Plasma and Dietary Vitamin E in Relation to Incidence of Type 2 Diabetes

The Insulin Resistance and Atherosclerosis Study (IRAS)

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OBJECTIVE — To evaluate the association of vitamin E with incidence of type 2 diabetes and to do so separately among individuals who did and those who did not report regular use of vitamin supplementation.

RESEARCH DESIGN AND METHODS — The Insulin Resistance Atherosclerosis Study (IRAS) included 895 nondiabetic adults at baseline (including 303 with impaired glucose tolerance [IGT]), 148 of whom developed type 2 diabetes according to World Health Organization (WHO) criteria during the 5-year follow-up. At baseline, dietary vitamin E was estimated by a validated food frequency interview, usual supplement use was confirmed by supplement label, and plasma α-tocopherol was measured. Analyses were conducted separately for individuals who did (n = 318) and did not (n = 577) use vitamin E supplements.

RESULTS — Among supplement nonusers, reported mean intake of vitamin E (mg α-tocopherol equivalents [α-TE]) did not differ between those who remained nondiabetic (n = 490) and those who developed diabetes (n = 87) (10.5 ± 5.5 vs. 9.5 ± 4.8 [means ± SD], respectively, NS). After adjustment for demographic variables, obesity, physical activity, and other nutrients, the association remained nonsignificant (odds ratio [OR] 0.80, 95% CI 0.13–5.06) for the highest level of intake (≥20 mg α-TE) compared with the lowest level (1–4 α-TE). However, results for plasma concentration of α-tocopherol showed a significant protective effect both before and after adjustment for potential confounders (adjusted OR 0.12, 95% CI 0.02–0.68, for the highest quintile vs. the lowest quintile; overall test for trend, $P < 0.01$). Among individuals who reported habitual use of vitamin E supplements (at least once per month in the year before baseline; 259 remained nondiabetic and 59 developed diabetes), no protective effect was observed for either reported intake of vitamin E or plasma concentration of α-tocopherol

CONCLUSIONS — A protective effect of vitamin E may exist within the range of intake available from food. This effect may go undetected within studies of high-dose supplement use, which appears to hold no additional protective benefit.

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In 2000, the prevalence of diagnosed diabetes in the U.S. was estimated at 7.3% (1), an alarming 49% increase from 1990 (2). The economic cost resulting from the numerous and severe complications of diabetes, which in 1997 was estimated at $98 billion (3), as well as the social burden associated with diabetes, have motivated the pursuit of prevention methods. Approaches for primary prevention of type 2 diabetes through lifestyle modifications that include weight management, diet, and physical activity have recently been reviewed (4).

The potential for antioxidant nutrients, particularly vitamin E, to prevent chronic diseases, including diabetes (5), remains uncertain. Results from a 4-year cohort study showed a 22% increment in diabetes risk per 1-μmol/l decrement in plasma α-tocopherol levels (P = 0.0004) (6). Of interest, the vast majority of participants (932 subjects, 98.7%) did not use supplements of vitamin E. A similar study produced quantitatively similar results; however, statistical significance was not achieved (7). It has been suggested that vitamin E improves insulin sensitivity, although studies generally have focused on the potential effect of supplemental vitamin E on insulin sensitivity and results have been equivocal (8–11). Therefore, we undertook this study to examine the potential effect of plasma α-tocopherol concentration and intake of vitamin E from foods and supplements on the development of type 2 diabetes in a large cohort of men and women who were observed in a 5-year prospective study. To clarify the range of exposure within which a beneficial effect of vitamin E may exist, we examined the data separately between individuals who did and those who did not report regular use of vitamin supplementation.

