Antioxidant vitamins and coronary heart disease risk : a pooled analysis of 9 cohorts.

Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts[1–3]

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ABSTRACT

Background: Epidemiologic studies have suggested a lower risk of coronary heart disease (CHD) at higher intakes of fruit, vegetables, and whole grain. Whether this association is due to antioxidant vitamins or some other factors remains unclear.

Objective: We studied the relation between the intake of antioxidant vitamins and CHD risk.

Design: A cohort study pooling 9 prospective studies that included information on intakes of vitamin E, carotenoids, and vitamin C and that met specific criteria was carried out. During a 10-y follow-up, 4647 major incident CHD events occurred in 293 172 subjects who were free of CHD at baseline.

Results: Dietary intake of antioxidant vitamins was only weakly related to a reduced CHD risk after adjustment for potential nondietary and dietary confounding factors. Compared with subjects in the lowest dietary intake quintiles for vitamins E and C, those in the highest intake quintiles had relative risks of CHD incidence of 0.84 (95% CI: 0.71, 1.00; $P = 0.17$) and 1.23 (1.04, 1.45; $P = 0.07$), respectively, and the relative risks for subjects in the highest intake quintiles for the various carotenoids varied from 0.90 to 0.99. Subjects with higher supplemental vitamin C intake had a lower CHD incidence. Compared with subjects who did not take supplemental vitamin C, those who took >700 mg supplemental vitamin C/d had a relative risk of CHD incidence of 0.75 (0.60, 0.93; P for trend $<$ 0.001). Supplemental vitamin E intake was not significantly related to reduced CHD risk.

Conclusions: The results suggest a reduced incidence of major CHD events at high supplemental vitamin C intakes. The risk reductions at high vitamin E or carotenoid intakes appear small. *Am J Clin Nutr* 2004;80:1508–20.

KEY WORDS Antioxidant, carotenoids, cohort, coronary heart disease, diet, Pooling Project of Cohort Studies on Diet and Coronary Disease, vitamin C, vitamin E

INTRODUCTION

Several observational epidemiologic studies have suggested that higher intakes of fruit, vegetables, and whole grain are related to a lower risk of coronary heart disease (CHD) (1, 2). One hypothesized explanation for this finding is a reduction in oxidatively modified LDL, which is thought to play an important role in the development of atherosclerosis. Because of their antioxidant properties, carotenoids, vitamin E, and vitamin C may protect against free oxygen radicals and lipid peroxidation and accordingly inhibit the development of atherosclerosis (3). Findings from observational cohort studies on this topic are inconsistent (1, 4). Most previous cohort studies have investigated α-tocopherol or vitamin E, vitamin C, and total carotene or β-carotene, and only scarce information exists on other carotenoids. Few studies have reported on vitamin supplement intake. The inconsistency of the results from these studies may, in part, be due to a lack of power to detect associations, misclassification of antioxidant intake, unsatisfactory control for potential confounding factors, or an inability to investigate subpopulations. Randomized intervention trials in primary prevention of cardiovascular disease have not shown substantial benefits from α-tocopherol (5, 6) or β-carotene (5–9) supplementation.

In the present Pooling Project of Cohort Studies on Diet and Coronary Disease, we studied the relations of the intakes of vitamin E, 5 carotenoids, and vitamin C to the incidence of all major CHD events (nonfatal myocardial infarction or fatal CHD) and CHD mortality by pooling primary data from 9 major cohort studies with the use of a standardized approach. This large database enabled us to examine several issues that would be difficult to address in any single cohort study, such as whether *1*)

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single antioxidants or combinations of them predict CHD occurrence, *2*) the strength of associations differs by dietary and supplemental intake, and *3*) nondietary or dietary risk factors of CHD modify the association.

SUBJECTS AND METHODS

Study population

Eleven cohort studies meeting the following criteria were included in the Pooling Project of Cohort Studies on Diet and Coronary Disease: *1*) the study included ≥150 incident CHD cases, *2*) usual total dietary intake was determined with the use of a food-frequency or dietary history method at baseline, and *3*) data were available from a validation or reproducibility study of the diet-assessment instrument. One study of those satisfying the criteria (Israel Ischemic Heart Disease Study) was excluded because it did not have data on antioxidant vitamin intake, and one ongoing trial (Women's Health Study) was excluded because the subjects receiving antioxidant vitamin supplements could not be identified. The basic characteristics of the remaining 9 studies are presented in **Table 1** (10–18). The cases and person-time experienced during follow up of the Nurses' Health Study was divided into 2 uncorrelated segments for analysis. The 1980–1986 follow-up period is referred to as Nurses' Health Study (a), and the 1986–1996 follow-up period is referred to as Nurses' Health Study (b). In accordance with the underlying theory of survival analysis, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same persons (19). Thus, pooling the estimates from the 2 time periods is equivalent to using a single time period but takes advantage of the enhanced exposure assessment in 1986 compared with 1980.

Criteria for exclusion of persons from the population at risk were age < 35 y, history of cardiovascular disease or cancer (except nonmalignant skin cancer), and extreme energy intake (ie, > or <3 SDs from the study-specific log-transformed energy intake) at baseline. Subjects receiving vitamin E or β-carotene supplements in the ATBC trial were also excluded from the analyses. A total of 293 172 subjects (77 948 men and 215 224 women) were included.

Exposure variables

Diet was measured by using a food-frequency questionnaire in 7 cohorts and by using a dietary history interview or food records in 2 cohorts. We studied dietary vitamin E, α-carotene, β-carotene, lutein, lycopene, β-cryptoxanthin, total carotene, and vitamin C (Table 1). Overall intakes (dietary and supplemental combined) of vitamin E, β-carotene, total carotene, and vitamin C were calculated in 4 cohorts (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; the Health Professionals Follow-Up Study; the Iowa Women's Health Study; and the Nurses' Health Study) with information on intakes of vitamin E, vitamin C, total carotene, and β-carotene and on multivitamin supplement intake (**Table 2**). Information on whether or not the subjects at risk took supplements at baseline was available for all cohorts except one (the Atherosclerosis Risk in Communities Study).

For all nutrients, the energy-adjusted intake was estimated by using the residual method (20), in which the log-transformed nutrient intake was regressed against the log-transformed energy intake and the residual represented the nutrient intake independently of energy intake. The results were standardized to a median energy intake of 2100 kcal in men and 1600 kcal in women. A carotene variety score combining α-carotene, β-carotene, lutein, lycopene, and β-cryptoxanthin was formed by summing individual standardized scores (*z* scores) calculated for each log-transformed carotenoid by subtracting its group mean from the individual values and then dividing by the SD.

Outcome variables

The outcomes studied were incidence of all major CHD events (including nonfatal myocardial infarction or fatal CHD) and CHD mortality. Validated methods to define nonfatal and fatal CHD cases (codes 410–414 in the *International Classification of Diseases*, 8th revision) were used in 8 studies (21). Because the Iowa Women's Health Study had only self-reported data on nonfatal CHD, we used only fatal coronary cases from that cohort.

The follow-up for cohorts varied from 6 to 22 y, but for studies with follow-up times > 10 y, the follow-up was restricted a priori to the first 10 y for this analysis. During follow-up, 4647 subjects developed major CHD events (2838 men and 1809 women). Of these, 1888 died of the disease (986 men and 902 women). In substudies of dietary vitamin intake, subjects who were taking vitamin E, vitamin C, β-carotene, carotene, or multivitamin supplements at the baseline examination were excluded. After this exclusion, 156 949 persons (46 521 men and 110 428 women) remained in the population at risk, and 2908 (1888 men and 1020 women) and 1124 (640 men and 484 women) of them developed CHD and died of the disease, respectively (Table 1). The total number of persons at risk in the subpopulation of 4 studies including subjects with information on both dietary and supplemental vitamin intake was 227 243 (48 326 men and 178 917 women), the number of incident CHD cases was 3036 (1737 men and 1299 women), and the number of deaths was 1364 (615 men and 749 women) (Table 2).

