The Journal of Nutrition
Nutritional Epidemiology

Plasma Vitamin E and Coenzyme Q10 Are Not Associated with a Lower Risk of Acute Myocardial Infarction in Singapore Chinese Adults[1,2]

Nasheen Naidoo,[3] Rob M. van Dam,[3,4]* Woon-Puay Koh,[3] Cynthia Chen,[3] Yian-Ping Lee,[5] Jian-Min Yuan,[6,7] and Choon-Nam Ong[3]

[3]Saw Swee Hock School of Public Health, and [4]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [5]Department of Cardiology, Khoo Teck Hospital, Yishun Central, Singapore; and [6]Division of Cancer Control and Population Sciences, University of Pittsburgh Cancer Institute, and [7]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

Abstract

Vitamin E and coenzyme Q10 (CoQ10) have antioxidant effects that may benefit cardiovascular health. Meta-analyses of randomized controlled trials have not shown a protective effect of supplementation with the vitamin E isomer α-tocopherol on the risk of acute myocardial infarction (AMI), but data on other isomers and CoQ10 are limited. Our objective was to examine the association of the plasma concentrations of vitamin E isomers (α-, γ-, and δ-tocopherol and α-, γ-, and δ-tocotrienol) and CoQ10 (ubiquinol and ubiquinone) with the incidence of AMI. We conducted a nested case-control study with 233 cases of incident AMI and 466 matched controls selected from the Singapore Chinese Health Study, aged 45–74 y at the time of recruitment and free of cardiovascular disease at the time of blood collection. We used conditional logistic regression to examine the association between vitamin E and CoQ10 and the risk of AMI adjusted for other risk factors. In the basic model, higher δ-tocopherol and ubiquinone concentrations were significantly associated with a higher risk of AMI, whereas there were no significant associations for the other vitamin E and CoQ10 isomers. After adjusting for lifestyle and other risk factors, only the association between δ-tocopherol and AMI risk remained significant [OR = 3.09 (95% CI: 1.53, 6.25) highest vs. lowest quintile; *P*-trend = 0.028]. We did not observe an inverse association between plasma concentrations of vitamin E isomers or CoQ10 and risk of AMI in Singapore Chinese. In contrast, plasma δ-tocopherol concentrations were associated with a higher risk of AMI. Our findings do not support a role of higher vitamin E or CoQ10 intakes in the prevention of AMI. J. Nutr. 142: 1046–1052, 2012.

Introduction

Vitamin E originates from plants and consists of 8 isomeric forms: α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol (1). Vitamin E intake has been associated with higher α-tocopherol concentrations in several studies (2–5) and has been suggested to have beneficial effects on cardiovascular health through inhibition of LDL cholesterol oxidation within the arterial endothelium during early atherogenesis (6). Meta-analyses of randomized controlled trials (7,8) have not shown a protective effect of vitamin E supplementation against the development of cardiovascular diseases. However, the evaluated supplements only contained the α-tocopherol isomer of vitamin E (9,10) and data on other isomers, including β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol, are limited (11–13). Supplementation with only α-tocopherol has been shown to reduce serum concentrations of γ- and δ-tocopherol (14,15), suggesting negative effects on the bioavailability and bioactivity of other tocopherols. γ-Tocopherol is the most common form of vitamin E in the U.S. diet (1) and may have greater antioxidant and antiinflammatory properties than α-tocopherol [which is more common in Southern European diets (16)], as shown in in vitro and animal studies (13). In a pooled analysis of 9 cohort studies, dietary vitamin E was associated with a modestly lower risk of myocardial infarction (12).

Rich dietary sources of vitamin E include wheat germ (α-tocopherol, β-tocopherol), alfalfa and almonds (α-tocopherol), safflower oil (α-tocopherol), soybean oil (γ-tocopherol, δ-tocopherol), corn oil (γ-tocopherol) (17), and whole cereals (β-tocopherol and α-tocotrienol) (18). The β-isomers have been found in only small amounts in the diet (19,20). The primary site of vitamin E regulation and metabolism is in the liver (21). In the

[1] Supported by the Singapore Singapore Biomedical Research Council 04/1/21/19/334. The Singapore Chinese Health Study was supported by NIH grants R01 CA55069, R35 CA53890, R01 CA80205, R01 CA98497, and R01 CA144034.
[2] Author disclosures: N. Naidoo, R. M. van Dam, W. P. Koh, C. Chen, Y. P. Lee, J. M. Yuan, and C. N. Ong, no conflicts of interest.
* To whom correspondence should be addressed. E-mail: rob_martinus_van_dam@nuhs.edu.sg.

Manuscript received November 18, 2011. Initial review completed January 4, 2012. Revision accepted March 6, 2012.
First published online April 18, 2012; doi:10.3945/jn.111.155341.

liver, the α-tocopherol-transport protein binds α-tocopherol into VLDL, whereas γ-tocopherol and other isomers are excreted in bile, thereby establishing an elevated α- tocopherol:γ-tocopherol ratio in serum. Increasing the intake of α-tocopherol results in the reduction of γ-tocopherol concentrations in human tissue (15). It is also well established that the plasma concentrations of vitamin E increase with the amount of total plasma lipids, because vitamin E is transported by the plasma lipoproteins (22). In the circulation, VLDL is catabolized to LDL, which then becomes the main carrier of vitamin E isomers to peripheral tissues (23). Coenzyme Q10 (COQ10)[8] is present in all living cells and plays an important role in the electron transport chain in mitochondria and as an intracellular antioxidant (24). It is found in large amounts in organs such as the heart, liver, and kidney (25,26) and rich dietary sources include meat, fish, and oils (26). There are 2 forms of CoQ10: ubiquinone (oxidized form) and the more antioxidant active form, ubiquinol (reduced form). Endogenous CoQ10 is derived from both dietary sources and biosynthesis via the mevalonate or hydroxymethylglutaryl CoA reductase pathway, which is important in cholesterol biosynthesis (24). CoQ10 intake has been associated with higher plasma CoQ10 concentrations in previous studies (27). Results from several randomized controlled trials suggest that CoQ10 supplementation can lower blood pressure (28) and CoQ10 may also affect atherosclerosis though inhibition of LDL cholesterol oxidation (29–31). There is some evidence from smaller trials for a beneficial effect on the risk of coronary heart disease in high-risk individuals (29–31).