RESEARCH DESIGN AND METHODS

Study design

The design and methods of the Insulin Resistance and Atherosclerosis Study (IRAS) have been previously described in detail (12). Briefly, IRAS is a longitudinal, multicenter study of the relationships among insulin, insulin resistance, cardiovascular disease, and its risk factors in individuals with a broad range of glucose tolerance. The baseline examination for IRAS (exam 1) was conducted from October 1992 to April 1994. A total of 1,625

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Abbreviations: α-TE, α-tocopherol equivalents; FFQ, food frequency questionnaire; IGT, impaired glucose tolerance; IRAS, Insulin Resistance and Atherosclerosis Study; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

individuals aged 40–69 years were recruited from four clinical centers. The centers in San Antonio, TX, and San Luis Valley, CO, recruited African-Americans and non-Hispanic whites, and the centers in Los Angeles, CA, and Oakland, CA, recruited Hispanics and non-Hispanic whites. By design, sufficient numbers of individuals in different age, sex, ethnic, and glucose tolerance groups were included to allow efficient study of relations between and among these groups. Individuals who took insulin or who had fasting plasma glucose levels ≥300 mg/dl were excluded. The 5-year follow-up examination of the IRAS cohort began in February 1998 and was completed in July 1999 (exam 2). The response rate for the follow-up examination was 81%. This report includes data on 895 individuals with either normal or impaired glucose tolerance (IGT) at baseline who also participated in the 5-year follow-up examination.

Diabetes diagnosis

At baseline and the 5-year follow-up, the IRAS clinical examination consisted of two 4-h visits scheduled 1 week apart. Before each clinic visit, participants were asked to refrain from alcohol and vigorous activity for 24 h, from food for 10–12 h, and from smoking on the day of the visit. A 2-h 75-g oral glucose tolerance test (Orange-dex; Custom Laboratories, Baltimore, MD) was performed during the first clinic visit, and blood was collected for fasting and 2-h glucose samples. Individuals taking oral hypoglycemic agents were assumed to have type 2 diabetes. Otherwise, the World Health Organization (WHO) criteria (13) were used to assign glucose tolerance status based on the results of the oral glucose tolerance test.

Laboratory measurements

Plasma glucose concentration was measured in duplicate using the glucose oxidase technique on an autoanalyzer (Yellow Springs Equipment, Yellow Springs, OH). For baseline α-tocopherol concentration, samples were drawn into an EDTA vacutainer tube and the resulting plasma was stored at −70°C until the assay was conducted ~5 years later. It was previously shown that α-tocopherol assays were stable under similar conditions over a 7-year period (I. King, personal communication). Sufficient stored sample volume allowed for the tocopherol assay to be conducted on 755 subjects.

The extraction of analytes from plasma, the quality control parameters, and the high-performance liquid chromatography (HPLC) methods for α- and γ-tocopherol have been previously published (14). A purified hexane extract of plasma was injected onto a 3-mm C-18 Ultrasphere HPLC column (Beckman, Folsom, CA) and eluted with an isocratic solvent consisting of 98% methanol, 2% methylene chloride, 0.025% ammonium acetate, and 0.05% diethylamine (vol/vol) at the flow rate of 1.2 ml/min. α-Tocopherol was detected at 292 nm. A blinded split sample was evaluated for 10% of IRAS participants. Coefficients of variation for both exams ranged from 0.04 to 0.06.

Plasma lipids and lipoprotein concentrations were assessed quantitatively in the laboratory of MedStar Research Institute (Washington, DC). All plasma values were obtained following an overnight fast.

Nutrient intake

Usual nutrient intake over the year before the baseline examination was assessed with a 114-item food frequency questionnaire (FFQ) modified from the National Cancer Institute–Health Habits and History Questionnaire (15,16) to incorporate regional and ethnic food choices. The nutrient database (HHHQ-DIETSYS Analysis Software, Version 3.0 NCI, 1993) was expanded to accommodate the new foods based on values obtained from the Minnesota Nutrition Data System, Program Version 2.3 (Minnesota Nutrition Data System, 1990). The validity and reproducibility of this instrument to measure nutrient intake has been demonstrated in a subset of non-Hispanic white, African-American, and Hispanic IRAS participants (186 women equally distributed by ethnicity and urban/rural clinical center) (17).