Statistical methods

Cox's proportional hazards model (22) was used to estimate the incidence rate ratio (relative risk, RR) for CHD in relation to antioxidant vitamin intake in each individual subcohort consisting of either men or women (Table 1). The calculations were performed with PROC PHREG of SAS, version 8 (23). The follow-up time was defined as the number of months from the baseline examination to the date of CHD occurrence, death, or withdrawal (ie, end of follow-up), whichever came first. Analyses with exclusion of the first 2 y of follow-up were also carried out. The models were stratified on age and calendar year at baseline. Energy intake was included as a continuous variable in all models.

To avoid assumptions regarding the shape of the relation between antioxidant vitamin exposure and CHD occurrence, RRs were estimated for quintiles of the antioxidant variables. Two-sided 95% CIs were calculated. The *P* value for trend was calculated by assigning the subjects the median value of their category of the antioxidant considered and including this as a continuous variable in the model. A weakness of this approach is that possible differences in absolute intakes between the different cohorts are neglected at the pooling stage. To minimize this shortcoming, we separately evaluated dietary intake (excluding supplement users) and overall intake (including cohorts with information on supplement intake) (Tables 1 and 2). Because the assumption of linearity on a logistic scale was

TABLE 1
Basic characteristics of the cohort studies included in the pooled analysis of daily dietary antioxidant intake and coronary heart disease (CHD) risk[1]

Study and reference	Baseline cohort size	Age	Follow-up period	Number of CHD cases[2]		Median dietary intake (1st–9th deciles)							
				Incidence	Mortality	Vitamin E	α-Carotene	β-Carotene	Lutein	Lycopene	β-Cryptoxanthin	Total carotene	Vitamin C
		y				*mg*	*μg*	*μg*	*μg*	*μg*	*μg*	*μg RE*	*mg*
AHS (10)			1977–1983										
Female	5043	35–99		36	17	4.45 (3.45–5.58)	—	—	—	—	—	—	—
Male	4321	35–99		71	23	5.08 (3.99–6.25)	—	—	—	—	—	—	—
ARIC (11)			1987–1998										
Female	7277	45–64		188	32	4.69 (3.15–6.86)	347 (20–1601)	2165 (829–6311)	2170 (697–6837)	2477 (0–10 916)	74 (13–212)	592 (235–1630)	123 (54–219)
Male	5859	45–64		345	71	5.61 (3.80–8.31)	350 (19–1449)	2039 (683–5738)	2150 (600–6771)	2852 (0–12 629)	69 (10–218)	567 (206–1503)	129 (55–253)
ATBC (12)													
Male	4739	50–70	1985–1993	296	117	8.02 (5.76–14.46)	366 (90–1046)	1373 (641–3088)	1102 (780–1536)	480 (87–1299)	15 (1–56)	532 (302–970)	72 (42–120)
FMC (13)			1966–1976										
Female	2113	35–86		141	47	4.47 (3.51–6.55)	264 (10–1511)	1167 (436–4018)	739 (474–1160)	510 (0–1793)	—	204 (75–699)	60 (34–108)
Male	2584	35–85		310	148	5.46 (4.47–7.86)	93 (1–897)	813 (443–2641)	805 (531–1190)	310 (0–1190)	—	141 (75–458)	56 (33–90)
GPS (14)			1974–1985										
Female	823	35–80		26	11	5.57 (3.69–8.88)	—	1302 (398–4724)	—	—	—	—	62 (27–131)
Male	1001	35–80		60	22	6.23 (3.85–10.45)	—	1098 (323–3800)	—	—	—	—	61 (29–130)
HPFS (15)													
Male	19 687	39–77	1986–1996	679	224	7.39 (5.26–10.58)	627 (283–1849)	4030 (1992–8500)	3129 (1261–6771)	8944 (3550–19 385)	56 (10–179)	744 (369–1709)	153 (77–268)
IWHS (16)													
Female	16 896	52–71	1986–1995	—	198	4.26 (3.10–5.89)	472 (218–1536)	3501 (1662–7217)	2077 (867–4672)	3284 (1149–7754)	53 (11–149)	632 (305–1428)	128 (68–210)
NHS (a) (17)													
Female	48 639	35–61	1980–1986	306	69	3.82 (2.60–5.57)	434 (189–1505)	3174 (1321–8215)	2738 (1123–11444)	3959 (847–11 125)	75 (18–214)	636 (287–1398)	117 (59–204)
NHS (b) (17)													
Female	21 450	40–66	1986–1996	305	107	5.78 (4.17–8.04)	547 (194–1310)	3367 (1697–6248)	2590 (1119–5291)	7874 (3680–15 664)	38 (7–109)	686 (332–1353)	125 (67–206)
VIP (18)			1992–1998										
Female	8187	39–71		18	3	5.64 (4.56–7.15)	894 (219–2861)	2429 (718–7312)	—	—	—	591 (177–1755)	92 (48–162)
Male	8330	39–71		127	35	6.84 (5.28–9.17)	394 (110–1527)	1222 (431–4028)	—	—	—	283 (90–956)	76 (39–142)
All studies	156 949			2908	1124								

[1] Supplement users were excluded. RE, retinol equivalents; AHS, Adventist Health Study; ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the placebo arm); FMC, Finnish Mobile Clinic Health Examination Survey; GPS, Glostrup Population Study; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; NHS (a), Nurses' Health Study, 1980–1986; NHS (b), Nurses' Health Study, 1986–1996; VIP, Västerbotten Intervention Program.

[2] During a maximal follow-up of 10 y. Incidence includes nonfatal myocardial infarction and coronary death.

TABLE 2
Characteristics of the cohort studies with information on supplement intake that were included in the pooled analysis of antioxidant intake and coronary heart disease (CHD) risk[1]

Study and reference	Baseline cohort size	Age	Follow-up period	Number of CHD cases[2]		Median daily total intake (1st–9th deciles)				Median daily supplement intake[3] (1st–9th deciles)			
				Incidence	Mortality	Vitamin E	Vitamin C	β-Carotene	Total carotene	Vitamin E	Vitamin C	β-Carotene	Total carotene
		y				*mg*	*mg*	*μg*	*μg RE*	*mg*	*mg*	*μg*	*μg RE*
ATBC (12)													
Male	5520	50–70	1985–1993	336	132	8.6 (6.0–16.6)	79 (44–156)	1435 (657–3363)	—	7 (7–67)	75 (30–1000)	6000 (2571–6000)	—
HPFS (15)													
Male	42 806	39–77	1986–1996	1401	483	9.6 (5.5–418.2)	231 (96–1187)	4293 (2087–9387)	793 (387–1886)	30 (4–430)	259 (34–1200)	6000 (6000–6000)	1000 (2–1000)
IWHS (16)													
Female	31 905	52–71	1986–1995	—	362	5.4 (3.3–178.2)	179 (84–664)	—	688 (327–1566)	20 (6–278)	185 (50–800)	—	250 (143–750)
NHS (a) (17)													
Female	83 218	35–67	1980–1986	464	120	4.7 (2.8–207.8)	154 (70–702)	—	—	15 (6–415)	200 (43–1050)	—	—
NHS (b) (17)													
Female	63 794	40–67	1986–1996	835	267	8.3 (4.7–350.2)	199 (91–811)	3792 (1918–7323)	764 (369–1567)	30 (4–417)	185 (34–1052)	6000 (6000–6000)	7 (1–27)
All studies	227 243			3036	1364								

[1] RE, retinol equivalents; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the placebo arm); HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; NHS (a), Nurses' Health Study, 1980–1986; NHS (b), Nurses' Health Study, 1986–1996.

