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Circulating γ-Tocopherol Concentrations Are Inversely Associated with Antioxidant Exposures and Directly Associated with Systemic Oxidative Stress and Inflammation in Adults

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Abstract

Background: Although α- and γ-tocopherol are co-consumed antioxidants, circulating γ-tocopherol concentrations were paradoxically found to be inversely associated with total vitamin E intake and circulating α-tocopherol concentrations. There are limited data on this apparent paradox or on determinants of circulating γ-tocopherol concentrations.

Objective: To help clarify possible determinants of circulating γ-tocopherol concentrations, we investigated associations of circulating γ-tocopherol concentrations with various dietary and lifestyle factors and biomarkers of oxidative stress and inflammation.

Methods: We pooled cross-sectional data from 2 outpatient, adult, elective colonoscopy populations (pooled $n = 419$) on whom extensive dietary, lifestyle, and medical information was collected, and the following plasma concentrations were measured: α- and γ-tocopherol (via HPLC), F_2-isoprostanes (FiPs; via gas chromatography–mass spectrometry), and high-sensitivity C-reactive protein (hsCRP; via latex-enhanced immunonephelometry). Multivariable general linear models were used to assess mean γ-tocopherol differences across quantiles of plasma antioxidant micronutrients, FiPs, and hsCRP; an oxidative balance score [OBS; a composite of anti- and pro-oxidant dietary and lifestyle exposures (a higher score indicates higher antioxidant relative to pro-oxidant exposures)]; and multiple dietary and lifestyle factors.

Results: Adjusted for serum total cholesterol, mean γ-tocopherol concentrations among those in the highest relative to the lowest tertiles of circulating α-tocopherol and β-carotene, the OBS, and total calcium and dietary fiber intakes were 31.0% ($P < 0.0001$), 29.0% ($P < 0.0001$), 27.6% ($P = 0.0001$), 29.7% ($P < 0.0001$), and 18.6% ($P = 0.008$) lower, respectively. For those in the highest relative to the lowest tertiles of circulating FiPs and hsCRP, mean γ-tocopherol concentrations were 50% ($P < 0.0001$) and 39.0% ($P < 0.0001$) higher, respectively.

Conclusions: These findings support the conclusion that circulating γ-tocopherol concentrations are inversely associated with antioxidant exposures and directly associated with systemic oxidative stress and inflammation in adults. Additional research on possible mechanisms underlying these findings and on whether circulating γ-tocopherol may serve as a biomarker of oxidative stress, inflammation, or both is needed. *J Nutr* 2018;148:1453–1461.

Keywords: γ-tocopherol, vitamin E, oxidative balance, inflammation, C-reactive protein, F_2-isoprostanes, cross-sectional study

Introduction

Oxidative stress, which refers to a harmful imbalance of pro-oxidant to antioxidant exposures and endogenous factors (1), has been implicated in the etiology of various chronic diseases (2–9). Vitamin E, which collectively refers to a group of 8 fat-soluble compounds, including 4 tocopherols and 4 tocotrienols, is a particularly important antioxidant exposure for maintaining an optimal oxidative balance (10). Although α-tocopherol is the most-studied form of vitamin E, the main form used in supplements (11), and the predominant form found in human tissues (10, 11), γ-tocopherol is the major form found in the US diet (11). The major food sources of γ-tocopherol are vegetable oils, nuts and seeds, and other plant foods (12). Although α- and γ-tocopherol are co-consumed antioxidants, circulating γ-tocopherol concentrations were found to be inversely associated with total vitamin E intake, circulating α-tocopherol concentrations, or both in human

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observational studies, whereas α-tocopherol supplementation was found to decrease circulating γ-tocopherol concentrations in intervention studies (13–24). However, many of the human studies in support of this seeming paradoxical association had very small sample sizes, nonrepresentative populations, minimal assessment of potential confounding, study design issues, or measured few relevant biomarkers. To our knowledge, there are no reported studies that comprehensively investigated potential determinants of circulating γ-tocopherol concentrations, or associations of circulating γ-tocopherol concentrations with biomarkers of oxidative stress and inflammation, within a single study population.

Accordingly, our aims were to help clarify possible determinants of circulating γ-tocopherol concentrations and their possible relations to systemic oxidative stress and inflammation in humans. To address these aims, we investigated cross-sectional associations of circulating γ-tocopherol concentrations with circulating concentrations of α-tocopherol and β-carotene; multiple antioxidant, pro-oxidant, and other dietary and lifestyle exposures; and circulating concentrations of biomarkers of systemic oxidative stress and inflammation in adults.

Methods

Study population. We pooled data from 2 cross-sectional studies conducted in outpatient elective colonoscopy populations. The first study, the Markers of Adenomatous Polyps (MAP) study (MAP I), was conducted in Winston-Salem and Charlotte, North Carolina, from 1994 to 1997. The second study, MAP II, was conducted in Columbia, South Carolina, in 2002. Both studies were conducted by the same principal investigator (RMB) and utilized the same study protocols and questionnaires.