Regular use of nutritional supplements was queried and defined as use at least once per month. Among those who used supplements regularly, usual frequency (number of pills per day, week, or month) and dosages were queried. Vitamin E dosage was confirmed from product labels brought into clinic by the participants and was summed across all products that contained vitamin E (multivitamins and vitamin E pills). To standardize the biologic activity of tocopherols from food and supplements so that total intake could be calculated, intake of vitamin E was expressed as milligrams of α-tocopherol equivalents (α-TE) (5).

Usual alcohol intake over the past year was assessed by the FFQ. Grams of alcohol per day were converted to drinks per day assuming an average of 12 g of ethanol per drink. Participants were classified as never drinkers, past drinkers, or within five categories of current drinkers.

Other measurements

BMI was computed as measured weight (in kilograms) divided by height (in meters) squared. Weight was measured to the nearest 0.1 kg, in light clothing. Height was measured to the nearest 0.5 cm, with shoes removed. Minimum waist circumference was measured and recorded to the nearest 0.5 cm. Standardized interviewing procedures were used to assess age, educational attainment, and smoking status. Frequency of participation in vigorous physical activity was ascertained using a validated five-level response set (18). Data collection staff were centrally trained and certified, and data quality was monitored throughout the study.

Statistical analysis

Statistical analyses were performed using the SAS statistical software (Release 6.12; SAS Institute, Cary, NC). All analyses were conducted separately for individuals who did and those who did not report use of vitamin E supplements (including multivitamins and/or single-nutrient supplementation).

The distribution of total vitamin E intake was distinctly different between users and nonusers of vitamin E supplements (Fig. 1). Therefore, categories of vitamin E intake were created separately for the two groups to facilitate interpretation of results in terms of typical dietary and supplement behaviors. Categories for intake from food sources alone (i.e., for supplement nonusers) were (in mg α-TE): <5, 5 to <10, 10 to <20, and ≥ 20. This scheme approximated cut points for the 25th, 75th, and 97–98th percentiles of intake, respectively, from the Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996 (5). For supplement users, categories were (in mg α-TE): <23.7, 23.7 to <37.1, 37.1 to <278.3, and ≥278.3. This scheme approximated

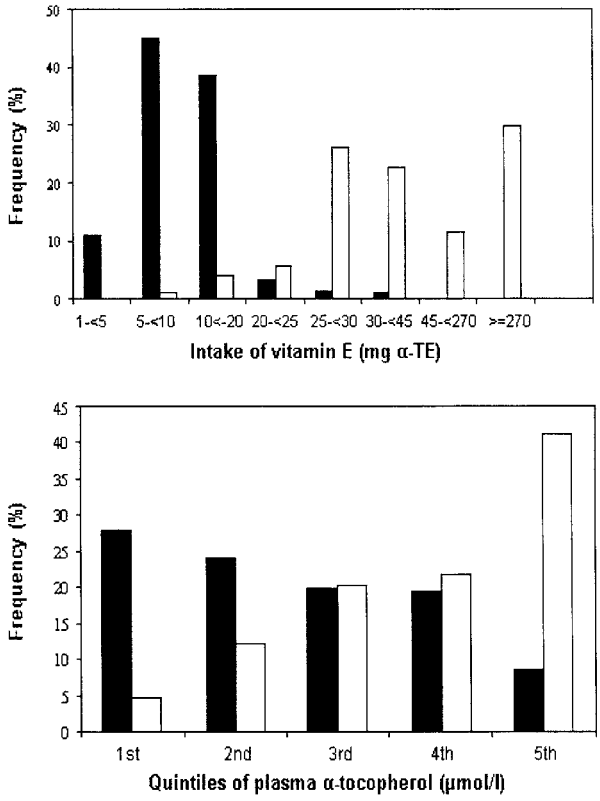

Figure 1—*Distribution of vitamin E intake and plasma α-tocopherol according to vitamin E supplement use.* ■*, Supplement nonusers;* □*, supplement users.*

intake from food plus supplements based on commonly available supplemental vitamin E doses. Thus, categories reflected intake from food plus occasional use of a multivitamin, daily use of a multivitamin, daily use of a single dose supplement of 40 to <400 IU vitamin E, and daily use of a single dose supplement of ≥400 IU vitamin E, respectively.