[2] During a maximal follow-up of 10 y. Incidence includes nonfatal myocardial infarction and coronary death.

[3] Includes supplement users only.

reasonable in some cases, we also carried out complementary analyses with the antioxidant vitamin variable included in the model as a continuous variable; thus, the RR per nutritionally meaningful increment was estimated.

Three main models were defined, the first of which included the energy-adjusted antioxidant vitamin considered, age, and energy intake. The second multivariate model also included the following potential, nondietary confounding factors, which were chosen a priori: smoking status [never, past, current (1–4, 5–14, 15–24, ≥25 cigarettes/d)], physical activity (5 levels), alcohol intake (0, <5, 5–9.9, 10–14.9, 15–29.9, 30–49.9, ≥50 g/d), body mass index (in kg/m^2; <23, 23–24.9, 25–27.4, 27.5–29.9, ≥30), education (less than high school, high school graduate, more than high school), history of diabetes, history of hypercholesterolemia, history of hypertension, and, for women, postmenopausal estrogen use. Every variable was standardized between cohorts to the extent possible (21). A missing indicator variable was created for each variable. In a third model, quintiles of the potential dietary confounding factors saturated fatty acids, cholesterol, cereal fiber, folic acid, vitamin B-6, and flavonoids, all of which are related to alternative hypotheses on CHD risk, were also included. The potential confounding factors race, aspirin use, iron intake, and n−3 fatty acid intake were not included in the final models because inclusion of them did not notably alter the results. Models including several antioxidant vitamins were also fit. Highly correlated variables (ie, with a mutual correlation coefficient > 0.6) were not included in the same model.

Modification by different risk factors of the association between a specific antioxidant vitamin and CHD risk was studied by including a cross-product interaction term between the antioxidant variable as a continuous variable and the potential modifying factor (ie, age, smoking status, alcohol intake, cholesterolemia, diabetes, hypertension, body mass index, and intakes of polyunsaturated fatty acids, cholesterol, and fiber) as a categorical variable. Interactions between vitamin E, vitamin C, total carotene, and β-carotene intakes were also evaluated.

Heterogeneity among the study-specific RRs was tested by using the Q statistic (24). The RRs of CHD per continuous increment of vitamin E and vitamin C were corrected for bias due to dietary measurement error by using the regression calibration method (25, 26). The cohort-specific logs of RRs were weighted by the inverse of their variance, and an overall pooled estimate of the RR was computed by using a random-effects model (24). The *P* value for the test of trend was based on a Wald test of the pooled estimates. Pooled *P* values for the test of interaction were obtained by using squared Wald statistics by pooling the study-specific interaction coefficients and dividing by the square of the SE of the pooled interaction term, and the resulting statistic was referred to a chi-square distribution with 1 df.

RESULTS

Dietary intake

We found significant inverse associations of age-adjusted intakes of energy-adjusted dietary vitamin E, α-carotene, β-carotene, lutein, and β-cryptoxanthin and of the energy-adjusted carotene score with the incidence of all major CHD events in the pooled population not taking vitamin supplements (**Table 3**). The pooled RRs of CHD between the highest and lowest quintiles of intake of these micronutrients varied from 0.75 to 0.91. Vitamin C intake was not related to CHD incidence (RR = 1.03). With the exception of vitamin E, testing for the presence of heterogeneity among studies did not indicate significant differences; the observed heterogeneity for vitamin E was due to a significant sex difference ($P = 0.001$), with a stronger inverse association among the women than among the men. Accordingly, the pooled RRs are apparently appropriate summaries of the study-specific data. The associations estimated when vitamins C and E were included as continuous variables in the model were consistent with those based on quintiles (data not shown). Correction for bias due to errors in the measurement of vitamins E and C did not substantially alter the main findings (data not shown).

After adjustment for potential nondietary and dietary confounding factors, dietary vitamin E was significantly related to the incidence of all major CHD events among the women (RR = 0.76; 95% CI: 0.65, 0.96; *P* for trend = 0.04; **Figure 1**) but not among the men (RR = 0.91; 95% CI: 0.71, 1.17; *P* for trend = 0.65; **Figure 2**; *P* for sex interaction = 0.10). The carotene score was inversely associated with CHD incidence among the men and the women combined (RR = 0.84; 95% CI: 0.70, 1.00; *P* for trend = 0.04; Table 3). Of the individual carotenoids, lutein was significantly inversely associated with CHD incidence (RR = 0.89; 95% CI: 0.75, 1.04; *P* for trend = 0.03), whereas the strength of association for the other carotenoids was nonsignificant. A nonsignificant positive association, mainly as a consequence of adjustment for dietary factors, was found for vitamin C intake (RR = 1.23; 95% CI: 1.04, 1.45; *P* for trend = 0.07).

The association between dietary vitamin E intake and CHD incidence was not notably altered by further adjustment for vitamin C and total carotene (data not shown). Nor was the association for lutein intake altered systematically by further inclusion of the 4 other carotenoids (RR = 0.91; 95% CI: 0.73, 1.13; *P* for trend = 0.09) or dietary intakes of vitamins E and C (RR = 0.88; 95% CI: 0.74, 1.03; *P* for trend = 0.04) in the model. Likewise, the results of the carotene score did not change to any great extent after inclusion of dietary intakes of vitamins E and C in the model (RR = 0.80; 95% CI: 0.66, 0.97; *P* for trend = 0.02). Both associations were, however, no longer significant after the exclusion of cases occurring during the first 2 y of follow-up. The RRs for lutein and the carotene score were 0.95 (95% CI: 0.79, 1.14; *P* for trend = 0.08) and 0.95 (95% CI: 0.77, 1.17; *P* for trend = 0.49), respectively. The associations for all these dietary antioxidants were similar but weaker for CHD mortality (data not shown).

With few exceptions, no significant interactions of vitamin E, vitamin C, or β-carotene with potential modifying factors (ie, age, smoking, alcohol intake, cholesterolemia, diabetes, hypertension, body mass index, and intakes of polyunsaturated fatty acids, cholesterol, and fiber) were found. Of 56 analyses, a significant interaction was found only between intakes of vitamin E and fiber and between β-carotene intake and alcohol consumption. The RRs of CHD incidence between the highest and lowest quintiles of vitamin E intake were 1.06 (95% CI: 0.86, 1.30) and 0.85 (95% CI: 0.65, 1.10) in the lowest and highest tertiles of fiber intake, respectively.