The plasma concentrations of α-tocopherol and CoQ10 were previously reported to be correlated (24). CoQ10 found in cellular membranes has also been shown to prevent the oxidation of α-tocopherol, suggesting that ubiquinol may be involved in the regeneration of reduced α-tocopherol (32). Experimental data also showed CoQ10 to be more efficient than α-tocopherol in inhibiting LDL oxidation (33).

Prospective data on different vitamin E isomers and CoQ10 concentrations in relation to risk of coronary heart disease are sparse. We therefore conducted a prospective study of the plasma concentrations of 6 isomers of vitamin E and 2 redox forms of CoQ10 in relation to incidence of myocardial infarction in the Singapore Chinese population.

Materials and Methods

Study population. We conducted a case-control study consisting of 233 incident cases of acute myocardial infarction (AMI) and 466 matched controls and nested within a population-based cohort, the Singapore Chinese Health Study (SCHS). The SCHS is a prospective cohort of 63,257 Chinese women and men aged 45–74 y at the time of recruitment between April 1993 and December 1998 and recruited from the 86% of the Singapore population residing in government housing estates at that time. Study participants were restricted to the 2 major dialect groups of Chinese in Singapore, Hokkiens and Cantonese (34).

A structured questionnaire was administered face-to-face in the participant's home by a trained interviewer at the time of recruitment between 1993 and 1998. Information on participant demographics, height, weight, education level, cigarette smoking, alcohol consumption, physical activity (weekly hours of strenuous sport), and past medical history were collected. We collected blood and urine specimens from a random 3% sample of study enrollees beginning in April 1994 and that was extended to all surviving cohort members beginning in January 2000. At completion (April 2005), biospecimens were obtained from 32,543 participants, representing a consent rate of 60% in contacted participants. Details of the biospecimen collection, processing, and storage procedures were previously described (35). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured during in-person visits by trained doctors or nurses using Omron Automatic Digital Blood Pressure Monitors (HEM 705CP) according to validated standard procedures (36). The blood pressures were taken after the participants were seated at rest for at least 5 min. Each participant had 3 blood pressure measurements, with a 3-min interval between measurements. The mean value of the 3 SBP and DBP readings was used in the data analysis.

This study was approved by the Institutional Review Boards at the National University of Singapore and the University of Minnesota.

Case selection. Incident AMI cases were identified by 2 independent methods via electronic linkages between the SCHS cohort database and *1*) the Singapore Myocardial Infarction Registry (SMIR), a centralized population-based AMI registry initiated in 1986, or *2*) a governmental national hospital discharge database that captured AMI cases based on inpatient discharge information since 1990. These 2 datasets were previously explained in more detail (37).

We first excluded 3401 participants who reported physician-diagnosed coronary heart disease or stroke at the baseline interview. Through linkage analysis between the remaining 59,856 participants in the cohort, and the SMIR (up to 2002) and hospital discharge databases (up to December 2004), we identified a total of 233 incident cases of definite or probable AMI (International Classification of Diseases-9 code 410) among the participants that provided blood. The medical records of these cases were reviewed by a cardiologist and confirmed as AMI cases using WHO diagnostic categories (38) and the Multi-Ethnic Study of Atherosclerosis criteria (39) respectively. Of the included cases that were identified through the hospital admission records, 94% was classified as definite AMI according to the Multi-Ethnic Study of Atherosclerosis criteria (37). Of the included cases that were identified through the SMIR, 79% were classified as definite AMI according to WHO criteria.

Control selection. For each case, 2 controls who were alive and free of cardiovascular disease (heart attack or angina and stroke) at the time of the AMI diagnosis of the case participants (up to 31 December 2005) were randomly selected from the SCHS cohort. Controls were matched to the case by gender, dialect group (Hokkien, Cantonese), year of birth (±2 y), year of recruitment (±1 y), and date of blood collection (±6 mo).

Laboratory measurements. Plasma samples of a given matched set (1 case and 2 matched controls) were arranged in random order and tested in the same laboratory batch for all subsequent measurements. HPLC was used to simultaneously measure the plasma concentrations of the isomers of vitamin E, redox forms of CoQ10, and carotenoids (β-cryptoxanthin and lutein) using a Waters Alliance 2695 separation module, an Agilent Zorbax SBC18 guard column (5 m, 12.5-mm × 4.6-mm i.d.) with 2 Phenomenex 2-positions 6-ports Synergi fluid processor (Models AVO-6082) integrated to a photodiode array detection system (Model 2996, Waters), a fluorescence detector (Model 2475, Waters), and an electrochemical detection system (Model 1049A, Agilent) based on the methods described by Lee et al. (40,41).

The within-day and between-day CV for the vitamin E and CoQ10 were as follows: α-tocopherol (5.2 and 13.4%), γ-tocopherol (3.8 and 5.3%), δ-tocopherol (19.1 and 32.6%), α-tocotrienol (9.4 and 11.2%), γ-tocotrienol (16.2 and 22.5%), δ-tocotrienol (19.1 and 32.6%), ubiquinol (8.5 and 6.6%), and ubiquinone (6.4 and 20.0%).

Total cholesterol was measured using a method based on an enzymatic method utilizing cholesterol esterase and cholesterol oxidase conversion (42). HDL cholesterol plasma concentrations were measured based on the methods of Izawa et al. (43).