Although the distribution of plasma concentrations of α-tocopherol between users and nonusers of vitamin E supplements overlapped to a greater extent than the distributions for total intake (Fig. 1), quintiles of α-tocopherol were constructed separately for users and nonusers of supplements, and statistical modeling was conducted stratified by vitamin E supplement use. The values for α-tocopherol (in μmol/l) quintiles were: <20.54, 20.54 to <24.48, 24.48 to <28.16, 28.16 to <33.68, and ≥33.68 for nonusers, and <27.95, 27.95 to <32.24, 32.24 to <38.67, 38.67 to <49.86, and ≥49.86 for vitamin E supplement-users.

Because α-tocopherol is transported in lipoprotein particles, linear regression was used to adjust for plasma concentration of cholesterol and triglycerides, as suggested by Jordan et al. (19). Multivariable logistic regression was used to estimate odds ratios (ORs) and their respective 95% confidence intervals to quantify the relationship between vitamin E (baseline intake or baseline plasma α-tocopherol at exam 1) and diabetes incidence (new diagnosis of type 2 diabetes at exam 2). Four series of models were constructed to evaluate separately the exposures of reported intake and plasma concentration among supplement users and nonusers. Variables included initially as potential confounders included glucose tolerance at baseline (normal or IGT), demographic variables (age, sex, ethnicity, and clinical center), family history of diabetes, perceived health, total caloric intake, and, for analyses of plasma α-tocopherol concentration, plasma cholesterol and triglycerides. A subsequent model added potential behavioral confounders: BMI, waist circumference, smoking status, frequency of participation in vigorous physical activity, alcohol intake, intake of dietary fat, fiber, and intake of magnesium and vitamin C from food and supplements. From each of these models, *P* values are reported from the F statistic that tested for overall difference across categories of vitamin E.

RESULTS — Because analyses were stratified according to vitamin E supplement use, participant characteristics were compared according to supplement use at exam 1. Compared with nonusers of vitamin E supplements, supplement users were more likely to be older (mean age [±SD] 55.8 ± 8.3 vs. 54.0 ± 8.5 years for supplement users and nonusers, respectively, $P = 0.002$) and to have attained a higher educational level (% with >12 years of education 68.2 vs. 59.6 for supplement users and nonusers, respectively, $P = 0.03$). No other statistically significant differences were observed between supplementation groups for BMI, weight, waist circumference, insulin sensitivity, alcohol use, smoking status, perceived health, and family history of diabetes.

Analyses among nonusers of vitamin E supplements

Table 1 presents baseline characteristics of participants who did not use vitamin E supplements, according to diabetes incidence confirmed at the follow-up examination. Nonusers of supplements who developed diabetes were more likely to have had higher baseline BMI, to have had a family history of diabetes, and more likely to perceive their health as fair or poor compared with those with normal or impaired glucose tolerance at follow-up. Differences in reported intake of vitamin E did not reach statistical significance; however, individuals with incident diabetes had significantly lower levels of plasma α-tocopherol at baseline than those who remained free of diabetes.

Table 2 presents two logistic regression models of the relationship between intake of vitamin E and diabetes incidence among nonusers of vitamin E supplements. Consistent with the descriptive data, after adjustment for potential confounders, no association was observed for intake of vitamin E from food and incidence of diabetes 5 years later.