Supplemental intake

We further analyzed supplemental vitamin E and vitamin C intakes in relation to the incidence of major CHD events by using

TABLE 3
Pooled relative risks of the incidence of major coronary heart disease (CHD) events by quintile of energy-adjusted dietary antioxidant vitamin intake among subjects who did not take vitamin supplements in the pooled analysis of all cohort studies[1]

Nutrient	Quintile					*P* for trend	*P* for heterogeneity
	1 (Lowest)	2	3	4	5 (Highest)		
Vitamin E							
Number at risk	28 009	28 009	27 993	28 045	27 997	—	—
Number of incident CHD cases	627	555	581	554	537	—	—
Median intake (mg)	3.92	4.90	5.59	6.53	8.17	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.87 (0.77, 0.99)	0.91 (0.81, 1.02)	0.83 (0.74, 0.94)	0.77 (0.64, 0.92)	0.01	0.005
Multivariate model 1	1.00	0.91 (0.80, 1.03)	0.98 (0.87, 1.11)	0.90 (0.79, 1.02)	0.85 (0.75, 0.97)	0.11	0.44
Multivariate model 2	1.00	0.89 (0.77, 1.03)	0.98 (0.86, 1.11)	0.89 (0.78, 1.02)	0.84 (0.71, 1.00)	0.17	0.24
α-Carotene							
Number at risk	25 772	25 773	25 774	25 775	25 771	—	—
Number of incident CHD cases	600	524	525	571	495	—	—
Median intake (μg)	100	227	380	591	1508	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.86 (0.76, 0.98)	0.86 (0.76, 0.98)	0.90 (0.79, 1.03)	0.77 (0.68, 0.87)	<0.001	0.48
Multivariate model 1	1.00	0.95 (0.83, 1.08)	0.95 (0.83, 1.08)	1.00 (0.88, 1.14)	0.89 (0.78, 1.01)	0.15	0.88
Multivariate model 2	1.00	0.96 (0.83, 1.10)	0.97 (0.84, 1.12)	1.01 (0.88, 1.17)	0.90 (0.77, 1.04)	0.22	0.87
β-Carotene							
Number at risk	26 137	26 138	26 139	26 138	26 137	—	—
Number of incident CHD cases	580	570	530	586	535	—	—
Median intake (μg)	662	1171	1706	2605	5231	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.96 (0.85, 1.09)	0.87 (0.77, 0.99)	0.92 (0.81, 1.05)	0.84 (0.74, 0.95)	0.01	0.77
Multivariate model 1	1.00	1.00 (0.89, 1.14)	0.92 (0.80, 1.06)	0.96 (0.83, 1.10)	0.91 (0.80, 1.04)	0.16	0.82
Multivariate model 2	1.00	1.01 (0.88, 1.15)	0.93 (0.80, 1.09)	0.98 (0.85, 1.13)	0.92 (0.79, 1.06)	0.29	0.94
Lutein							
Number at risk	22 469	22 471	22 468	22 471	22 469	—	—
Number of incident CHD cases	542	539	500	497	492	—	—
Median intake (μg)	739	1447	2159	3109	6029	—	—
Relative risk							
Age- and energy-adjusted model	1.00	1.02 (0.88, 1.20)	0.93 (0.82, 1.06)	0.92 (0.81, 1.04)	0.91 (0.80, 1.04)	0.05	0.62
Multivariate model 1	1.00	1.09 (0.95, 1.25)	0.98 (0.86, 1.12)	0.94 (0.82, 1.08)	0.94 (0.82, 1.07)	0.05	0.90
Multivariate model 2	1.00	1.07 (0.94, 1.23)	0.97 (0.84, 1.11)	0.92 (0.79, 1.07)	0.89 (0.75, 1.04)	0.03	0.79
Lycopene							
Number at risk	22 439	22 500	22 483	22 462	22 464	—	—
Number of incident CHD cases	530	521	485	511	523	—	—
Median intake (μg)	43	1333	2665	5172	11 015	—	—
Relative risk							
Age- and energy-adjusted model	1.00	1.00 (0.88, 1.14)	0.93 (0.82, 1.06)	0.95 (0.84, 1.09)	0.97 (0.85, 1.11)	0.52	0.72
Multivariate model 1	1.00	1.06 (0.93, 1.21)	0.98 (0.86, 1.12)	0.96 (0.84, 1.10)	0.98 (0.85, 1.12)	0.37	0.85
Multivariate model 2	1.00	1.08 (0.95, 1.24)	1.01 (0.88, 1.16)	0.99 (0.86, 1.13)	0.99 (0.85, 1.14)	0.42	0.88
β-Cryptoxanthin							
Number of risk	21 530	21 530	21 530	21 531	21 530	—	—
Number of incident CHD cases	399	347	347	338	383	—	—
Median intake (μg)	10	39	69	113	212	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.89 (0.76, 1.04)	0.84 (0.73, 0.97)	0.78 (0.68, 0.90)	0.85 (0.74, 0.97)	0.04	0.81
Multivariate model 1	1.00	0.97 (0.83, 1.14)	0.93 (0.81, 1.08)	0.87 (0.75, 1.01)	0.93 (0.80, 1.07)	0.28	0.79
Multivariate model 2	1.00	0.94 (0.79, 1.12)	0.96 (0.81, 1.13)	0.88 (0.74, 1.05)	0.94 (0.79, 1.12)	0.48	0.52
Total carotene							
Number at risk	25 771	25 773	25 776	25 772	25 773	—	—
Number of incident CHD cases	556	547	534	566	512	—	—
Median intake (μg RE)	221	407	579	864	1375	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.98 (0.85, 1.14)	0.90 (0.80, 1.02)	0.93 (0.82, 1.05)	0.83 (0.73, 0.95)	0.007	0.51
Multivariate model 1	1.00	1.03 (0.88, 1.19)	0.94 (0.80, 1.10)	0.98 (0.86, 1.11)	0.91 (0.79, 1.04)	0.15	0.84
Multivariate model 2	1.00	1.03 (0.89, 1.20)	0.96 (0.83, 1.12)	0.99 (0.86, 1.14)	0.91 (0.78, 1.06)	0.24	0.94
Carotene score							
Number at risk	21 528	21 530	21 533	21 532	21 528	—	—

(*Continued*)

TABLE 3 (*Continued*)

Nutrient	Quintile 1 (Lowest)	2	3	4	5 (Highest)	*P* for trend	*P* for heterogeneity
Number of incident CHD cases	458	439	375	446	401	—	—
Median intake	−4.09	−1.23	0.36	1.77	3.75	—	—
Relative risk							
Age- and energy-adjusted model	1.00	0.94 (0.79, 1.11)	0.76 (0.66, 0.88)	0.83 (0.67, 1.04)	0.75 (0.66, 0.87)	<0.001	0.29
Multivariate model 1	1.00	1.01 (0.86, 1.17)	0.85 (0.73, 0.98)	0.94 (0.80, 1.10)	0.85 (0.73, 0.98)	0.02	0.75
Multivariate model 2	1.00	0.99 (0.83, 1.17)	0.85 (0.72, 0.99)	0.93 (0.78, 1.12)	0.84 (0.70, 1.00)	0.04	0.79
Vitamin C							
Number at risk	26 136	26 138	26 140	26 139	26 136	—	—
Number of incident CHD cases	586	571	504	519	621	—	—
Median intake (mg)	45	65	84	107	152	—	—
Relative risk							
Age- and energy-adjusted model	1.00	1.00 (0.85, 1.16)	0.83 (0.71, 0.97)	0.87 (0.77, 0.99)	1.03 (0.91, 1.16)	0.97	0.86
Multivariate model 1	1.00	1.10 (0.97, 1.24)	0.88 (0.77, 1.02)	0.96 (0.84, 1.10)	1.12 (0.98, 1.27)	0.30	0.58
Multivariate model 2	1.00	1.12 (0.97, 1.28)	0.92 (0.79, 1.07)	1.04 (0.89, 1.21)	1.23 (1.04, 1.45)	0.07	0.53

[1] 95% CI in parentheses. Quintiles were derived from the entire cohort. Medians were reported for multivariate model 2. For multivariate model 1, relative risks were adjusted for age, energy intake (kcal/d), smoking status [never, past, current smoker (1–4, 5–14, 15–24, ≥25 cigarettes/d)], BMI (in kg/m^2; <23, 23–24.9, 25–27.4, 27.5–29.9, ≥30), physical activity (levels 1–5), education (less than high school, high school graduate, more than high school), alcohol intake (0, <5, 5–9.9, 10–14.9, 15–29.9, 30–49.9, ≥50 mL/d), history of diabetes, hypercholesterolemia or serum cholesterol (quintile), hypertension or blood pressure, and postmenopausal hormone use among the women. For multivariate model 2, relative risks were adjusted for all of the factors in multivariate model 1 plus quintiles of intake of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. The following cohorts were excluded from some analyses because the models did not converge: women in the Adventist Health Study and the Västerbotten Intervention Program were excluded from the vitamin E analyses, and subjects in the Nurses' Health Study (1986–1996) were excluded from the β-cryptoxanthin analyses. RE, retinol equivalents.