Details on the study protocols were previously published (25, 26). Participants for the studies were recruited from patients scheduled for an elective outpatient colonoscopy at several large local gastroenterology practices. Eligibility for the studies included being age 30–74 y, English speaking, and capable of providing written informed consent. Exclusion criteria included a history of inflammatory bowel disease, a personal history of any cancer other than nonmelanoma skin cancer, and previous colorectal adenomatous polyps. Of those who met the eligibility criteria, the consent rates were 67% and 76%, respectively, for the MAP I and MAP II studies, yielding sample sizes of 420 and 204, respectively. All of the participants provided written informed consent, and the studies were approved by the institutional review boards of the institutions where these studies were conducted (Wake Forest University for MAP I and the University of South Carolina for MAP II).

Data collection and laboratory analysis. Questionnaires were mailed to study participants 1–2 wk before the colonoscopy asking them to provide detailed demographic, medical, family history, anthropometric (self-measured height, weight, and waist and hip circumferences), lifestyle, and dietary information. Usual diet and vitamin/mineral supplement use over the previous 12 mo were assessed by using semi-quantitative Willett FFQs (27, 28). A standard portion size and 9 possible frequency-of-consumption responses, ranging from "never, or less than once per month" to "6 or more times per day" were given for each food. For specific vitamin and mineral supplements, doses and numbers of pills taken daily or weekly were collected. The names of multivitamin/minerals being taken were recorded and coded, along with the numbers of pills taken daily or weekly. Total energy and nutrient intakes were calculated by adding energy and nutrients from all food and supplement sources using the dietary database developed by Willett and colleagues (27, 28). Physical activity was assessed by using modified Paffenbarger questionnaires (29), which queried usual times spent in specified moderate and vigorous activities on weekdays and weekends. The times spent in each category of activity were summed, and the metabolic equivalent task hours per week calculated; then the metabolic equivalent task hours per week from moderate and vigorous physical activities were summed. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and used as an indicator of adiposity. Participants brought their completed questionnaires to their colonoscopy visit at which time fasting peripheral venous blood samples were drawn into prechilled, red-coated evacuated tubes before their colonoscopy procedure. The blood samples were then placed in ice and protected from light to minimize degradation, and immediately taken to the laboratory. In the laboratory, the samples were immediately fractionated via centrifugation in a refrigerated centrifuge and placed into aliquots in amber-colored cryopreservation tubes; the air in the aliquots was displaced with nitrogen in MAP I and argon in MAP II, and then the aliquot tubes were capped with O-ring screw caps and immediately placed in a −70°C freezer until analysis. All of the biomarker assays for the present study were conducted at the Molecular Epidemiology and Biomarker Research Laboratory at the University of Minnesota, as follows.

Plasma α-tocopherol, γ-tocopherol, β-cryptoxanthin, α-carotene, β-carotene, lycopene, and lutein concentrations were measured via HPLC-based assays. Details on the original method (30), calibration (31), sample handling (32), and modifications to the original method (33) were previously reported. Calibration for the analysis was performed with pure compounds (Hoffman-La Roche; Sigma Chemical Co.). Quality control of control pools showed CVs of <11% for all analytes.

Plasma F_2-isoprostanes (FiPs) were measured via a highly specific and quantitative GC-MS method (34). This method, considered the gold standard for measuring FiPs, measures a well-defined set of FiP isomers. These were extracted from participants' samples with the use of deuterium-4–labeled 8-iso-prostaglandin $F_2\alpha$ as an internal standard. Quality-control procedures included the analysis of 2 control pools that had varying concentration ranges of FiPs (CVs of 9.5% and 11%).

Plasma high-sensitivity C-reactive protein (hsCRP) was measured via latex-enhanced immunonephelometry on a Behring Nephelometer II analyzer (interassay CV of 4%; Behring Diagnostics). Serum 25-hydroxyvitamin D_3 [$25(OH)D_3$] concentrations were measured by using an LC–tandem MS method, as previously described (35); the average intra-assay CV was 3%.

Serum cholesterol was measured via an enzymatic, timed endpoint method on a SYNCHRON CX5 system (Beckman Instruments, Inc.) (36, 37). Cholesterol tests on SYNCHRON CX5 systems have been certified by the National Cholesterol Education Program. The CV for the total cholesterol measurements was 6%.

Statistical analysis. For the present analysis, we excluded participants with serum cholesterol concentrations <100 mg/dL or >400 mg/dL ($n = 146$), those who did not answer ≥10% of the FFQ items or reported implausibly high or low total energy intakes (<500 or >6000 kcal/d) ($n = 1$), and those who were missing plasma samples for measurements of antioxidant micronutrients ($n = 58$), leaving a final sample size of 419. Of these, sufficient plasma samples were available for FiPs on 76.9% of participants ($n = 322$) and hsCRP on 99.8% of participants ($n = 418$). The characteristics of the study participants were summarized and compared across tertiles of plasma γ-tocopherol concentrations with the use of general linear models for continuous variables (normalized by the natural logarithm when indicated) and extended chi-square tests for categorical variables.