Also consistent with the descriptive data, after adjustment for demographic as well as dietary and other potential confounding variables in the multivariable logistic regression analysis, a statistically significant inverse association was ob-

Table 1—*Baseline characteristics of users and nonusers of vitamin E supplements, according to follow-up diabetes status: IRAS*

	Supplement nonusers		Supplement users	
	NGT/IGT	Diabetes	NGT/IGT	Incident diabetes
n	490	87	259	59
Age (years)	53.8 ± 8.6	55.0 ± 7.8	55.3 ± 8.4	57.8 ± 7.6*
BMI (kg/m^2)	28.1 ± 5.3	30.6 ± 6.2†	27.5 ± 5.3	31.9 ± 6.5†
Family history of diabetes (%)	39.4	55.2†	38.2	47.5
Perceived health (%)				
Excellent health	33.7	23.0	35.1	25.4
Good	51.6	56.3	51.0	50.9
Fair	13.7	17.2	13.5	23.7
Poor	1.0	3.5*	0.4	0.0
Vitamin E, diet (mg α-TE)	10.5 ± 5.5	9.5 ± 4.8	9.9 ± 5.2	10.6 ± 5.5
Vitamin E, supplements (mg α-TE)	—	—	223.5 ± 332.1	168.5 ± 223.6
Plasma α-tocopherol (μmol/l)‡	28.0 ± 8.8	25.7 ± 7.5*	38.9 ± 15.6	41.7 ± 17.8
Lipid-adjusted plasma α-tocopherol (μmol/l)§	28.1 ± 8.8	25.1 ± 7.5†	39.3 ± 15.6	39.9 ± 17.8

Data are means ± SD, *$P < 0.05$, †$P < 0.01$; ‡$n = 483$ (supplement nonusers) and $n = 272$ (supplement users); §$n = 483$ (supplement nonusers) and $n = 272$ (supplement users), adjusted for total cholesterol and triglyceride concentration by linear regression. NGT, normal glucose tolerance.

served across levels of plasma α-tocopherol in relation to diabetes incidence (fully adjusted OR 0.12, 95% CI 0.02–0.68 for the highest quintile compared with the lowest quintile; overall $P < 0.01$) among individuals who did not regularly use vitamin E supplements (Table 2).

Analyses among users of vitamin E supplements

Characteristics of supplement users according to diabetes status at the follow-up examination are presented in Table 1. Individuals who developed incident diabetes were older at baseline and had a higher BMI. Results from the multivariable logistic regression analysis did not reveal an association between total intake of vitamin E (from food plus supplements) and diabetes incidence (Table 3). After adjustment for potential confounding variables, no protective effect of plasma concentration of α-tocopherol on diabetes incidence was observed among supplement users (Table 3).

All models shown in Tables 2 and 3 were repeated with the addition of the appropriate interaction term to test whether associations of vitamin E with type 2 diabetes incidence differed according to baseline status of having normal glucose tolerance versus IGT. All interaction terms were nonsignificant (all $P >$ 0.35). Finally, associations with γ-tocopherol were evaluated, following the same statistical procedures as were used for α-tocopherol. No statistically significant associations were observed for γ-tocopherol in relation to type 2 diabetes incidence (data not shown).

CONCLUSIONS — Results of the present prospective study showed a statistically significant protective effect of increasing concentration of plasma α-tocopherol with reduced risk of diabetes incidence; however, this effect was limited to subjects who did not take vitamin E supplements. Among these supplement nonusers, the statistically significant protective effect was independent of potentially confounding variables, including BMI, family history of diabetes, physical activity, and a number of dietary factors (total energy intake, total fat, fiber, vitamin C, and magnesium).

The result for plasma α-tocopherol concentration among supplement nonusers was similar to that reported by Salonen et al. (6), who conducted a prospective study of vitamin E intake and plasma levels on the development of type 2 diabetes among 944 middle-aged men in Eastern Finland. The average dietary intake of vitamin E among these men (9.9 mg), as well as plasma levels of α-tocopherol (19 μmol/l), were low and the use of supplements rare (1.3%); thus, con-

Table 2—*ORs for development of type 2 diabetes by category of vitamin E intake (mg α-TE) and quintile of plasma α-tocopherol (μmol/l) among nonusers of vitamin E supplements: IRAS*