absolute cutoffs for amounts of vitamins ingested. An inverse gradient between intake and CHD incidence was found for both vitamins after adjustment for nondietary confounding factors (**Table 4**). The RRs of CHD incidence among subjects who consumed vitamin E supplements in amounts of <25 mg/d and among subjects who consumed vitamin C supplements at 400–699 mg/d in comparison with nonusers were 0.87 (95% CI: 0.78, 0.97; *P* for trend = 0.02) and 0.72 (95% CI: 0.62, 0.83; *P* for trend < 0.001), respectively. Intakes of vitamin E supplements of ≥25 mg/d or of vitamin C supplements of ≥700 mg/d did not strengthen the association. After further inclusion of dietary intakes of vitamin E, vitamin C, and carotene in the same model, the associations for vitamin C supplement use persisted, whereas the association for vitamin E was no longer significant. With the exception of supplemental vitamin C intakes of ≥700 mg, all associations for CHD mortality were nonsignificant (Table 4).

Overall intake

The pooled RRs of CHD incidence for quintiles of energy-adjusted overall intakes (dietary and supplemental intakes combined) of vitamins E and C, adjusted for nondietary risk factors of CHD, showed inverse associations (**Table 5**, multivariate model 1). The RRs between the highest and lowest quintiles of intake were 0.80 (95% CI: 0.72, 0.91; *P* for trend = 0.008) for vitamin E and 0.76 (95% CI: 0.67, 0.86; *P* for trend < 0.001) for

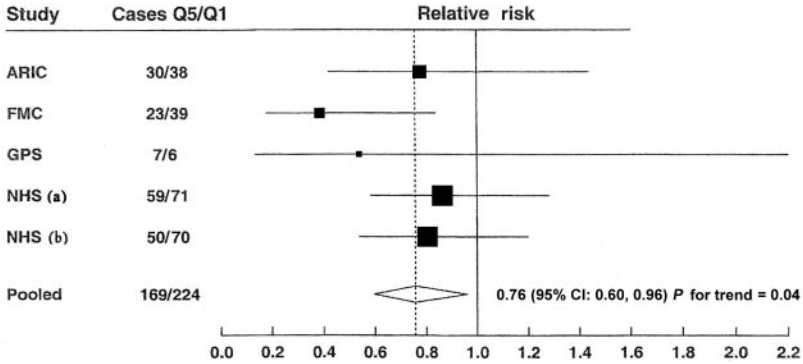

FIGURE 1. Study-specific and pooled multivariate-adjusted relative risks of incident major coronary heart disease events in women in the highest quintile (Q5) of dietary vitamin E intake compared with those in the lowest quintile (Q1). Multivariate model 2 was used. In this model, relative risks were adjusted for age, energy intake, smoking status, body mass index, physical activity, education, alcohol intake, history of diabetes, hypercholesterolemia or serum cholesterol, hypertension or blood pressure, postmenopausal hormone use, and intakes of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. *P* for heterogeneity = 0.75. The black squares and horizontal lines represent the study-specific relative risks and 95% CIs, respectively. The area of the black squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled relative risk and 95% CI. The vertical dashed line represents the pooled relative risk. ARIC, Atherosclerosis Risk in Communities Study; FMC, Finnish Mobile Clinic Health Examination Survey; GPS, Glostrup Population Study; NHS (a), Nurses' Health Study, 1980–1986; NHS (b), Nurses' Health Study, 1986–1996.

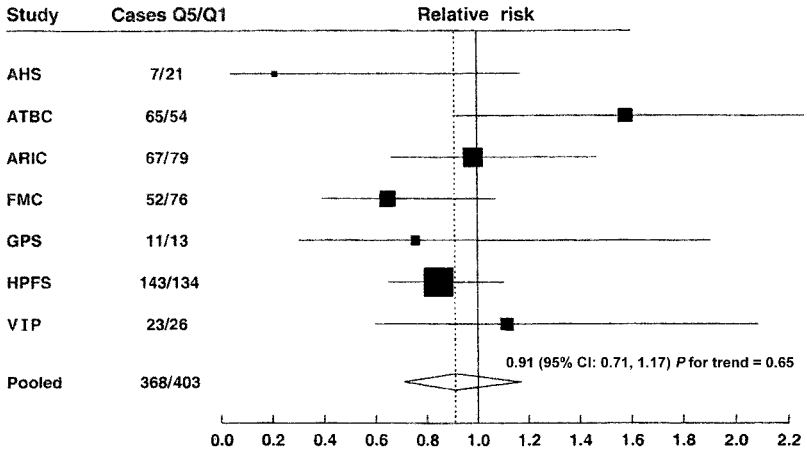

FIGURE 2. Study-specific and pooled multivariate-adjusted relative risks of incident major coronary heart disease events in men in the highest quintile (Q5) of dietary vitamin E intake compared with those in the lowest quintile (Q1). Multivariate model 2 was used. In this model, relative risks were adjusted for age, energy intake, smoking status, body mass index, physical activity, education, alcohol intake, history of diabetes, hypercholesterolemia or serum cholesterol, hypertension or blood pressure, and intakes of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. *P* for heterogeneity = 0.16. The black squares and horizontal lines represent the study-specific relative risks and 95% CIs, respectively. The area of the black squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled relative risk and 95% CI. The vertical dashed line represents the pooled relative risk. AHS, Adventist Health Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the placebo arm); ARIC, Atherosclerosis Risk in Communities Study; FMC, Finnish Mobile Clinic Health Examination Survey; GPS, Glostrup Population Study; HPFS, Health Professionals Follow-Up Study; VIP, Västerbotten Intervention Program.

vitamin C. The strongest risk reduction for vitamin E was observed for cohort-specific median intakes up to 18.7 mg/d (ie, the left end of the distribution), whereas for vitamin C, the strongest risk reduction was observed from a median vitamin C intake of 268 mg/d (ie, the right end of the distribution). Because the use of β-carotene supplements was low, the RR for overall β-carotene (RR = 0.82; 95% CI: 0.72, 0.93; *P* for trend = 0.07) and dietary β-carotene (RR = 0.87; 95% CI: 0.71, 1.05; *P* for trend = 0.18) intakes were similar. The significance of the association persisted for vitamin C but not for vitamin E or β-carotene after further adjustment for dietary factors (Table 5). Exclusion of the CHD events occurring during the first 2 y of follow-up did not notably alter the results. The possible simultaneous effect of intakes of vitamin E, vitamin C, and β-carotene on CHD occurrence was studied by estimating the pairwise interactions between the 3 micronutrients. No significant interactions were found (data not shown). Total intakes of vitamin E, vitamin C, or β-carotene did not predict CHD mortality after adjustment for nondietary confounding factors. Pooled RRs of CHD incidence for total intakes of vitamin E, vitamin C, β-carotene, and total carotene within categories of potential effect-modifying factors showed only a few significant interactions. The RR of CHD between the highest and lowest quintiles of β-carotene intake was 0.72 (95% CI: 0.60, 0.87) among subjects who consumed <30 g alcohol/d, whereas the RR did not differ from unity in nonusers (RR = 0.97; 95% CI: 0.81, 1.16) or subjects who consumed ≥30 g/d (RR = 0.89; 95% CI: 0.65, 1.20). The RR for β-carotene differed significantly from unity in the highest tertile of fiber intake (RR = 0.73; 95% CI: 0.53, 1.00) but not in the 2 lower tertiles. The RR between the highest and lowest quintiles of total vitamin E intake differed significantly from unity in nondiabetic subjects (RR = 0.80; 95% CI: 0.69, 0.92) but not in diabetic subjects (RR = 0.96; 95% CI: 0.61, 1.51).

