1.02 (0.90–1.15)	0.82
At least once a month	21,539	308	353	0.88 (0.76–1.03)	0.11	0.88 (0.75–1.02)	0.10
Multivitamin use							
Yes	15,064	284	311	0.90 (0.77–1.06)	0.19	0.91 (0.77–1.07)	0.25
No	23,652	543	558	0.99 (0.88–1.11)	0.82	0.99 (0.88–1.11)	0.83
BMI (kg/m^2)							
<25	19,655	105	117	0.91 (0.70–1.18)	0.46	0.92 (0.70–1.19)	0.52
25 to <30	11,713	252	268	0.93 (0.78–1.10)	0.38	0.93 (0.78–1.11)	0.42
≥30	6,563	441	463	0.96 (0.84–1.09)	0.51	0.98 (0.86–1.12)	0.77
Physical activity (kcal/week)							
≤1,000	25,192	601	632	0.94 (0.84–1.06)	0.31	0.96 (0.86–1.08)	0.48
>1,000	13,043	208	228	0.93 (0.77–1.12)	0.42	0.95 (0.79–1.15)	0.61
Menopausal status and HT use							
Premenopausal	10,757	172	183	0.95 (0.77–1.17)	0.62	0.98 (0.79–1.22)	0.86
Uncertain	6,926	175	196	0.89 (0.73–1.10)	0.28	0.89 (0.72–1.10)	0.27
Postmenopausal, current HT use	11,686	206	218	0.94 (0.78–1.14)	0.54	0.96 (0.79–1.17)	0.69
Postmenopausal, past HT use	2,627	91	83	1.10 (0.82–1.48)	0.52	1.12 (0.82–1.52)	0.47
Postmenopausal, never used HT	6,621	182	183	0.98 (0.80–1.21)	0.86	0.94 (0.76–1.16)	0.56
Hypertension‡							
Yes	9,590	422	466	0.93 (0.81–1.06)	0.25	0.92 (0.81–1.06)	0.24
No	29,117	404	403	1.00 (0.87–1.14)	0.95	1.00 (0.87–1.15)	0.97
Hyperlipidemia§							
Yes	11,208	347	381	0.92 (0.80–1.07)	0.28	0.93 (0.80–1.08)	0.34
No	27,492	480	486	0.98 (0.87–1.11)	0.77	0.97 (0.86–1.11)	0.68
Randomized aspirin							
Yes	19,326	405	444	0.91 (0.80–1.04)	0.17	0.92 (0.80–1.05)	0.21
No	19,390	422	425	0.99 (0.87–1.14)	0.93	1.00 (0.87–1.15)	0.99
Family history of diabetes							
Yes	9,621	393	378	1.05 (0.91–1.21)	0.53	1.05 (0.91–1.21)	0.54
No	29,095	434	491	0.88 (0.78–1.00)	0.06	0.89 (0.78–1.01)	0.07

*Adjusted for age and randomized assignment of aspirin and β-carotene. †Adjusted for age, aspirin assignment, β-carotene assignment, smoking status, alcohol intake, physical activity, BMI, history of high cholesterol or hypertension, multivitamin use, menopausal status and hormone therapy (HT) use, and family history of diabetes; none of the interactions were significant. ‡Hypertension was defined as a self-reported systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or physician-diagnosed hypertension. §Hyperlipidemia was defined as a self-reported total cholesterol ≥240 mg/dl or physician-diagnosed high cholesterol.

diabetes via an antioxidant effect. In that randomized, placebo-controlled trial of 22,071 healthy U.S. male physicians, β-carotene supplementation at 50 mg on alternate days had no effect on the risk of developing type 2 diabetes; the RR was 0.98 (95% CI 0.85–1.12) after 12 years (39).

Only one of our subgroup analyses showed that vitamin E supplementation conferred a modest benefit on type 2 diabetes only among women without family history of diabetes. The observed reduction in the risk of type 2 diabetes could be due to chance. It is also possible that the underlying genetic predisposition among women with a family history for developing type 2 diabetes is so strong that it is unlikely to be subject to modulation by any modest beneficial effects of vitamin E supplementation. However, this specific finding from subgroup analysis needs to be confirmed in future studies.

