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Dietary antioxidants and long-term risk of dementia

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Abstract

OBJECTIVE—To study consumption of major dietary antioxidants in relation to long-term risk of dementia.

DESIGN AND SETTING—The Rotterdam Study, a population-based, prospective cohort study in the Netherlands.

PARTICIPANTS—A total of 5,395 participants, aged 55+ years, who were free of dementia and provided dietary information at study baseline.

MAIN OUTCOME MEASURES—Incidence of dementia and Alzheimer's disease (AD), based on internationally accepted criteria, in relation to dietary intake of vitamin E, vitamin C, beta carotene, and flavonoids.

RESULTS—During an average follow-up period of 9.6 years, dementia developed in 465 participants, of whom 365 were diagnosed with AD. In multivariate models adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, body-mass index (BMI), and supplement use, higher intake of vitamin E at baseline was associated with a lower long-term risk of dementia (p-trend=0.02). Compared to participants in the lowest tertile of vitamin E intake, those in the highest tertile were 25% less likely to develop dementia (HR, 0.75; 95% CI, 0.59–0.95 with adjustment for potential confounders). Dietary intakes of vitamin C, beta carotene, and flavonoids were not associated with dementia risk (after multivariate adjustment, p-trend=1.0 for both vitamin C and beta carotene and p-trend=0.6 for flavonoids). Results were similar when AD risk was specifically examined.

CONCLUSION—Higher intake of foods rich in vitamin E may modestly reduce long-term risk of dementia and AD.

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Author contributions

Dr. Devore takes responsibility for integrity of the data and accuracy of the data analysis.

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INTRODUCTION

Oxidative stress is thought to play an important role in the pathogenesis of Alzheimer's disease (AD)[1, 2] – a disease that likely begins years, if not decades, prior to clinical onset of dementia. In line with this hypothesis, experimental data support the notion that antioxidants protect against neurodegeneration[3–8]. Although clinical trials have shown no benefit of antioxidant supplements for AD[9, 10], the wider variety of antioxidants in food sources is not well studied in relation to dementia risk; a small number of studies have yielded inconsistent results with varying lengths of follow-up[11–14]. In a previous report from the Rotterdam Study, we found that higher dietary intakes of vitamins E and C were related to a lower risk of dementia and AD over six years of follow-up. Still, substantial evidence indicates that earlier exposures are important for predicting dementia risk in later life[15], and specific evidence indicates that antioxidants may influence early stages of dementia development[16–18]. Therefore, we evaluated the associations of dietary vitamin E, vitamin C, beta carotene, and flavonoids with long-term risk of dementia based on ten years of follow-up – taking advantage of both longer follow-up and substantially more dementia cases than were available in our previous study.

METHODS

The Rotterdam Study is a population-based cohort study in Ommoord (a district of Rotterdam, Netherlands) designed to investigate determinants of disease in the elderly. In 1990, 7,983 residents of Omoord, aged 55 years and older, agreed to participate in the study (78% response rate)[19]. From 1990–1993, participants underwent a baseline examination consisting of an extensive home interview and two clinical examinations to obtain health and lifestyle information. Subsequently, follow-up examinations were performed in 1993–1994, 1997–1999, and 2002–2004. The cohort is also continuously monitored for mortality and major morbidity. The medical ethics committee of the Erasmus University Rotterdam approved this study.

Population for analysis

Of the 7,983 individuals who agreed to participate, 7,046 (88%) underwent cognitive screening and were free of dementia at baseline. For dietary assessment, 125 participants were excluded due to questionable cognitive status (defined as a score of < 80 on the Cambridge Examination of Mental Disorders in the Elderly [CAMDEX]), which might lead to unreliable reporting. An additional 477 individuals were excluded due to nursing home residence because their institutional diet may not have reflected previous eating habits. Thus, 6,444 participants at risk of incident dementia were eligible for dietary assessment. However, we did not include dietary information from 1,049 of these individuals (16%): 212 (3%) participants had inconsistencies in their responses, 192 (3%) were not present during the exam when dietary interviews were conducted, and 645 (10%) were without a dietician at their exam. Hence, we analyzed 5,395 participants who were free of dementia, non-institutionalized, and provided dietary information at baseline.