DISCUSSION

Vitamin C

In cohorts with information on supplemental vitamin C intake, higher overall intake of vitamin C was associated with lower CHD rates. Subjects in the highest quintile of vitamin C intake (median intake of 756 mg/d) had a 24% lower risk than did those in the lowest quintile. The lower risk was independent of nondietary risk factors of CHD, and a dose-response association was observed. Because vitamin C supplement use may be an indicator of a "healthy" lifestyle, we further adjusted for many relevant constituents of foods (eg, dietary fiber and saturated fat). The adjustment had no notable effect on this association. Our finding is inconsistent with the suggestion of no notable additional benefit from vitamin C intakes over 200 mg/d because of tissue saturation (27) but agrees with results from previous cohort studies showing a significantly (28–30) or nonsignificantly (15, 16, 31) lower CHD risk at intakes of >500 mg/d. One cohort study (32) that reported no association had considerably lower vitamin C intakes.

To examine associations between antioxidant vitamins from dietary sources and CHD risk, we excluded subjects who took supplements. We found no reduction of CHD risk at higher dietary intakes of vitamin C. In fact, after adjustment for potentially confounding dietary factors, vitamin C was positively related to CHD incidence. The possibility of a chance finding cannot be excluded. Several previous studies also failed to find an inverse association for vitamin C status (16, 29, 33–39). In contrast, several studies reported a lower risk of CHD at higher vitamin C intakes and concentrations (13, 40–45). A higher serum ascorbic acid concentration indicates dietary patterns featuring a variety of fruit and vegetables. The reported associations may be due in part to incomplete adjustments for other

TABLE 4
Pooled relative risks (RRs) of the incidence of major coronary heart disease (CHD) events and CHD mortality according to the use of vitamin supplements[1]

Supplement	Number at risk	Number of cases	Model 1		Model 2		Model 3	
			RR	95% CI	RR	95% CI	RR	95% CI
Incidence								
Vitamin E								
Amount (mg/d)								
0	111 110	1629	1.00	—	1.00	—	1.00	—
<25	38 579	458	0.87	(0.78, 0.97)	0.93	(0.81, 1.06)	0.92	(0.81, 1.06)
25–99	12 405	200	0.88	(0.76, 1.03)	1.00	(0.83, 1.20)	1.00	(0.83, 1.20)
100–249	7451	88	0.80	(0.64, 1.00)	0.88	(0.70, 1.11)	0.88	(0.70, 1.12)
≥250	20 273	325	0.86	(0.76, 0.97)	0.94	(0.81, 1.09)	0.94	(0.81, 1.09)
P for trend	—	—	0.02	—	0.47	—	0.52	—
P for heterogeneity	—	—	0.86	—	0.83	—	0.83	—
Vitamin C								
Amount (mg/d)								
0	105 764	1767	1.00	—	1.00	—	1.00	—
<100	31 885	437	0.90	(0.80, 1.00)	0.93	(0.80, 1.07)	0.93	(0.80, 1.07)
100–399	24 431	373	0.89	(0.79, 1.00)	0.89	(0.76, 1.05)	0.89	(0.76, 1.05)
400–699	16 298	213	0.72	(0.62, 0.83)	0.74	(0.63, 0.88)	0.75	(0.63, 0.88)
≥700	16 960	246	0.74	(0.62, 0.90)	0.75	(0.60, 0.93)	0.75	(0.60, 0.93)
P for trend	—	—	<0.001	—	0.002	—	<0.001	—
P for heterogeneity	—	—	0.23	—	0.34	—	0.36	—
Mortality								
Vitamin E								
Amount (mg/d)								
0	131 239	740	1.00	—	1.00	—	1.00	—
<25	45 595	242	1.02	(0.87, 1.18)	1.02	(0.84, 1.23)	1.03	(0.85, 1.25)
25–99	13 031	60	0.75	(0.57, 0.99)	0.81	(0.58, 1.13)	0.82	(0.59, 1.14)
100–249	8519	53	1.09	(0.79, 1.51)	1.15	(0.83, 1.58)	1.18	(0.86, 1.69)
≥250	23 339	137	0.94	(0.65, 1.37)	0.95	(0.63, 1.43)	0.98	(0.64, 1.48)
P for trend	—	—	0.81	—	0.94	—	1.00	—
P for heterogeneity	—	—	0.03	—	0.05	—	0.04	—
Vitamin C								
Amount (mg/d)								
0	123 224	664	1.00	—	1.00	—	1.00	—
<100	36 920	202	0.99	(0.84, 1.16)	0.97	(0.80, 1.18)	0.98	(0.81, 1.20)
100–399	29 282	157	0.85	(0.60, 1.19)	0.82	(0.57, 1.18)	0.84	(0.58, 1.21)
400–699	19 232	118	0.96	(0.72, 1.28)	0.94	(0.68, 1.32)	0.96	(0.70, 1.32)
≥700	18 585	91	0.77	(0.61, 0.97)	0.75	(0.58, 0.98)	0.76	(0.58, 0.99)
P for trend	—	—	0.11	—	0.16	—	0.17	—
P for heterogeneity	—	—	0.22	—	0.27	—	0.26	—

[1] For multivariate model 1, RRs were adjusted for age, energy intake (kcal/d), smoking status [never, past, current smoker (1–4, 5–14, 15–24, ≥25 cigarettes/d)], BMI (in kg/m^2; <23, 23–24.9, 25–27.4, 27.5–29.9, ≥30), physical activity (levels 1–5), education (less than high school, high school graduate, more than high school), alcohol intake (0, <5, 5–9.9, 10–14.9, 15–29.9, 30–49.9, ≥50 mL/d), history of diabetes, hypercholesterolemia or serum cholesterol (quintiles), hypertension or blood pressure, and postmenopausal hormone use among the women. For multivariate model 2, RRs, were adjusted for all of the factors in multivariate model 1 plus intakes of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. For multivariate model 3, RRs were adjusted for all of the factors in multivariate model 2 plus dietary intakes of total carotene, vitamin C, and vitamin E. Data for vitamin E were from the Health Professionals Follow-Up Study (HPFS); the Iowa Women's Health Study (IWHS); the Nurses' Health Study, 1980–1986 [NHS (a)], and the Nurses' Health Study, 1986–1996 [NHS (b)]. Data for vitamin C were from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the placebo arm), the HPFS, the IWHS, the NHS (a), and the NHS (b).

substances in plant foods. In addition, low blood vitamin C concentrations reflect smoking and other physiologic stressors.

Vitamin E

We found a lower CHD risk at higher intakes of dietary vitamin E when the results were adjusted for age and energy intake. The relation persisted for women but not for men after further adjustment for potential confounders. Some (13, 16), but not all (17), previous cohort studies in women found a lower risk at higher dietary vitamin E intakes. With a few exceptions (13, 39), studies in men alone or in men and women combined failed to find an association for dietary vitamin E (15, 17, 37, 44) or serum α-tocopherol concentration (5, 46–48). The suggestion of a lower risk in women but not in men is in line with the observation of higher lipid peroxidation in women than in men (49) and the fact that women may have fewer competing risk factors than do men.