Several alternative explanations should be considered for the lack of overall benefit on type 2 diabetes in the WHS. First, the dose of vitamin E may be a matter of debate. Previous secondary prevention trials showing that vitamin E supplementation can reduce oxidative stress and improve glycemic control in diabetic patients who used doses of 600–1,600 IU per day (32,35–38). However, an effective vitamin E dose for nondiabetic individuals seems to be as low as 300 IU per day. For example, in the Antioxidant Supplementation in Atherosclerosis Prevention study of 48 Finnish men and women with hypercholesterolemia, daily supplementation of 272 IU vitamin E increased plasma vitamin E levels >60% and decreased

lipid peroxidation by 50% during the first 12 or 36 months (30). The WHS used a roughly equivalent dose of 600 IU every other day; thus, insufficient dose of vitamin E is an unlikely explanation for the null findings observed. Of note, concerns have also been raised regarding the potential adverse effect of high-dose vitamin E supplementation in apparently healthy people. There is evidence to show that vitamin E supplementation at dosages >400 IU per day increased all-cause mortality (40), and high doses of α-tocopherol may have the potential as a possible prooxidant (41).

Second, declining compliance over time in the WHS may have diluted the findings. However, in sensitivity analyses where follow-up time was censored among women taking less than two-thirds of their study pills and where follow-up time was censored when outside use of vitamin E exceeded guidelines, there was little change in the findings. Furthermore, vitamin E from diet or other sources is an unlikely explanation for our null findings, since dietary intake should have been comparable in the active treatment and placebo groups and additional accounting for outside use of vitamin E also did not make a difference. Third, the hypothesis has been raised that antioxidants may provide a greater benefit in prevention of type 2 diabetes among women who smoke or who have hypertension or hyperlipidemia because these risk factors are associated with increased production of reactive oxygen species and lipid peroxidation. We did not have a direct measure of oxidative stress; however, we found no evidence of benefit of vitamin E among individuals with these conditions of increased oxidative stress. Additionally, a lack of benefit was observed among both users and nonusers of multivitamins, who would presumably have lower and higher levels of oxidative stress, respectively. These findings provide little support for a potentially important effect of vitamin E supplementation in the primary prevention of type 2 diabetes.

Fourth, the possibility exists that γ-tocopherol, rather than vitamin E (or α-tocopherol), may have important antioxidant activity (42). γ-Tocopherol is the most common form of vitamin E from foods, and vitamin E intake from food sources alone may impact the biologic effects of vitamin E supplements. However, α-tocopherol also has been shown to have high antioxidant and anti-inflammatory activities (6, 7). Additionally, α-tocopherol is the most common form used in vitamin supplements (43) in the U.S. and thus deserves evaluation of its clinical benefits among healthy populations. In addition, our cohort is a well-nourished, healthy population, likely to have adequate antioxidant status; thus, the power to detect a potentially modest protective effect of α-tocopherol may be limited.

Finally, underdiagnosis of type 2 diabetes may be a concern because the study population was not screened for glucose tolerance and the diagnosis was self-reported. However, our validation study of self-reported diabetes in the WHS indicated a high rate of agreement with medical record review. This validation result reflects the fact that all participants in this study are health professionals, who are likely to have more robust and valid self-reported diagnostic information. More importantly, the relatively high screening rate of WHS health professionals (85–90% for blood glucose screening) also reduces the likelihood of underdiagnosis. In addition, the proportions of underdiagnosed cases are likely to be nondifferential between the vitamin E group and placebo group due to effective randomization and double-blinding strategies. Thus, underdiagnosis would be less likely to bias the RR estimates in our intent-to-treat analysis.

In conclusion, 600 IU of vitamin E administered every other day for 10 years had no significant beneficial effect on risk of type 2 diabetes in apparently healthy women aged ≥45 years. These findings do not support recommending vitamin E supplementation for the primary prevention of type 2 diabetes, at least in middle-aged or older women.

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