	Model 1*		Model 2†	
	OR	95% CI	OR	95% CI
Vitamin E intake (mg α-TE)				
1–4.9 ($n = 47$)	1.00	Referent	1.00	Referent
5–9.9 ($n = 217$)	1.08	0.42–3.80	1.00	0.43–2.31
10–19.9 ($n = 190$)	0.71	0.22–2.25	0.61	0.21–1.84
≥20 ($n = 29$)	1.01	0.16–6.33	0.80	0.13–5.06
	Overall F statistic *P* value, NS		Overall F statistic *P* value, NS	
α-Tocopherol quintile value (μmol/l)				
<20.54	1.00	Referent	1.00	Referent
20.54 to <24.48	0.42	0.18–0.96	0.52	0.22–1.27
24.48 to <28.16	0.75	0.32–1.75	0.99	0.40–2.45
28.16 to <33.68	0.13	0.04–0.45	0.16	0.04–0.60
≥33.68	0.12	0.02–0.63	0.12	0.02–0.68
	Overall F statistic *P* value <0.01		Overall F statistic *P* value <0.01	

*Adjusted for glucose tolerance status at baseline, age, ethnicity, clinic, sex, general health, family history of diabetes, and calories; †adjusted for all covariates included in model 1, plus BMI, waist circumference, smoking status, participation in vigorous physical activity, total fat intake, fiber intake, alcohol intake, and intake of magnesium and vitamin C from food and supplements.

Table 3—*OR for development of type 2 diabetes by category of total vitamin E intake (mg α-TE) and quintile of plasma α-tocopherol (μmol/l) among users of vitamin E supplements: IRAS*

	Model 1*		Model 2†	
	OR	95% CI	OR	95% CI
Vitamin E intake (mg α-TE)				
1 to <23.7 (n = 17)	1.00	Referent	1.00	Referent
23.7 to <37.1 (n = 121)	0.90	0.21–3.81	0.94	0.22–3.96
37.1 to <278.3 (n = 49)	1.19	0.26–5.52	1.34	0.29–6.19
≥278.3 (n = 75)	0.65	0.14–2.93	0.70	0.17–3.51
	Overall F statistic *P* value, NS		Overall F statistic *P* value, NS	
α-Tocopherol quintile value (μmol/l)				
<27.95	1.00	Referent	1.00	Referent
27.95 to <32.24	1.38	0.17–11.41	2.94	0.24–35.53
32.24 to <38.67	0.41	0.05–3.44	0.56	0.04–7.16
38.67 to <49.86	1.41	0.18–10.81	3.10	0.25–38.23
≥49.86	0.77	0.10–6.19	1.37	0.11–17.18
	Overall F statistic *P* value, NS		Overall F statistic *P* value, NS	

*Adjusted for glucose tolerance status at baseline, age, ethnicity, clinic, sex, general health, family history of diabetes, and calories; †adjusted for all covariates included in model 1, plus BMI, waist circumference, smoking status, participation in vigorous physical activity, total fat intake, fiber intake, alcohol intake, and intake of magnesium and vitamin C from food and supplements.

clusions could not be drawn about the potential effect of vitamin E supplementation. Although the original IRAS did not put forth an a priori hypothesis of a protective effect of vitamin E on diabetes incidence, the consistency of the present report with the Finnish data, as well as the magnitude of effect observed and the *P* value (<0.01), lend credence to the results presented for α-tocopherol among supplement nonusers.

The present study allowed for evaluation of the potential effect of plasma α-tocopherol concentrations among both individuals who did and those who did not take vitamin E supplements. Because of the highly discrepant distribution of plasma α-tocopherol concentration in supplement users versus nonusers, it was necessary to construct quintiles for these groups separately. Thus, it was not possible to evaluate possible protective effects of α-tocopherol at comparable concentrations for supplement users and nonusers. Our results suggest, however, that while a significant protective effect was detected clearly within supplement nonusers, no protective effect was demonstrated across the higher concentrations observable among individuals who regularly used vitamin E supplements, either before or after adjustment for potential confounders. This finding was unexpected, although Kushi et al. (20) noted that a protective effect of vitamin E intake on mortality from coronary heart disease among over 34,000 women was limited to those women who did not take vitamin E supplements.