An equal-weight, 15-component oxidative balance score (OBS) was calculated for each participant with the use of previously described methods (the equal weight method was found to yield results

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Abbreviations used: FiP, F_2-isoprostane; hsCRP, high-sensitivity C-reactive protein; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; α-TTP, α-tocopherol transfer protein; $25(OH)D_3$, 25-hydroxyvitamin D_3.

comparable to those using various weighting schemes) (38, 39). Briefly, the 15 components were chosen a priori on the basis of their expected anti- or pro-oxidant effects, and included dietary and supplemental antioxidants [pro-vitamin A carotenoids, lutein, lycopene, vitamin C, vitamin E, omega-3 (n–3) FAs, flavonoids, and glucosinolates], dietary pro-oxidants (iron, n–6 FAs, and saturated fats), and lifestyle factors, including physical activity (considered to have predominantly antioxidant effects) and adiposity (BMI), smoking, and alcohol intake (considered to have predominantly pro-oxidant effects). Antioxidant exposures were assigned a weight of +1, and pro-oxidants a weight of −1. The component values were then summed, with a higher score representing a higher balance of anti- to pro-oxidant exposures.

Mean adjusted plasma γ-tocopherol concentrations according to tertiles of multiple dietary and lifestyle exposures (including the OBS) and the circulating antioxidant micronutrients and biomarkers of oxidative stress (FiPs) and inflammation (hsCRP) described above were calculated and compared by using general linear models. The multiple exposures were chosen on the basis of literature review and biological plausibility and included macronutrients (e.g., intakes of fats, protein, carbohydrates, sucrose), micronutrients (e.g., intakes of calcium, dietary fiber, all of the anti- and pro-oxidants included in the OBS described above, riboflavin, niacin, magnesium, manganese, zinc), waist-to-hip ratio, and circulating 25(OH)D_3 concentrations. When indicated, continuous variables were transformed by the natural logarithm to improve normality before hypothesis testing. Because plasma γ-tocopherol concentrations were log-transformed, geometric means and their 95% CIs were calculated and reported. Because γ-tocopherol and fat are absorbed by the intestine and secreted in chylomicron particles along with cholesterol (11, 40), as is customary in the literature, serum cholesterol was included in all final models. All potential covariates listed above were considered as potential confounding variables. The criteria for inclusion in the final models were biological plausibility, previous literature, and whether inclusion or exclusion of the variable from the model changed the estimated proportional differences in mean γ-tocopherol concentrations between the upper and lower categories of the primary exposure variable by ≥10%. When the potential confounders were added to the model individually or collectively, there was no appreciable change in the observed associations (i.e., no evidence of confounding), so only serum cholesterol was retained as a covariate in the final models. In addition to these primary analyses, the analyses were repeated stratified by sex and after excluding vitamin E supplement users.

All of the analyses were conducted with the use of SAS statistical software, version 9.4. A 2-sided P-value ≤0.05 was considered significant.

Results

Selected characteristics of the participants according to tertiles of plasma γ-tocopherol concentrations are summarized in Table 1. The mean age of the participants was 56.3 y, and

TABLE 1 Characteristics of participants by tertiles of plasma γ-tocopherol concentrations, in the pooled MAP I and II cross-sectional studies[1]