The Friedewald formula was used to calculate the plasma concentrations of LDL cholesterol (44). TG were measured based on the Fossati 3-step enzymatic reaction with a Trinder endpoint (45). Total cholesterol, HDL cholesterol, and TG were measured using the Bayer Advia 1650 Autoanalyzer using standard reagents (46,47).

Statistical analysis. Statistical analysis of all data were performed using the statistical package STATA v10 (StataCorp, 2009). Demographic

[8] Abbreviations used: AMI, acute myocardial infarction; CoQ10, coenzyme Q10; DBP, diastolic blood pressure; SBP, systolic blood pressure; SCHS, Singapore Chinese Health Study; SMIR, Singapore Myocardial Infarction Registry.

TABLE 1 Selected demographic characteristics and risk factors for AMI in cases and controls in the SCHS[1]

Characteristics	Cases (n = 233)	Controls (n = 466)	P value
Age, *y*	60.4 ± 0.5	60.3 ± 0.4	0.94
Gender, *n (%)*			
Male	152 (65.2)	304 (65.2)	1.00
Female	81 (34.8)	162 (34.8)	
BMI, *kg/m²*	23.3 ± 0.2	22.9 ± 0.1	0.15
Education, *n (%)*			
No formal school	58 (24.9)	108 (23.2)	0.043
Primary school	127 (54.5)	221 (47.4)	
Secondary or higher	48 (20.6)	137 (29.4)	
Cigarette smoking, *n (%)*			
Never	112 (48.1)	270 (58.0)	0.001
Former smokers	35 (15.0)	86 (18.5)	
Current smokers	86 (36.9)	110 (23.6)	
Alcohol intake, *g/d*	2.2 ± 0.6	2.9 ± 0.5	0.40
Physical activity (strenuous sports), *n (%)*			
None	223 (95.7)	429 (92.1)	0.18
<2 h/wk	2 (0.9)	10 (2.1)	
≥2 h/wk	8 (3.4)	27 (5.8)	
History of diabetes, *n (%)*	51 (21.9)	37 (7.9)	<0.001
History of hypertension, *n (%)*	120 (51.5)	169 (36.3)	<0.001
SBP,[2] *mm Hg*	152.8 ± 1.5	141.1 ± 0.9	<0.001
DBP,[2] *mm Hg*	82.8 ± 0.7	80.6 ± 0.5	0.007
Plasma concentrations			
Total cholesterol, *mmol/L*	5.4 ± 0.1	5.2 ± 0.04	0.019
HDL cholesterol, *mmol /L*	1.3 ± 0.02	1.3 ± 0.02	0.003
LDL cholesterol, *mmol /L*	3.3 ± 0.1	3.1 ± 0.04	0.002
TG, *mmol /L*	1.8 ± 0.1	1.7 ± 0.04	0.022
α-Tocopherol, *μmol/L*	34.9 ± 0.7	33.0 ± 0.4	0.015
γ-Tocopherol, *μmol/L*	1.5 ± 0.05	1.4 ± 0.04	0.65
δ-Tocopherol, *μmol/L*	0.5 ± 0.01	0.4 ± 0.01	0.001
α-Tocotrienol, *nmol/L*	46.8 ± 3.1	37.1 ± 1.5	0.005
γ-Tocotrienol, *nmol/L*	79.1 ± 4.5	68.3 ± 2.7	0.040
δ-Tocotrienol, *nmol/L*	42.0 ± 1.7	45.1 ± 2.0	0.23
Ubiquinol, *μmol/L*	0.8 ± 0.02	0.7 ± 0.01	0.13
Ubiquinone, *μmol/L*	0.2 ± 0.005	0.1 ± 0.003	0.006

[1] Values are mean ± SE for continuous variables and *n* (%) for categorical variables. AMI, acute myocardial infarction; DBP, diastolic blood pressure; SBP, systolic blood pressure; SCHS, Singapore Chinese Health Study.

characteristics and risk factors for AMI in the cases and controls were compared using the chi-squared and Student's *t* tests. Partial correlation analyses were performed in the control group to examine the correlations between the isomers of vitamin E and redox forms of CoQ10 and were adjusted for age, gender, dialect, year of interview, year of blood specimen collection, and plasma total cholesterol and TG.

The independent variables analyzed were the plasma concentrations of α-, γ-, and δ-tocopherol, α-, γ-, and δ-tocotrienol, ubiquinone, and ubiquinol. Natural logarithm transformations were performed for γ-tocopherol and α-, γ-, and δ-tocotrienol, because the distributions of these variables were skewed. Back-transformations were subsequently performed so that variables could be interpreted on the original scale.

A conditional logistic regression model was used to test the associations between vitamin E (α-, γ-, and δ-tocopherol and α-, γ-, and δ-tocotrienol) and CoQ10 (ubiquinone and ubiquinol) and the risk of AMI. Study participants were grouped into quintiles based on the plasma concentrations of vitamin E and CoQ10 measured in the cases and controls. The measure of the association between the exposure and outcome variable used was the OR with corresponding 95% CI. *P*-trends were calculated by modeling the medians of the quintiles as a continuous variable. Covariates were adjusted for in the regression models. The first model adjusted for total cholesterol (mmol/L) and TG (mmol/L). It also adjusted for the matching factors, age at blood collection (years), gender (male, female), dialect group (Hokkien, Cantonese), year of interview (1993–1995, 1996–1998), and year of blood drawn (year) because of the conditional logistic regression used. The second model also adjusted for cigarette smoking (never smoker, former smoker, current smoker <13 cigarettes/d, 13–22 cigarettes/d, ≥23 cigarettes/d), BMI (kg/m^2), education (no formal education, primary school and less, secondary school, more than secondary school), moderate-intensity physical activity (0, <2 h/wk, ≥2 h/wk), strenuous sports (0, <2 h/wk, ≥2 h/wk), strenuous work activity (0, <2 h/wk, ≥2 h/wk), alcohol (g/d), plasma β-cryptoxanthin (mmol/L), plasma lutein (mmol/L), history of hypertension (present, not present), and history of diabetes mellitus (present, not present). Information on alcohol intake was obtained from a FFQ capturing the average use of various alcoholic beverages during the past year and the participant's usual serving size. Alcohol content was determined by comparison with established ethanol contents of standard alcoholic drinks. A positive history of hypertension or diabetes was based on a participant's positive reply at baseline to the question, "Have you been told by a doctor to have hypertension/diabetes." We also evaluated possible 2-way interactions between vitamin E isomers and the redox forms of CoQ10. We added multiplicative interaction terms for the vitamin E and CoQ10 variables to the multivariable model, including diabetes and smoking, and used log-likelihood tests to compare nested models with and without the interaction terms. For this purpose, we used summed tocopherol and tocotrienol plasma concentrations and the ubiquinol and ubiquinone plasma concentrations, all modeled as tertiles to avoid cells with small numbers. All *P* values mentioned were 2-sided and considered significant if <0.05. Values in the text are mean ± SD unless otherwise stated.