Recently, it has been noted that vitamin E obtained from foods containing relatively small amounts of the nutrient may provide a range of health benefits to a greater extent than large doses of vitamin E taken in supplemental form, even after considering the known difference in biologic activity in the form of tocopherol found in supplements compared with the tocopherols found in food (which was accounted for in the present analysis) (21). Such differential effects may relate to nutrient (or nonnutrient) interactions that impact vitamin E activity in vivo, including the potential for vitamin E to act as a pro-oxidant under some circumstances, rather than an antioxidant. Plasma concentration of α-tocopherol has been a focus of much research because, although the most common form of vitamin E in food is γ-tocopherol, α-tocopherol is preferentially transported in lipoproteins as a result of α-tocopherol transfer protein activity (22). Biologic mechanisms for these and other forms of vitamin E may play different and perhaps complementary roles in health status. For example, although the antioxidant effects of α-tocopherol have been postulated as a mechanism for improved insulin sensitivity (6), other mechanisms may operate as well, including an effect of γ-tocopherol on insulin secretion (23). In the present study, however, γ-tocopherol concentration was not significantly associated with diabetes incidence.

With regard to results for reported total intake of vitamin E on diabetes incidence, results among supplement nonusers suggested that intake was lower among individuals who developed diabetes (Table 1), but after adjustment for all potential confounders, this was not statistically significant (Table 2). For those who obtained vitamin E from a combination of food and supplements, total intake was not associated with significantly reduced risk for diabetes incidence. A previously conducted study of the validity of the dietary assessment instrument in a subset of 186 female participants in IRAS showed that the correlation coefficient of reported intake of vitamin E from the food frequency interview with the average of eight 24-h recalls was 0.20 for food sources alone and was 0.82 for total intake (food and supplements combined) (17). Under-reporting of vitamin E from food may occur because major food sources of this nutrient tend to be high in fat, and these foods may be systematically underreported (24). However, it can be reasonably assumed that the error in estimated vitamin E intake from food is likely to be nondifferential relative to diabetes incidence 5 years after the dietary assessment. Thus, for the subgroup of individuals with intake only from food sources, measurement error is likely to have resulted in attenuation of any potential association of vitamin E intake with diabetes incidence.

Given the much higher degree of agreement for total intake of vitamin E from food plus supplements, it seems less likely that attenuation of the statistical association due to measurement error would account for the nonsignificant findings for total vitamin E intake in relation to diabetes incidence among individuals who regularly took vitamin E

supplements. It is possible that intake of vitamin E may exert a beneficial effect over a period of time longer than the years of follow-up data available in the IRAS. However, the association of α-tocopherol concentration with diabetes incidence within this time frame and the relatively short time required for plasma concentrations to increase in response to increases in intake (22) suggest that adequate duration of follow-up was available. Additionally, patterns of intake (whether from food or supplements) that cannot be discerned from food frequency methodology may impact the biologic effects of vitamin E. It may be that intake of vitamin E may be relatively unimportant in terms of diabetes incidence compared with the complex processes of vitamin E absorption, transport, demand, and utilization that are reflected by plasma concentrations. Finally, plasma concentrations may be a rather poor surrogate for vitamin E activity in key target tissues, perhaps including muscle, liver, or the pancreas itself.

In conclusion, study findings suggest that a protective effect of vitamin E against the incidence of type 2 diabetes may exist within the range of intake available from food. This effect may go undetected in studies that include a wide range of intake including high-dose supplementation, which appears to hold no additional protection. Further studies will be required to understand vitamin E intake and metabolism in relation to glucose tolerance, including how metabolism of α-tocopherol and other forms of vitamin E may impact insulin sensitivity and/or insulin secretion across the range of vitamin E intake, whether from food sources alone or with the addition of regular use of vitamin E supplements.

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