	Tertiles of plasma γ-tocopherol			
Selected characteristics	<0.156 mg/dL (n = 142)	0.156–0.247 mg/dL (n = 136)	>0.247 mg/dL (n = 141)	P[2]
Age, y	56.8 ± 9.6	55.6 ± 9.0	56.5 ± 8.5	0.58
Male, %	48.6	52.9	38.3	0.04
White, %	59.2	61.2	75.2	0.06
More than high school education, %	95.0	89.6	80.6	0.0001
Current smoker, %	17.7	23.7	23.1	0.61
Current drinker, %	19.9	22.2	38.0	0.008
Physical activity,[3] MET-h/wk	534 ± 399	569 ± 416	588 ± 376	0.08
BMI, kg/m^2	26.5 ± 5.4	27.3 ± 5.3	30.3 ± 7.2	0.0001
OBS[4]	1.6 ± 4.6	−0.3 ± 4.2	−1.1 ± 4.2	0.0001
Dietary intakes				
Total energy, kcal/d	1730 ± 597	1775 ± 580	1818 ± 651	0.49
Red and processed meats, servings/d	2.4 ± 3.7	2.3 ± 2.8	1.5 ± 1.9	0.04
Total vegetables and fruit, servings/d	5.1 ± 3.2	5.0 ± 2.9	5.1 ± 3.5	0.94
Total calcium intake,[5] mg · 1000 $kcal^{-1}$ · d^{-1}	607 ± 401	453 ± 272	407 ± 249	0.0001
Dietary fiber intake, g · 1000 $kcal^{-1}$ · d^{-1}	11.7 ± 3.6	11.4 ± 4.4	10.7 ± 3.4	0.13
Serum 25(OH)D_3, ng/mL	27.8 ± 12.7	28.7 ± 12.6	22.9 ± 9.9	0.08
Serum cholesterol, mg/dL	216.2 ± 75.4	237.9 ± 77.9	236.7 ± 81.3	0.04
Plasma C-reactive protein, μg/mL	3.5 ± 4.2	6.7 ± 21.6	7.3 ± 6.9	0.0001
Plasma F_2-isoprostanes, pg/mL	70.3 ± 23.7	80.3 ± 29.9	116.3 ± 54.8	0.0001
Plasma antioxidants				
α-Carotene, μg/dL	4.1 ± 3.6	3.5 ± 4.2	2.6 ± 2.7	0.0002
β-Carotene, μg/dL	20.6 ± 17.6	14.9 ± 12.3	11.1 ± 8.2	0.0001
Zeaxanthin, μg/dL	16.8 ± 7.0	16.6 ± 7.9	17.0 ± 8.8	0.86
β-Cryptoxanthin, μg/dL	6.9 ± 4.6	7.3 ± 6.9	6.6 ± 5.9	0.32
α-Tocopherol, mg/dL	1.5 ± 0.7	1.1 ± 0.5	1.0 ± 0.3	0.0001

[1] Values are means ± SDs unless otherwise indicated, n = 419. MAP, Markers of Adenomatous Polyps; MET-h, metabolic equivalents of task hours; OBS, oxidative balance score; 25(OH)D_3, 25-hydroxyvitamin D_3.
[2] Based on chi-square test for categorical variables and general linear models for continuous variables; for continuous variables, P values were based on analyses using ln-transformed values.
[3] Moderate + vigorous activity; assessed via Paffenberger physical activity questionnaires (see text).
[4] A composite of anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher antioxidant relative to pro-oxidant dietary and lifestyle exposures; study population range: −13.3 to 15.6.
[5] Total = dietary + supplemental.

the total serum cholesterol–adjusted circulating γ-tocopherol concentrations ranged from 0.04 to 0.61 mg/dL. Participants in the upper relative to the lower γ-tocopherol tertile were more likely to be white, less likely to be male or have higher than a high school education, and more likely to currently drink alcohol. They also were, on average, more physically active, and had a higher BMI and circulating hsCRP and FiP concentrations, lower intakes of red and processed meats and total calcium, and lower circulating 25(OH)D_3, α- and β-carotene, and α-tocopherol concentrations.

The total serum cholesterol–adjusted mean circulating γ-tocopherol concentrations, by tertiles of factors hypothesized to be associated with circulating γ-tocopherol concentrations, are shown in **Table 2**. Mean circulating γ-tocopherol concentrations were statistically significantly lower among those in the upper relative to the lowest tertiles of circulating α-tocopherol (31.0% lower), β-carotene (29.0% lower), α-carotene (23.4% lower), and 25(OH)D_3 (18.2% lower); the OBS (27.6% lower); and intakes of total calcium (29.7% lower) and dietary fiber (18.6% lower). In contrast, mean plasma γ-tocopherol concentrations were statistically significant higher among those who were obese relative to those who were less than overweight (15.1% higher) and in those in the upper relative to the lowest tertiles of FiP (50% higher) and hsCRP (39.0% higher) concentrations. The estimated strengths of the findings for the individual OBS components were weaker than those for the overall OBS (data not shown); in addition to BMI, the other OBS pro-oxidant dietary and lifestyle exposure components tended to be modestly associated with higher γ-tocopherol concentrations, and the other OBS antioxidant exposures tended to be modestly associated with lower γ-tocopherol concentrations. In addition, other dietary micronutrients that are commonly found in vitamin/mineral supplements along with α-tocopherol (e.g., niacin, vitamin B-12, riboflavin, magnesium, and manganese) tended to be modestly inversely associated with circulating γ-tocopherol and directly associated with circulating α-tocopherol (data not shown). Finally, the estimated associations of the macronutrients and major food groups with γ-tocopherol concentrations were close to null (data not shown).

The analyses for Table 2 were repeated after excluding those who took vitamin E supplements (**Table 3**). After excluding those who took vitamin E supplements, circulating γ-tocopherol concentrations ranged from 0.05 to 0.61 mg/dL. The median γ-tocopherol concentrations for those in the middle and, especially, the upper tertiles of factors hypothesized to be associated with circulating γ-tocopherol concentrations were less than those noted in the analyses for the full study population. The results were similar to those found in Table 2, except that, for the most part, the proportional differences were of lower magnitudes. Finally, there were no substantial differences in our findings by sex (data not shown).