Results

There were 233 incident AMI cases (65% male and 35% female) and 466 matched controls in our study and the mean age was

TABLE 2 Partial Pearson correlation coefficients of plasma concentrations of tocopherols, tocotrienols, ubiquinol, and ubiquinone in the control group (n = 466) in the SCHS[1]

	α-Tocopherol	γ-Tocopherol	δ-Tocopherol	α-Tocotrienol	γ-Tocotrienol	δ-Tocotrienol	Ubiquinol	Ubiquinone
α-Tocopherol	1.00	0.17*	0.23*	−0.04	−0.01	−0.03	0.27*	0.07
γ-Tocopherol		1.00	0.56*	0.04	0.01	0.003	0.25*	0.07
δ-Tocopherol			1.00	0.25*	0.13*	−0.04	0.26*	0.08
α-Tocotrienol				1.00	0.62*	0.02	0.07	−0.01
γ-Tocotrienol					1.00	0.11*	−0.05	−0.11*
δ-Tocotrienol						1.00	−0.03	0.01
Ubiquinol							1.00	0.14*
Ubiquinone								1.00

[1] Adjusted for age, gender, dialect, year of interview, and year of blood specimen collection, total cholesterol, and TG. *$P < 0.001$. SCHS, Singapore Chinese Health Study.

~60 y. The length of follow-up was 1.8 ± 1.4 y for the cases and 4.7 ± 1.9 y for the controls. Participants who developed AMI tended to have a higher BMI and a lower education level and were more likely to be cigarette smokers and to have a history of diabetes and hypertension. They also had a higher blood pressure, higher concentrations of total cholesterol, LDL cholesterol, and TG, but lower HDL cholesterol than control participants (**Table 1**). Compared with controls, AMI patients had significantly elevated concentrations of plasma α- and δ-tocopherols, α- and γ-tocotrienols, and ubiquinone (Table 1).

The strongest partial correlations between the isomers of vitamin E and CoQ10 in the control group were between α-tocotrienol and γ-tocotrienol ($r = 0.62$; $P < 0.001$) and between δ-tocopherol and γ-tocopherol ($r = 0.56$; $P < 0.001$) after adjusting for age, gender, dialect, year of interview, year of blood specimen collection, and total cholesterol and TG concentrations (**Table 2**).

We evaluated the association between quintiles of the plasma concentrations of the isomers of vitamin E and risk of AMI (**Table 3**). Plasma cholesterol and TG concentrations were included in the multivariable models, because plasma lipids are carriers of vitamin E. In the basic model (model 1), only a higher δ-tocopherol concentration was significantly associated with a higher risk of AMI, whereas there were no significant associations for the other vitamin E isomers. After adjustment for other potential confounders, the association between δ-tocopherol concentrations and AMI risk remained significant (Table 3).

TABLE 3 OR of AMI according to quintiles of plasma α-, γ-, and δ-tocopherols and α-, γ-, and δ-tocotrienols in the SCHS[1–3]