We did not find any benefits of higher supplemental intakes of vitamin E. Cohort studies on the association between dietary or supplemental intake combined or supplemental intake of vitamin E alone have produced contradictory results. Two studies

TABLE 5
Pooled relative risks of the incidence of major coronary heart disease (CHD) events and CHD mortality for quintiles of energy-adjusted overall (dietary and supplemental combined) antioxidant vitamin intake in the pooled analysis of the cohort studies reporting supplemental intakes[1]

Nutrient	Quintile of overall antioxidant vitamin intake					*P* for trend	*P* for heterogeneity
	1 (Lowest)	2	3	4	5 (Highest)		
Incidence							
Vitamin E							
Number at risk	39 063	39 076	39 062	39 071	39 066	—	—
Number of incident CHD cases	658	619	622	568	569	—	—
Median intake (mg)	5.10	6.74	8.45	18.7	279	—	—
Relative risk							
Multivariate model 1	1.00	0.94 (0.84, 1.06)	0.92 (0.81, 1.05)	0.86 (0.73, 1.01)	0.80 (0.72, 0.91)	0.008	0.77
Multivariate model 2	1.00	0.97 (0.86, 1.09)	0.96 (0.85, 1.09)	0.95 (0.76, 1.21)	0.90 (0.78, 1.05)	0.44	0.85
Multivariate model 3	1.00	0.96 (0.86, 1.08)	0.96 (0.85, 1.09)	0.95 (0.76, 1.19)	0.95 (0.81, 1.12)	0.85	0.84
β-Carotene							
Number at risk	22 425	22 422	22 426	22 422	22 423	—	—
Number of incident CHD cases	519	483	499	569	502	—	—
Median intake (μg)	1918	2918	3791	4925	7323	—	—
Relative risk							
Multivariate model 1	1.00	0.90 (0.79, 1.03)	0.91 (0.78, 1.06)	1.01 (0.84, 1.21)	0.82 (0.72, 0.93)	0.07	0.25
Multivariate model 2	1.00	0.92 (0.81, 1.05)	0.94 (0.79, 1.12)	1.07 (0.85, 1.34)	0.88 (0.73, 1.06)	0.38	0.20
Multivariate model 3	1.00	0.92 (0.81, 1.05)	0.94 (0.76, 1.15)	1.06 (0.83, 1.36)	0.88 (0.71, 1.10)	0.44	0.12
Total carotene							
Number at risk	21 320	21 320	21 321	21 319	21 320	—	—
Number of incident CHD cases	445	434	447	486	424	—	—
Median intake (μg RE)	369	578	764	1015	1567	—	—
Relative risk							
Multivariate model 1	1.00	0.95 (0.83, 1.08)	0.94 (0.82, 1.08)	0.99 (0.87, 1.13)	0.83 (0.71, 0.96)	0.17	0.06
Multivariate model 2	1.00	0.96 (0.84, 1.10)	0.98 (0.85, 1.12)	1.05 (0.91, 1.21)	0.88 (0.70, 1.11)	0.43	0.03
Multivariate model 3	1.00	0.96 (0.84, 1.11)	0.98 (0.85, 1.13)	1.04 (0.87, 1.25)	0.88 (0.68, 1.16)	0.50	0.02
Vitamin C							
Number at risk	39 066	39 073	39 061	39 072	39 066	—	—
Number of incident CHD cases	641	624	645	605	521	—	—
Median intake (mg)	81	128	177	268	756	—	—
Relative risk							
Multivariate model 1	1.00	0.96 (0.86, 1.08)	0.95 (0.85, 1.06)	0.89 (0.79, 1.00)	0.76 (0.67, 0.86)	<0.001	0.68
Multivariate model 2	1.00	1.02 (0.90, 1.15)	1.04 (0.92, 1.19)	1.01 (0.86, 1.18)	0.87 (0.74, 1.01)	0.004	0.91
Multivariate model 3	1.00	1.01 (0.89, 1.14)	1.05 (0.92, 1.20)	1.03 (0.86, 1.23)	0.88 (0.75, 1.03)	0.007	0.90
Mortality							
Vitamin E							
Number at risk	45 044	45 458	45 443	45 451	45 447	—	—
Number of CHD deaths	304	278	240	270	272	—	—
Median intake (mg)	4.71	6.23	8.27	16.0	208	—	—
Relative risk							
Multivariate model 1	1.00	0.94 (0.79, 1.11)	0.80 (0.66, 0.95)	0.90 (0.76, 1.07)	0.88 (0.71, 1.10)	0.65	0.10
Multivariate model 2	1.00	0.97 (0.82, 1.16)	0.84 (0.69, 1.01)	0.99 (0.79, 1.23)	0.97 (0.71, 1.33)	0.79	0.04
Multivariate model 3	1.00	0.97 (0.81, 1.16)	0.84 (0.70, 1.02)	0.98 (0.78, 1.23)	1.01 (0.70, 1.45)	0.89	0.03
β-Carotene							
Number at risk	22 425	22 422	22 426	22 422	22 423	—	—
Number of CHD deaths	190	172	162	185	173	—	—
Median intake (μg)	1918	2918	3791	4925	7323	—	—
Relative risk							
Multivariate model 1	1.00	0.88 (0.71, 1.09)	0.82 (0.57, 1.16)	0.89 (0.70, 1.12)	0.78 (0.62, 0.97)	0.06	0.82
Multivariate model 2	1.00	0.90 (0.72, 1.13)	0.84 (0.58, 1.23)	0.92 (0.72, 1.17)	0.84 (0.66, 1.07)	0.27	0.79
Multivariate model 3	1.00	0.89 (0.71, 1.11)	0.82 (0.55, 1.24)	0.90 (0.71, 1.14)	0.84 (0.65, 1.07)	0.34	0.68
Total carotene							
Number at risk	27 701	27 701	27 702	27 700	27 701	—	—
Number of CHD deaths	236	228	212	221	215	—	—
Median intake (μg RE)	369	578	764	1015	1567	—	—
Relative risk							
Multivariate model 1	1.00	0.97 (0.80, 1.16)	0.89 (0.72, 1.09)	0.90 (0.75, 1.09)	0.87 (0.72, 1.06)	0.17	0.48
Multivariate model 2	1.00	1.01 (0.83, 1.21)	0.93 (0.73, 1.19)	0.97 (0.79, 1.18)	0.94 (0.74, 1.20)	0.68	0.32
Multivariate model 3	1.00	1.01 (0.83, 1.22)	0.94 (0.72, 1.22)	0.98 (0.80, 1.20)	0.96 (0.73, 1.25)	0.81	0.29
Vitamin C							
Number at risk	45 447	45 454	45 442	45 453	45 447	—	—
Number of CHD deaths	269	288	290	267	250	—	—
Median intake (mg)	84	132	179	265	701	—	—

(*Continued*)

TABLE 5 (*Continued*)

Nutrient	Quintile of overall antioxidant vitamin intake					*P* for trend	*P* for heterogeneity
	1 (Lowest)	2	3	4	5 (Highest)		
Relative risk							
Multivariate model 1	1.00	1.11 (0.92, 1.33)	1.06 (0.87, 1.29)	0.96 (0.81, 1.15)	0.94 (0.77, 1.14)	0.38	0.17
Multivariate model 2	1.00	1.19 (0.99, 1.44)	1.17 (0.94, 1.44)	1.06 (0.86, 1.32)	1.05 (0.85, 1.31)	0.58	0.25
Multivariate model 3	1.00	1.20 (0.99, 1.44)	1.18 (0.95, 1.47)	1.07 (0.86, 1.33)	1.08 (0.81, 1.44)	0.61	0.24