Discussion

Our findings support that circulating γ-tocopherol concentrations are *1*) inversely associated with tocopherol intakes, *2*) inversely associated with other antioxidant exposures, and *3*) directly associated with systemic oxidative stress and inflammation. These findings initially may seem paradoxical, considering that *1*) increased ingestion of dietary constituents tends to increase circulating concentrations of them [except, e.g., when circulating concentration are tightly regulated (e.g., calcium, sodium)] and *2*) γ-tocopherol is a known antioxidant (42) and anti-inflammatory agent (43, 44). However, as discussed below, there are several lines of evidence to support our findings.

First, our findings are biologically plausible. An apparent mechanism for the inverse association of tocopherol intakes with circulating γ-tocopherol concentrations, despite γ-tocopherol being the major form of vitamin E in the human diet (11, 45), involves the hepatic α-tocopherol transfer protein (α-TTP). The affinity of α-TTP, which is responsible for reincorporating tocopherols in nascent VLDL and maintaining plasma tocopherol concentrations (11, 46), is 100% for α-tocopherol but only 9% for γ-tocopherol (47). Because the 2 tocopherols competitively bind to α-TTP, and α-tocopherol is preferred, more α- than γ-tocopherol is transferred from the liver into plasma (11, 40). This leaves more γ-tocopherol to be catabolized by cytochrome P450 into the hydrophilic metabolite γ-carboxyethyl-hydroxychromanol, which is excreted primarily in urine (45, 48).

A proposed mechanism for the inverse association of γ-tocopherol with other antioxidant exposures, and the direct association with systemic oxidative stress and inflammation, is that oxidative stress and its resulting inflammation can inhibit cytochrome P450's catabolism of γ-tocopherol (49, 50), leaving more of it to be reincorporated into plasma (11). This is particularly important to note because cytochrome P450 activity is a strong determinant of plasma γ-tocopherol concentrations (11). In support of this is that, in several studies, proinflammatory cytokines and interleukins were found to inhibit the metabolic function of cytochrome P450 (51–54).

Second, there is support for our findings of inverse associations of circulating γ-tocopherol concentrations with tocopherol intakes and circulating α-tocopherol concentrations from previous human observational and interventional studies. In cross-sectional analyses of small (sample sizes of 86–162) study populations, circulating γ-tocopherol concentrations were moderately, statistically significant negatively correlated ($r = -0.45$ to -0.49) with circulating α-tocopherol concentrations (13, 18). Similarly, in cross-sectional analyses of baseline data from women ($n = 5450$) participating in a clinical trial (55) and from a subset of men ($n = 657$) in a prospective cohort study (49), circulating γ-tocopherol concentrations were moderately, statistically significant negatively correlated ($r = -0.38$ and -0.40, respectively) with circulating α-tocopherol concentrations. Finally, in a cross-sectional analysis of 65 men, there was a moderate negative correlation of α-tocopherol intake with plasma γ-tocopherol concentrations ($r = -0.33$; $P = 0.0007$) (23). Although the results of these cross-sectional studies support our findings, the studies were limited by not being conducted in representative populations and there was no adjustment for potential confounding variables.

Several trials tested the effects of administering α-tocopherol on circulating γ-tocopherol concentrations, or of γ-tocopherol on circulating α-tocopherol concentrations. In 5 small uncontrolled trials ($n = 4$–14) (14, 17, 18, 22, 24), 2 small ($n = 12$ and 20) controlled trials (15, 20), 1 small ($n = 12$) crossover trial (16), and 3 larger ($n = 184$–575) controlled trials (19, 21, 56), participants administered various doses/formulations of α-tocopherol for various durations were found to develop increases in circulating α-tocopherol concentrations and decreases in circulating γ-tocopherol concentrations. In a small ($n = 13$) randomized controlled trial in Japanese men (57),

TABLE 2 Mean plasma γ-tocopherol concentrations by tertiles of selected participant characteristics: pooled MAP I and II cross-sectional studies[1]