		Quintiles					
		Q1	Q2	Q3	Q4	Q5	*P* trend
α-Tocopherol, μ*mol/L*							
Cases:controls, *n:n*		36:104	47:93	42:98	51:89	57:82	
Range		14.9–26.8	26.8–30.4	30.4–34.0	34.1–39.8	39.8–101.2	
Median (IQR)		24.5 (22.5–25.5)	28.6 (27.7–29.6)	32.1 (31.1–33.2)	36.5 (35.1–37.9)	44.2 (42.3–47.7)	
Model 1	OR (95% CI)	1.00	1.37 (0.82–2.29)	1.09 (0.61–1.93)	1.41 (0.78–2.56)	1.58 (0.82–3.07)	0.19
Model 2	OR (95% CI)	1.00	1.69 (0.96–2.99)	1.33 (0.69–2.53)	1.62 (0.81–3.24)	2.09 (0.96–4.52)	0.11
γ-Tocopherol, μ*mol/L*							
Cases:controls, *n:n*		49:91	46:94	43:97	42:98	53:86	
Range*		0.22–0.84	0.84–1.08	1.09–1.41	1.42–1.95	1.96–7.33	
Median (IQR)*		0.69 (0.59–0.77)	0.98 (0.90–1.03)	1.23 (1.14–1.32)	1.64 (1.54–1.79)	2.44 (2.20–2.95)	
Model 1	OR (95% CI)	1.00	0.83 (0.50–1.37)	0.68 (0.40–1.15)	0.67 (0.40–1.14)	0.94 (0.55–1.62)	0.71
Model 2	OR (95% CI)	1.00	0.88 (0.50–1.54)	0.72 (0.40–1.28)	0.69 (0.38–1.22)	0.96 (0.52–1.77)	0.72
δ-Tocopherol, μ*mol/L*							
Cases:controls, *n:n*		25:116	52:87	48:93	47:92	61:78	
Range		0.07–0.31	0.31–0.38	0.38–0.46	0.46–0.59	0.59–1.46	
Median (IQR)		0.26 (0.21–0.28)	0.34 (0.32–0.36)	0.42 (0.40–0.43)	0.52 (0.48–0.55)	0.68 (0.63–0.77)	
Model 1	OR (95% CI)	1.00	2.87 (1.60–5.16)	2.37 (1.32–4.25)	2.29 (1.26–4.15)	3.31 (1.77–6.18)	0.005
Model 2	OR (95% CI)	1.00	2.96 (1.55–5.66)	2.27 (1.19–4.31)	2.21 (1.14–4.29)	3.09 (1.53–6.25)	0.028
α-Tocotrienol,* *nmol/L*							
Cases:controls, *n:n*		46:97	36:102	53:86	46:97	52:84	
Range*		8.24–16.5	16.6–25.9	26.0–36.0	36.2–54.2	54.8–423	
Median (IQR)*		9.4 (9.4–12.4)	22.1 (18.8–24.0)	31.1 (28.6–33.7)	43.6 (40.3–48.0)	78.1 (63.1–104.2)	
Model 1	OR (95% CI)	1.00	0.79 (0.44–1.45)	1.32 (0.70–2.48)	1.06 (0.56–2.02)	1.33 (0.70–2.51)	0.30
Model 2	OR (95% CI)	1.00	0.66 (0.34–1.29)	0.94 (0.46–1.91)	0.87 (0.42–1.78)	1.21 (0.60–2.44)	0.48
γ-Tocotrienol,* *nmol/L*							
Cases:controls, *n:n*		41:103	44:92	50:90	44:97	54:84	
Range*		1.22–24.4	25.2–44.3	44.4–68.1	69.0–108	110–460	
Median (IQR)*		11.0 (2.44–24.4)	36.5 (30.2–41.2)	56.4 (49.1–62.1)	85.7 (77.6–96.8)	151 (130–199)	
Model 1	OR (95% CI)	1.00	1.31 (0.72–2.36)	1.49 (0.82–2.73)	1.29 (0.69–2.42)	1.77 (0.91–3.45)	0.11
Model 2	OR (95% CI)	1.00	1.15 (0.60–2.20)	1.40 (0.72–2.74)	1.08 (0.55–2.13)	1.58 (0.77–3.26)	0.27
δ-Tocotrienol,* *nmol/L*							
Cases:controls, *n:n*		45:95	53:87	38:103	51:90	46:91	
Range*		2.27–21.3	21.3–34.4	34.7–43.5	43.9–54.7	55.1–391	
Median (IQR)*		13.9 (9.58–17.7)	29.0 (25.2–31.9)	38.8 (37.1–41.6)	48.2 (45.4–51.1)	70.6 (60.6–90.8)	
Model 1	OR (95% CI)	1.00	1.35 (0.74–2.45)	0.74 (0.38–1.43)	1.26 (0.61–2.58)	1.09 (0.52–2.28)	0.98
Model 2	OR (95% CI)	1.00	1.34 (0.71–2.52)	0.71 (0.35–1.45)	0.92 (0.41–2.06)	0.95 (0.42–2.14)	0.74

[1] Asterisks indicate log-transformed and back-transformed variables. AMI, acute myocardial infarction; SCHS, Singapore Chinese Health Study.
[2] Model 1: Covariates adjusted for through matching included age (y) at collection, sex (M,F), dialect group (Hokkien, Cantonese), year of interview (1993–1995, 1996–1998), and year blood was drawn. In addition, we adjusted for total cholesterol (mmol/L) and TG (mmol/L).
[3] Model 2: adjustment for variables in model 1, cigarette smoking (never smoker, former smoker, current smoker <13, 13–22, ≥23 cigarettes/d), BMI (kg/m^2), education (no formal education, primary school and below, secondary school, above secondary school), moderate intensity physical activity (0, <2, ≥2 h/wk), strenuous sports (0, <2, ≥2 h/wk), strenuous work activity (0, <2 h/wk, ≥2 h/wk), alcohol consumption (g/d), plasma β-cryptoxanthin (mmol/L), plasma lutein (mmol/L), hypertension (yes, no), and diabetes (yes, no).

We also examined the association between quintiles of the plasma concentrations of CoQ10 and risk of AMI (**Table 4**). In the basic model, higher ubiquinone concentrations were significantly associated with a higher risk of AMI. However, this association was attenuated and not significant after further adjustment for other potential confounders (model 2). There was no significant association between the plasma concentration of ubiquinol and risk of AMI.

We did not observe significant interactions between concentrations of the vitamin E isomers and the redox forms of CoQ10 in relation to AMI risk (all *P*-interaction between summed tocopherols or tocotrienols and ubiquinone or ubiquinone > 0.07).

Discussion

Few previous studies have evaluated plasma concentrations of δ-tocopherol, tocotrienols, ubiquinone, and ubiquinol in relation to risk of incident AMI. The findings from our nested case-control study of Singapore Chinese men and women suggest that higher plasma concentrations of vitamin E and CoQ10 compounds are not associated with a lower risk of incident AMI. In contrast, higher plasma δ-tocopherol concentrations were associated with a higher risk of AMI.

We did not observe a clear dose-response relationship for δ-tocopherol concentrations in relation to risk of AMI, but there was a similarly elevated risk for the upper 4 quintiles of δ-tocopherol compared with the lowest quintile. For α-tocopherol concentrations, RR were also higher for the upper 4 quintiles compared with the lowest quintile, but this association was not significant. It is currently unclear why specifically δ-tocopherol may affect risk of AMI, because few mechanistic studies have focused on this form of vitamin E. However, previous in vitro (48) and in vivo (49) studies have observed that α-tocopherol has the potential to have a prooxidant effect in a preexisting environment with increased oxidative stress, e.g., related to atherosclerosis and smoking. Increased oxidative stress has been postulated to liberate transition-metal ions from cell metalloproteins in unstable plaques (49), which α-tocopherol may interact with to exert prooxidant effects on lipoproteins (50).