[1] 95% CIs in parentheses. Data for vitamins E and C were from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the placebo arm; ATBC); the Health Professionals Follow-Up Study (HPFS); the Iowa Women's Health Study (IWHS); the Nurses' Health Study, 1980–1986 [NHS (a)]; and the Nurses' Health Study, 1986–1996 [NHS (b)]. Data for β-carotene were from the ATBC, the HPFS, and the NHS (b). Data for total carotene were from the HPFS, the IWHS, and the NHS (b). For multivariate model 1, relative risks were adjusted for age, energy intake (kcal/d), smoking status [never, past, current smoker (1–4, 5–14, 15–24, ≥25 cigarettes/d)], BMI (in kg/m^2; <23, 23–24.9, 25–27.4, 27.5–29.9, ≥30), physical activity (levels 1–5), education (less than high school, high school graduate, more than high school), alcohol intake (0, <5, 5–9.9, 10–14.9, 15–29.9, 30–49.9, ≥50 mL/d), history of diabetes, hypercholesterolemia or serum cholesterol (quintiles), hypertension or blood pressure, and postmenopausal hormone use among the women. For multivariate model 2, relative risks were adjusted for all of the factors in multivariate model 1 plus intakes of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. For multivariate model 3, relative risks were adjusted for all of the factors in multivariate model 2 plus additional factors as follows: vitamin E was adjusted for vitamin C and total carotene, β-carotene and total carotene were adjusted for vitamins E and C, and vitamin C was adjusted for vitamin E and total carotene. RE, retinol equivalents.

included in the pooling project (15, 17) reported an inverse association for vitamin E, whereas 3 other studies (16, 29, 31) found no association. One intervention trial on vitamin E supplementation in a relatively low amount (50 mg/d) reported no protection against fatal CHD (5), and another trial that used higher amounts (300 mg/d) found that the supplementation did not provide any significant protection before it was prematurely stopped (50). Because vitamin C can help to regenerate oxidized vitamin E, an interaction between vitamins E and C was expected but not observed in our data.

Carotenoids

We found a lower risk of major CHD events at higher total intakes of β-carotene and at higher dietary intakes of several carotenoids after adjustment for age and energy intake. The relations were considerably reduced after further adjustment for potential nondietary confounding factors. Because a high intake of carotenoids is essentially the result of a diet rich in fruit and vegetables and possibly low in meat products, we also adjusted for many constituents of these foods. After these adjustments, the inverse associations with all individual carotenoids except lutein disappeared. Our lutein finding was in accordance with previous epidemiologic, in vitro, and animal model findings (51). A carotene score combining all carotenoids also had a significant inverse association with CHD risk. Because the association for lutein disappeared after further exclusion of cases occurring during the first 2 y of follow-up, our results can be interpreted as suggesting that none of the carotenoids considered, when consumed in typical dietary amounts, predicts a reduced incidence of CHD.

Results from the few cohort studies available on intakes or serum concentrations of total carotene or β-carotene and CHD are contradictory: some of the studies (5, 7, 15, 37, 44, 52–54) found an inverse association, whereas others found no inverse association (13, 16, 29, 39, 41, 48, 55, 56). At least some of the studies, especially the serologic ones that suggested an inverse association, were apparently not adjusted for all potential confounding factors, including details of smoking behavior. Therefore, inverse associations may, at least in part, have been due to residual confounding.

Intervention studies using supplemental β-carotene in the prevention of cardiovascular diseases have found no benefit (5–9, 57, 58). Because supplements in the intervention studies provided much higher β-carotene intakes (20–50 mg/d) than reported in the cohort studies, the results from cohort and intervention studies are not comparable.

Methodologic aspects

To obtain a more comprehensive picture of the association between intakes of the antioxidant vitamins considered and CHD occurrence, we used 2 different approaches. First, we estimated the RR of CHD between quintiles of micronutrient intake. The advantage of this lies in the lack of assumption on the pattern of the relation. The shortcoming that the differences in absolute micronutrient intakes between the studies were ignored was reduced by conducting separate analyses for dietary intake and total intake. Second, we estimated the strength of association for a specific increment of the antioxidant vitamin considered; in this approach, the absolute intakes are considered, but a linear relation with the outcome is assumed. Because several of the associations appeared to be present only at higher intakes of the antioxidant vitamin and thus the linearity assumption on a logistic scale was violated, the quintile approach was favorable. Nonetheless, the results from the 2 approaches did not differ materially.

An advantage of the pooling project is that publication bias is reduced because of the inclusion of studies from which results on this topic have never been published. Other advantages include a higher power to detect associations, a more satisfactory control of confounding, a better ability to investigate potential effect modification, and an ability to differentiate the associations for dietary and supplemental intakes. However, there remain some methodologic factors that may have masked associations or caused artificial associations. First, we cannot exclude the possibility that other carotenoids or single vitamin E compounds or some combination of them may have afforded protection. Second, possible changes in dietary habits during the 6–10-y follow-up period in some cohorts may have biased the observed associations between antioxidant intake and CHD. However, inclusion of only the first 5 y of follow-up did not notably alter the results. Third, lack of or limited information on particular dietary (eg, iron) and lifestyle factors may have resulted in residual confounding or interactions. Fourth, the adjustment for certain

nutrients may have caused overadjustment. Our results for dietary vitamin C are consistent with this hypothesis. Fifth, methodologic issues related to the dietary questionnaire and to the estimation of nutrient intakes may have affected the results, most likely biasing estimates toward the null hypothesis. Sixth, in addition to antioxidant intakes, the oxidative balance between prooxidants and antioxidants may affect antioxidant efficiency (49, 59). Because polyunsaturated fatty acids are sensitive to oxidation and may increase the formation of free radicals, the intake of polyunsaturated fatty acids may modify the associations between antioxidant vitamins and CHD risk (60). In addition, oxidative stress is increased in smokers and diabetic persons (49). Therefore, we examined whether smoking, diabetes, and polyunsaturated fat intake modified the associations observed but found little evidence for interaction. Furthermore, because of metabolic interrelations between antioxidants, synergistic inhibition of LDL oxidation by several antioxidants is possible. However, we found no notable interaction between the intakes of vitamin E, vitamin C, and carotene (β-carotene) or between different carotenoids. Our findings in this regard disagree with those of one cohort study (32) but agree with those of one intervention (57).

Conclusions

In conclusion, the results of the present study suggest that the use of vitamin C supplements may reduce CHD incidence in men and women. The results weakly support the hypothesis that a higher dietary intake of vitamin E or lutein reduces the risk of CHD. Because the effects of high antioxidant vitamin intake are not fully understood, the present study does not provide adequate support for recommending high doses of vitamin C supplements.

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PK participated in the analysis and interpretation of data and in the drafting of the manuscript and supervised the conducting of the study. JR conducted all of the statistical analyses and was closely involved in the interpretation of the results and in the editing of the manuscript. MAP participated in the study concept and design; the acquisition, analysis, and interpretation of data; and the drafting of the manuscript. He also supervised the conducting of the study. DS participated in the study concept and design, the analysis and interpretation of data, and the critical revision of the manuscript for important intellectual content and provided statistical expertise. EBR participated in the analysis and interpretation of data and in the drafting of the manuscript. WCW participated in the study concept and design, the analysis and interpretation of data, and the critical revision of the manuscript for important intellectual content. He also provided statistical expertise; obtained funding; provided administrative, technical, and material support; and supervised the conducting of the study. AA participated in the study concept and design; the acquisition, analysis, and interpretation of data; and the critical revision of the manuscript for important intellectual content. He also provided statistical expertise, obtained funding, and supervised the conducting of the study. EJO was instrumental as the main data manager and analyst. The remaining investigators (KA, GEF, UG, BLM, GH, SL, PP, JS, and JV) represent the off-site investigators of the individual cohort studies. All of these investigators contributed in important ways, through various means of written, verbal, and face-to-face communication to the assimilation, analysis, and interpretation of the data and to the development and writing of the manuscript. None of the authors had any conflicts of interest.

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