Characteristics; tertiles (tertile medians)	*n*/tertile	Mean (95% CI),[2] mg/dL	Proportional difference,[3] %	*P*[4]	*P*-trend[5]
Plasma α-tocopherol, mg/dL				<0.0001	<0.0001
1 (0.75)	140	0.213 (0.196, 0.232)	—		
2 (1.05)	139	0.208 (0.192, 0.227)	−2.3		
3 (1.61)	140	0.147 (0.135, 0.160)	−31.0		
Plasma β-carotene, μg/dL				<0.0001	<0.0001
1 (5.5)	140	0.217 (0.199, 0.236)	—		
2 (11.0)	139	0.196 (0.180, 0.213)	−9.7		
3 (25.3)	140	0.154 (0.141, 0.167)	−29.0		
Plasma α-carotene, μg/dL				0.0002	<0.0001
1 (0)	141	0.209 (0.192, 0.231)	—		
2 (2.6)	138	0.195 (0.178, 0.212)	−6.7		
3 (5.3)	140	0.160 (0.150, 0.177)	−23.4		
Plasma cryptoxanthin, μg/dL				0.14	0.03
1 (2.8)	139	0.202 (0.185, 0.221)	—		
2 (5.4)	139	0.183 (0.168, 0.200)	−9.4		
3 (10.4)	141	0.176 (0.161, 0.192)	−12.9		
Plasma zeaxanthin, μg/dL				0.46	0.25
1 (10.0)	140	0.187 (0.171, 0.204)	—		
2 (15.4)	139	0.195 (0.179, 0.213)	4.3		
3 (23.8)	140	0.178 (0.164, 0.195)	−4.8		
Serum 25(OH)D_3, ng/mL				0.0005	0.0004
1 (15.5)	217	0.203 (0.190, 0.218)	—		
2 (25.0)	97	0.176 (0.159, 0.195)	−13.3		
3 (38.0)	105	0.166 (0.150, 0.183)	−18.2		
OBS[6]				0.0001	0.0001
1 (−4.4)	141	0.214 (0.196, 0.233)	—		
2 (−0.2)	140	0.196 (0.180, 0.214)	−8.4		
3 (4.3)	138	0.155 (0.142, 0.169)	−27.6		
BMI,[7] kg/m^2				0.001	0.002
<25.0	14	0.169 (0.128, 0.222)	—		
25.0–29.9	139	0.168 (0.154, 0.184)	0.6		
≥30.0	266	0.199 (0.186, 0.212)	15.1		
Total calcium intake,[8] mg · 1000 $kcal^{-1}$ · d^{-1}				<0.0001	<0.0001
1 (256.5)	139	0.219 (0.200, 0.240)	—		
2 (382.1)	140	0.193 (0.178, 0.211)	−11.9		
3 (741.0)	140	0.154 (0.141, 0.168)	−29.7		
Dietary fiber intake, g · 1000 $kcal^{-1}$ · d^{-1}				0.008	0.001
1 (8.0)	140	0.204 (0.187, 0.222)	—		
2 (10.9)	139	0.193 (0.177, 0.211)	−5.4		
3 (14.4)	140	0.166 (0.152, 0.181)	−18.6		
Plasma F_2-isoprostanes, pg/mL				<0.0001	<0.0001
1 (56.3)	205	0.164 (0.153, 0.175)	—		
2 (78.0)	106	0.183 (0.166, 0.201)	11.6		
3 (118.8)	108	0.246 (0.224, 0.271)	50.0		
Plasma hsCRP, μg/mL				<0.0001	<0.0001
1 (0.9)	141	0.164 (0.150, 0.178)	—		
2 (2.7)	138	0.175 (0.160, 0.190)	6.7		
3 (10.0)	140	0.228 (0.209, 0.248)	39.0		

[1] $n = 419$. hsCRP, high-sensitivity C-reactive protein; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; 25(OH)D_3, 25-hydroxyvitamin D_3.
[2] Adjusted for serum total cholesterol concentrations.
[3] Proportional difference, in percentage, between the mean value in the corresponding tertile and the mean value in the first tertile: e.g., [(tertile 3 mean – tertile 1 mean)/tertile 1 mean] × 100.
[4] For differences between means from the general linear model, adjusted for serum total cholesterol concentration; nontransformed means (shown) were transformed by natural logarithm to improve normality before hypothesis testing.
[5] For trends across means from general linear models, adjusted for serum total cholesterol concentration.
[6] A composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher antioxidant relative to pro-oxidant dietary and lifestyle exposures; study population range: −13.3 to 15.6.
[7] Categories for BMI (kg/m^2) based on WHO guidelines (41) for underweight–normal weight (<25), overweight (25.0–29.9), and obese (≥30.0).
[8] Total = dietary + supplemental.

TABLE 3 Mean plasma γ-tocopherol concentrations by tertiles of selected participant characteristics (vitamin E supplement users excluded): pooled MAP I and II cross-sectional studies[1]