α-Tocopherol is the predominant lipid-soluble antioxidant in plasma and LDL and has been suggested to play a role in the prevention of atherosclerosis via the inhibition of atherogenic mechanisms such as LDL oxidation (macrophage mediated), IL-1β release from monocytes, platelet adhesion and aggregation (thus limiting progression of the fibrous plaque), and smooth muscle proliferation (important in fibrous plaque formation) (51). However, almost all of these mechanisms have only been shown in in vitro studies and it is thus unclear whether they act under in vivo conditions. Consistent with our findings, a meta-analysis of 4 randomized controlled trials found that α-tocopherol supplements did not significantly decrease risk of nonfatal AMI or cardiovascular mortality [OR = 1.0 (95% CI: 0.94, 1.07)] (7). Similarly, in later randomized trials, no significant effect of α-tocopherol supplementation on the incidence of AMI was found in the Women's Health Study (52) or the Physicians' Health Study I (53) or II (10).

With regard to γ-tocopherol concentrations, we did not observe a substantial association with risk of AMI in our study. In several cohort studies, higher dietary vitamin E intake, mainly representing γ-tocopherol, was associated with a lower risk of coronary heart disease, but this inverse association was modest and not significant in a pooled analysis of 9 cohort studies [RR = 0.84 (95% CI: 0.71, 1.00); $P = 0.17$] (12). In a nested case-control study in the US, Evans et al. (11) did not observe significant associations between serum γ-tocopherol concentrations in nonsmokers and risk of coronary heart disease deaths [OR = 2.34 (95% CI: 0.56, 9.81] for highest vs. lowest quartile] or nonfatal myocardial infarction [OR = 0.79 (95% CI: 0.14, 4.58)]. Hak et al. (53) reported a significant direct association between plasma γ-tocopherol concentrations and AMI [RR = 2.14 (95% CI: 1.18, 3.87) for the highest vs. lowest quartile; *P*-trend = 0.01] in the U.S. Physicians Health Study. The authors postulated that this direct association could be due to residual confounding by elevated plasma lipids or higher *trans*-fat intake.

Reduced concentrations of CoQ10 in plasma and circulating LDL in patients with atherosclerosis and heart disease, as

TABLE 4 OR of AMI according to quintiles of plasma ubiquinol and ubiquinone in the SCHS[1,2]

		Quintiles					
		Q1	Q2	Q3	Q4	Q5	*P*-trend
Ubiquinol, $\mu mol/L$							
Cases:controls, *n:n*		46:94	36:104	47:93	47:93	57:82	
Range		0.08–0.53	0.53–0.65	0.65–0.79	0.79–0.96	0.97–2.49	
Median (IQR)		0.44 (0.35–0.50)	0.60 (0.56–0.62)	0.71 (0.68–0.75)	0.85 (0.83–0.91)	1.14 (1.04–1.25)	
Model 1	OR (95% CI)	1.00	0.67 (0.38–1.17)	0.92 (0.53–1.59)	0.84 (0.48–1.46)	1.07 (0.59–1.92)	0.46
Model 2	OR (95% CI)	1.00	0.61 (0.33–1.13)	0.82 (0.44–1.52)	0.91 (0.49–1.69)	1.22 (0.62–2.40)	0.19
Ubiquinone, $\mu mol/L$							
Cases:controls, *n:n*		38:102	44:97	47:92	47:94	57:81	
Range		0.03–0.10	0.01–0.12	0.12–0.15	0.14–0.18	0.18–0.58	
Median (IQR)		0.08 (0.06–0.09)	0.11 (0.10–0.12)	0.13 (0.13–0.14)	0.16 (0.15–0.17)	0.22 (0.20–0.26)	
Model 1	OR (95% CI)	1.00	1.36 (0.77–2.40)	1.42 (0.78–2.56)	1.36 (0.74–2.49)	1.93 (1.08–3.44)	0.032
Model 2	OR (95% CI)	1.00	1.51 (0.81–2.82)	1.40 (0.72–2.71)	1.41 (0.72–2.79)	1.81 (0.95–3.43)	0.11

[1] Model 1: Adjusted for age at blood collection (y), gender (M,F), dialect group (Hokkien, Cantonese), year of interview (1993–1995, 1996–1998), and year blood was drawn. In addition, we adjusted for total cholesterol (mmol/L) and TG (mmol/L). AMI, acute myocardial infarction; SCHS, Singapore Chinese Health Study.

[2]Model 2: adjustment for variables in model 1, cigarette smoking (never smoker, former smoker, current smoker <13, 13–22, ≥23 cigarettes/d), BMI (kg/m^2), education (no formal education, primary school and below, secondary school, above secondary school), moderate intensity physical activity (0, <2, ≥2 h/wk), strenuous sports (0, <2, ≥2 h/wk), strenuous work activity (0, <2 h/wk,

≥2 h/wk), alcohol consumption (g/d), plasma β-cryptoxanthin (mmol/L), plasma lutein (mmol/L), hypertension (yes, no), and diabetes (yes, no).

observed in experimental studies (54,55), may result in a reduced capacity of the antioxidant defense system (24). Previous in vitro studies identified CoQ10 as the preferred antioxidant consumed when LDL is exposed to various oxidants (33,56). Our study did not support the findings of a randomized trial by Singh et al. (30,31) that showed a protective effect of CoQ10 supplements on risk of nonfatal AMI at 28 d of post-AMI/unstable angina follow-up [RR = 0.37 (95%CI: 0.28, 0.77)] and 1 y of follow-up (RR = 0.54; $P < 0.05$).

Steinberg and Witztum (57) have suggested that dietary antioxidants are more effective in inhibiting early stages of atherogenesis such as fatty streak formation than in preventing complications at more advanced stages of atherosclerosis such as plaque instability and rupture. It cannot be excluded that higher vitamin E or CoQ10 exposure earlier in life has a beneficial effect on risk of AMI.

A strength of our study was the prospective study design with collection of blood samples of participants before disease onset. This reduces the likelihood of reverse causation, i.e., an effect of AMI onset on biomarker concentrations. The use of biomarkers of vitamin E and CoQ10 avoids errors related to reporting of food consumption and incomplete food composition databases that affect studies of questionnaire-based estimates of nutrient intake. All incident AMI cases were verified based on the review of medical records by a cardiologist using internationally established diagnostic criteria. A limitation of our study was the modest sample size reducing the statistical power to detect modest effects. Furthermore, our study was based on the measurement of plasma concentrations of vitamin E and CoQ10 at a single point in time, which may not accurately reflect long-term exposure. We recognize that plasma vitamin E concentrations are imperfect measures of dietary intake, with correlations being higher for γ-tocopherol than for α-tocopherol (58). We adjusted for potential confounding by multiple cardiovascular disease risk factors. However, as is true for all observational studies, we cannot rule out the possibility that residual confounding influenced our findings.

In conclusion, our study examined the association of a wide range of vitamin E and CoQ10 isomers in relation to risk of incident AMI. We did not observe an inverse association between plasma concentrations of isomers of vitamin E or CoQ10 and risk of AMI in Singapore Chinese. In contrast, we observed a significant direct association between plasma δ-tocopherol concentrations and risk of AMI that requires further study. Our findings do not support a role of higher vitamin E or CoQ10 intakes in the prevention of myocardial infarction.

Acknowledgments

The authors thank Siew-Hong Low of the National University of Singapore for supervising the field work of the SCHS and Kazuko Arakawa and Renwei Wang for the development and maintenance of the cohort study database. The authors also thank the founding principal investigators of the SCHS: Professors Mimi C. Yu and Hin-Peng Lee. N.N. drafted the manuscript and contributed to the data analysis and interpretation of the data; R.M.v.D. conceived the data analysis, contributed to the drafting of the manuscript and interpretation of the data, and takes primary responsibility for the final content; W.P.K. led the data collection and edited the manuscript; C.C. conducted the data analysis; Y.P.L. contributed to the study design and collection and verification of data; J.M.Y. led the data collection, contributed to the conception of the study, and edited the manuscript; and C.N.O. contributed to the conception of the study, led the biochemical analyses, and edited the manuscript. All authors read and approved the final manuscript.

Literature Cited

1. Colombo ML. An update on vitamin E, tocopherol and tocotrienol-perspectives. Molecules. 2010;15:2103–13.
2. Willett WC, Stampfer M, Underwood B, Taylor J, Hennekens C, Vitamins A. E, and carotene: effects of supplementation on their plasma levels. Am J Clin Nutr. 1983;38:559–66.
3. Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. Am J Epidemiol. 1988;127:283–96.
4. Ascherio A, Stampfer MJ, Colditz GA, Rimm EB, Litin L, Willett WC. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. J Nutr. 1992;122:1792–801.
5. Jacques PF, Sulsky S, Sadowski J, Phillips J, Rush D, Willett W. Comparison of micronutrient intake measured by a dietary questionnaire and biochemical indicators of micronutrient status. Am J Clin Nutr. 1993;57:182–9.
6. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. N Engl J Med. 1989;320:915–24.
7. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet. 2003;361:2017–23.
8. Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. Arch Intern Med. 2004;164:1552–6.
9. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma R, Appel L, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37–46.
10. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Glynn RJ, Gaziano JM. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2008;300:2123–33.
11. Evans RW, Shaten BJ, Day BW, Kuller LH. Prospective association between lipid soluble antioxidants and coronary heart disease in men. The Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1998; 147:180–6.
12. Knekt P, Ritz J, Pereira MA, O'Reilly EJ, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Liu S, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr. 2004;80:1508–20.
13. Dietrich M, Traber MG, Jacques PF, Cross CE, Hu Y, Block G. Does gamma-tocopherol play a role in the primary prevention of heart disease and cancer? A review. J Am Coll Nutr. 2006;25:292–9.
14. Huang H-Y, Appel LJ. Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. J Nutr. 2003;133:3137–40.
15. Handelman GJ, Epstein W, Peerson J, Spiegelman D, Machlin L, Dratz E. Human adipose alpha-tocopherol and gamma-tocopherol kinetics during and after 1 y of alpha-tocopherol supplementation. Am J Clin Nutr. 1994;59:1025–32.
16. Olmedilla B, Granado F, Southon S, Wright AJ, Blanco I, Gil-Martinez E, Berg H, Corridan B, Roussel AM, Chopra M, et al. Serum concentrations of carotenoids and vitamins A, E, and C in control subjects from five European countries. Br J Nutr. 2001;85:227–38.
17. Slover HT, Lehmann J, Valis R. Vitamin E in foods: determination of tocols and tocotrienols. J Am Oil Chem Soc. 1969;46:417–20.
18. Bieri JG, Evarts RP. Gamma tocopherol: metabolism, biological activity and significance in human vitamin E nutrition. Am J Clin Nutr. 1974;27:980–6.
19. Wang L, Newman RK, Newman CW, Jackson LL, Hofer PJ. Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism. Plant Foods Hum Nutr. 1993;43:9–17.
20. Mahabir S, Schendel K, Dong YQ, Barrera SL, Spitz MR, Forman MR. Dietary α-, β-, γ- and δ-tocopherols in lung cancer risk. Int J Cancer. 2008;123:1173–80.
21. Yoshida H, Yusin M, Ren I, Kuhlenkamp J, Hirano T, Stolz A, Kaplowitz N. Identification, purification, and immunochemical characterization of a tocopherol-binding protein in rat liver cytosol. J Lipid Res. 1992;33:343–50.