Characteristics; tertiles (tertile medians)	*n*/tertile	Mean (95% CI),[2] mg/dL	Proportional difference,[3] %	*P*[4]	*P*-trend[5]
Plasma α-tocopherol, mg/dL				0.14	0.02
1 (0.7)	82	0.210 (0.192, 0.231)	—		
2 (0.9)	80	0.245 (0.223, 0.270)	16.7		
3 (1.2)	82	0.231 (0.210, 0.253)	10.0		
Plasma β-carotene, μg/dL				0.08	0.01
1 (5.2)	82	0.235 (0.214, 0.258)	—		
2 (9.3)	80	0.245 (0.223, 0.269)	4.3		
3 (19.7)	82	0.207 (0.189, 0.228)	−12.0		
Plasma α-carotene, μg/dL				0.047	0.008
1 (0)	83	0.235 (0.215, 0.258)	—		
2 (2.6)	103	0.241 (0.222, 0.261)	2.6		
3 (5.9)	58	0.199 (0.179, 0.223)	−15.3		
Plasma cryptoxanthin, μg/dL				0.76	0.32
1 (2.8)	82	0.231 (0.210, 0.253)	—		
2 (5.1)	80	0.234 (0.213, 0.258)	1.3		
3 (9.7)	82	0.220 (0.200, 0.242)	−4.8		
Plasma zeaxanthin, μg/dL				0.46	0.21
1 (9.8)	82	0.223 (0.203, 0.245)	—		
2 (14.9)	80	0.243 (0.221, 0.267)	9.0		
3 (23.5)	82	0.220 (0.200, 0.242)	−1.3		
Serum 25(OH)D_3, ng/mL				0.0005	0.002
1 (16)	133	0.252 (0.234, 0.270)	—		
2 (24.5)	48	0.217 (0.193, 0.245)	−13.8		
3 (36)	63	0.193 (0.174, 0.214)	−23.4		
OBS[6]				0.46	0.18
1 (−4.7)	83	0.237 (0.215, 0.260)	—		
2 (−1.3)	81	0.234 (0.213, 0.258)	−1.3		
3 (3.2)	50	0.215 (0.195, 0.236)	−9.3		
BMI,[7] kg/m^2				0.02	0.003
<25.0	6	0.202 (0.184, 0.222)	—		
25.0–29.9	72	0.241 (0.219, 0.265)	19.3		
≥30.0	166	0.243 (0.222, 0.266)	20.3		
Total calcium intake,[8] mg · 1000 $kcal^{-1}$ · d^{-1}				0.02	0.03
1 (244.2)	82	0.258 (0.235, 0.283)	—		
2 (345.4)	81	0.219 (0.199, 0.240)	−15.1		
3 (510.2)	81	0.211 (0.192, 0.232)	−18.2		
Dietary fiber intake, g · 1000 $kcal^{-1}$ · d^{-1}				0.05	0.05
1 (7.6)	81	0.240 (0.219, 0.264)	—		
2 (10.4)	82	0.242 (0.221, 0.265)	0.8		
3 (13.9)	81	0.205 (0.187, 0.225)	−14.6		
Plasma F_2-isoprostanes, pg/mL				0.0004	<0.0001
1 (59.9)	119	0.206 (0.191, 0.222)	—		
2 (84.2)	61	0.232 (0.209, 0.257)	12.6		
3 (130.2)	64	0.272 (0.246, 0.302)	32.0		
Plasma hsCRP, μg/mL				<0.0001	<0.0001
1 (0.9)	82	0.198 (0.181, 0.216)	—		
2 (2.9)	80	0.222 (0.203, 0.243)	12.1		
3 (10.0)	82	0.271 (0.247, 0.296)	36.9		

[1] $n = 419$. hsCRP, high-sensitivity C-reactive protein; MAP, Markers of Adenomatous Polyps; OBS, oxidative balance score; 25(OH)D_3, 25-hydroxyvitamin D_3.
[2] Adjusted for serum total cholesterol concentrations.
[3] Proportional difference, in percentage, between the mean value in the corresponding tertile and the mean value in the first tertile: e.g., [(tertile 3 mean – tertile 1 mean)/tertile 1 mean] × 100.
[4] For differences between means from the general linear model, adjusted for serum total cholesterol concentration; nontransformed means (shown) were transformed by natural logarithm to improve normality before hypothesis testing.
[5] For trends across means from general linear models, adjusted for serum total cholesterol concentration.
[6] A composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher antioxidant relative to pro-oxidant dietary and lifestyle exposures; study population range: −13.3 to 15.6.
[7] Categories for BMI (kg/m^2) based on WHO guidelines (41) for underweight–normal weight (<25), overweight (25.0–29.9), and obese (≥30.0).
[8] Total = dietary + supplemental.

7 participants received 372.8 mg γ-tocopherol + 10 mg RRR-α-tocopherol, and 6 received 5 mg RRR-α-tocopherol daily over 28 d. In the γ- + α-tocopherol group relative to the low-dose α-tocopherol comparison group, there was a mean plasma γ-tocopherol increase of 13 μmol/L (0.56 mg/dL) and a mean plasma α-tocopherol decrease of 6 μmol/L (0.26 mg/dL) ($P < 0.01$) (57).

Some investigators suggested that an inverse correlation of α-tocopherol intake/circulating concentrations with circulating γ-tocopherol concentrations may be limited to persons who take α-tocopherol supplements (23). In the cross-sectional analysis of 65 men noted above in which there was a negative correlation between total vitamin E intake and circulating γ-tocopherol concentrations ($r = -0.33$, $P = 0.0007$), there was no correlation when vitamin E supplement users were excluded from the analysis ($r = 0.008$, $P = 0.57$) (23). However, in a cross-sectional analysis of 482 men and women, of whom only ~5% took a vitamin E supplement, dietary α-tocopherol was modestly to moderately positively correlated with plasma γ-tocopherol concentrations ($r = 0.24$; 95% CI: 0.15, 0.32) (58). In our study, whereas the association of plasma γ- with α-tocopherol concentrations among participants who did not take vitamin E supplements (vitamin E supplement nonusers) was not significant (an estimated modest direct association), the directions of the associations of all the other factors with γ-tocopherol concentrations were the same as among all participants combined, but generally weaker. We attribute any differences between our findings limited to vitamin E supplement nonusers and those in which all participants were included to the relative lack of heterogeneity in vitamin E intakes and plasma γ-tocopherol concentrations among vitamin E supplement nonusers, and suggest that this is a likely explanation for the findings in the previous study (23) that addressed this issue.

Third, there is also support from previous studies in humans for our findings of direct associations of γ-tocopherol concentrations with systemic oxidative stress and inflammation, and inverse associations of γ-tocopherol concentrations with various antioxidant exposures. In the above-mentioned cross-sectional analysis of 657 men in a prospective cohort study, plasma γ-tocopherol concentrations were modestly positively correlated with plasma concentrations of hsCRP ($r = 0.14$, $P < 0.0001$) and FiPs ($r = 0.13$, $P < 0.0001$) (49). In a cross-sectional analysis of participants in a trial of the effect of antioxidant supplements on oxidative damage in smokers ($n = 298$; 121 men and 177 women), there was a pattern of stepwise higher mean plasma FiP concentrations across increasing plasma γ-tocopherol concentration quartiles, culminating in an 88.2% higher mean concentration in the fourth relative to the first quartile ($P < 0.0001$) (59). Increased adiposity has been associated with higher levels of oxidative stress and inflammation (60). In a cross-sectional analysis of questionnaire data and stored serum samples from 207 adolescent girls and 183 premenopausal women, serum γ-tocopherol concentrations were modestly positively correlated with BMI in the girls and the women [$r = 0.17$ ($P = 0.02$) and $r = 0.25$ ($P = 0.0008$), respectively] (61).

We found statistically significant, substantially lower mean circulating γ-tocopherol concentrations among those with higher total calcium and dietary fiber intakes and circulating $25(OH)D_3$ concentrations, none of which was included in our oxidative balance score. These exposures were selected a priori on the basis of their effects in the gut (a source of circulating biomarkers of oxidative stress and inflammation) as well as on other effects of vitamin D. In the gut, *1*) fiber dilutes pro-oxidant/proinflammatory bile acids and toxins (62) and, when fermented, produces anti-inflammatory butyrate (63); *2*) calcium binds bile acids, preventing their pro-oxidant/proinflammatory effects (64); and *3*) when vitamin D binds to the vitamin D receptor, it upregulates CYP3A4, which catabolizes lithocholic acid, a particularly toxic secondary bile acid (65). Vitamin D also modulates various genes involved in modulating oxidative balance and inflammation (66). In the above-noted cross-sectional analysis of baseline data from 657 men in a prospective cohort study, plasma γ-tocopherol and 25-hydroxyvitamin D concentrations were modestly to moderately negatively correlated ($r = -0.24$, $P < 0.0001$) (49). To our knowledge, there are no previous reports of investigations of associations of calcium and fiber intakes with circulating γ-tocopherol concentrations.

Our study has several limitations and strengths. Limitations include the cross-sectional design, which prohibits assessing the temporality of the associations, and the known limitations of assessing diet with FFQs, such as recall error and limited food choices (27, 28, 67). However, it would be expected that error related to assessing diet would be nondifferential, which would most likely attenuate the estimated diet-biomarker associations. Another limitation was that the study population was mostly white and, rather than being randomly selected and recruited from a general population, was limited to persons scheduled for colonoscopies, both of which may limit the generalizability of our findings. On the other hand, strengths of the study included the relatively large sample size, especially for a biomarker-heavy study; the inclusion of both men and women; the high-quality measurement of multiple biomarkers of exposure and outcome; and the collection of data on, and investigation of, an extensive number of potential confounding variables.

In conclusion, our results, taken together with previous basic science and human studies, strongly support that circulating γ-tocopherol concentrations are *1*) inversely associated with α-tocopherol intake, *2*) inversely associated with other antioxidant exposures, and *3*) directly associated with systemic oxidative stress and inflammation. Further investigations into the exact mechanisms behind these associations, as well as circulating γ-tocopherol concentrations as a potential biomarker of oxidative stress, are warranted.

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