22. Horwitt MK, Harvey CC, Dahm CH Jr, Searcy MT. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. Ann N Y Acad Sci. 1972;203:223–36.
23. Lodge JK. Vitamin E bioavailability in humans. J Plant Physiol. 2005; 162:790–6.
24. Hargreaves IP. Ubiquinone: cholesterol's reclusive cousin. Ann Clin Biochem. 2003;40:207–18.
25. Kalén A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. Lipids. 1989;24:579–84.
26. Pravst I, Žmitek K, Žmitek J. Coenzyme Q10 Contents in foods and fortification strategies. Crit Rev Food Sci Nutr. 2010;50:269–80.
27. Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. Mitochondrion. 2007; Suppl 7:S78–88.
28. Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst Rev. 2009;CD007435.
29. Kuklinski B, Weissenbacher E, Fähnrich A. Coenzyme Q10 and antioxidants in acute myocardial infarction. Mol Aspects Med. 1994;15:s143–7.
30. Singh RB, Wander GS, Rastogi A, Shukla PK, Mittal A, Sharma JP, Mehrotra SK, Kapoor R, Chopra RK. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther. 1998;12:347–53.
31. Singh RB, Neki NS, Kartikey K, Pella D, Kumar A, Niaz MA, Thakur AS. Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. Mol Cell Biochem. 2003;246:75–82.
32. Constantinescu A, Maguire JJ, Packer L. Interactions between ubiquinones and vitamins in membranes and cells. Mol Aspects Med. 1994;Suppl 15: s57–65.
33. Stocker R, Bowry VW, Frei B. Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol. Proc Natl Acad Sci USA. 1991;88:1646–50.
34. Hankin JH, Stram D, Arakawa K, Park S, Low S-H, Lee H-P, Yu M. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer. 2001;39:187–95.
35. Koh WP, Yuan JM, Sun CL, van den Berg D, Seow A, Lee HP, Yu MC. Angiotensin I-converting enzyme (ACE) gene polymorphism and breast cancer risk among Chinese women in Singapore. Cancer Res. 2003; 63:573–8.
36. Vera-Cala LM, Orostegui M, Valencia-Angel LI, Lopez N, Bautista LE. Accuracy of the Omron HEM-705 CP for blood pressure measurement in large epidemiologic studies. Arq Bras Cardiol. 2011;96:393–8.
37. Koh WP, Yuan JM, Wang R, Lee YP, Lee BL, Yu MC, Ong CN. Plasma carotenoids and risk of acute myocardial infarction in the Singapore Chinese Health Study. Nutr Metab Cardiovasc Dis. 2011;21:685–90.
38. WHO. WHO MONICA project. MONICA manual. 1998–1999 [cited 2011 Sep 12]. Available from: http://www.ktl.fi/publications/monica/manual/index.htm.
39. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871–81.
40. Lee BL, New AL, Ong CN. Simultaneous determination of tocotrienols, tocopherols, retinol, and major carotenoids in human plasma. Clin Chem. 2003;49:2056–66.
41. Lee BL, Ong CN. Comprehensive high-performance liquid chromatographic method for the measurements of lipophilic antioxidants in human plasma. J Chromatogr A. 2009;1216:3131–7.
42. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974;20:470–5.
43. Warnick GR, Nauck M, Rifai N. Evolution of Methods for Measurement of HDL-Cholesterol: From Ultracentrifugation to Homogeneous Assays. Clinical Chemistry, 2001. 47:1579–96.
44. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
45. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem. 1982;28:2077–80.
46. Sung KC, Hwang ST. Association between insulin resistance and apolipoprotein B in normoglycemic Koreans. Atherosclerosis. 2005;180:161–9.
47. Neumann T, Woiwod T, Neumann A, Miller M, Von Birgelen C, Volbracht L, Esser S, Brockmeyer N, Gerken G, Erbel R. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients. Part III: age differences. Eur J Med Res. 2004;9:267–72.
48. Bowry VW, Ingold KU, Stocker R. Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. Biochem J. 1992;288:341–4.
49. Sampson MJ, Astley S, Richardson T, Willis G, Davies IR, Hughes DA, Southon S. Increased DNA oxidative susceptibility without increased plasma LDL oxidizability in Type II diabetes: effects of alpha-tocopherol supplementation. Clin Sci. 2001;101:235–41.
50. Halliwell B. The antioxidant paradox. Lancet. 2000;355:1179–80.
51. Devaraj S, Jialal I. The effects of alpha-tocopherol on critical cells in atherogenesis. Curr Opin Lipidol. 1998;9:11–5.
52. Lee I-M, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Vitamin E in the primary prevention of cardiovascular disease and cancer. JAMA. 2005;294:56–65.
53. Hak AE, Stampfer MJ, Campos H, Sesso HD, Gaziano JM, Willett W, Ma J. Plasma carotenoids and tocopherols and risk of myocardial infarction in a low-risk population of US male physicians. Circulation. 2003;108:802–7.
54. Hanaki Y, Sugiyama S, Ozawa T, Ohno M. Coenzyme Q10 and coronary artery disease. J Mol Med. 1993;71:S112–5.
55. Kontush A, Reich A, Baum K, Spranger T, Finckh B, Kohlschütter A, Beisiegel U. Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia. Atherosclerosis. 1997;129:119–26.
56. Thomas SR, Neuzil J, Mohr D, Stocker R. Coantioxidants make alpha-tocopherol an efficient antioxidant for low-density lipoprotein. Am J Clin Nutr. 1995;62:S1357–64.
57. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Circulation. 2002;105:2107–11.
58. El-Sohemy A, Baylin A, Ascherio A, Kabagambe E, Spiegelman D, Campos H. Population-based study of alpha- and gamma-tocopherol in plasma and adipose tissue as biomarkers of intake in Costa Rican adults. Am J Clin Nutr. 2001;74:356–63.