Dementia assessment

The diagnosis of dementia was made following a three-step protocol at baseline and follow-up examinations[20]. First, a combined Mini-Mental State Examination (MMSE)[21] and Geriatric Mental State schedule (GMS)[22] organic level was used to screen all subjects. Second, those with MMSE scores <26 or GMS scores >0 underwent the CAMDEX[23]. Finally, if necessary, subjects were evaluated by a neurologist and neuropsychologist; when available, neuroimaging data were used. In addition, the total cohort was continuously monitored for memory problems and dementia via computerized linkage of the study

database to digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. For this study, dementia was diagnosed by a panel consisting of a neurologist, neuropsychologist, and research physician using all existing information. Diagnoses were made in accordance with internationally accepted criteria for dementia (DSM-III-R)[24], AD (NINCDS-ADRDA)[25], and vascular dementia (NINDS-AIREN)[26]. Follow-up for incident dementia was complete through January 1, 2005.

Dietary assessment

Diet was measured at baseline examination using a two-step protocol designed to maximize the accuracy of dietary reporting in an older population[27]. During the home interview, participants used a meal-based checklist to indicate which foods they had consumed at least twice per month during the previous year. Using this checklist to prompt recall, a validated semi-quantitative food-frequency questionnaire (SFFQ) was administered to each participant by a trained dietician at the time of clinical examination[27]. The SFFQ was designed to measure 'typical' diet by asking questions about frequency and amount of food consumption over the past year; it contained 170 food items in 13 food groups. Frequency of food intake was recorded in times per day, week or month, and serving sizes were specified in natural units, household measures, or grams. SFFQ data were then converted to energy and nutrient intakes using the Dutch Food Composition Table (2006)[28].

In this cohort, major contributors to between-person variation were: for vitamin E, margarine (44%), sunflower oil (19%), butter (4%), soybean oil (3%), cooking fat (3%), and mayonnaise (2%); for vitamin C, oranges (45%), kiwi (13%), grapefruit juice (11%), grapefruit (9%), cauliflower (5%), red bell peppers (2%), and red cabbage (2%); for beta carotene, carrots (73%), spinach (3%), vegetable soup (2%), endive (2%), and tomato (2%); and for flavonoids, tea (45%), onions (20%), apples (9%), endive (2%), and kale (2%).

Covariates

At the baseline home interview, participants provided information on their highest level of education, smoking habits, and medications (including supplements). Baseline height and weight were measured at the study center, and total energy intake and alcohol consumption were assessed by SFFQ. APOE genotype was assessed on coded DNA samples using polymerase chain reaction without knowledge of dementia diagnosis[29].

Statistical analysis

We used age- and multivariate-adjusted Cox proportional hazard models to evaluate the relations of antioxidants with risk of dementia and AD, with censoring at time of dementia or AD, death, or loss to follow-up. Dietary intakes of antioxidants (vitamin E, vitamin C, beta carotene, and flavonoids) were derived from food sources only (not supplements), and evaluated across sex-specific tertiles based on energy-adjusted values[30]. To evaluate possible confounding, we considered adjustment for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking, body mass index (BMI), and supplement use (including multivitamins and single supplements for vitamin E, vitamin C, beta carotene, flavonoids, or omega-3s). Since only 19 participants reported use of omega-3 supplements, the covariate "supplement use" essentially reflects use of antioxidant supplements. Level of education was categorized into three groups: low (primary education only), intermediate (lower vocational or general education), and high (intermediate or higher vocational or general education, college or university). Smoking habits were categorized into current, former, and never smoking, and alcohol intake was divided into the following five categories: none, <1 drink per week, ≥1 drink per week but <1 drink per day, 1–3 drinks per day, and 4+ drinks per day. BMI was analyzed as a continuous variable, supplement use was

dichotomized (yes/no), and APOE ε4 genotype was dichotomized based on the presence of at least one ε4 allele.

We further evaluated an interaction term of vitamins E and C (assigning median values for tertiles), and interaction terms for each antioxidant (using tertile medians) with education (low, intermediate, high), smoking status (current, former, never), and APOE ε4 carrier status (yes/no). To assess whether relations of antioxidant intake with dementia risk differed over shorter versus longer follow-up, we evaluated associations over follow-up years 0–8 and 9–14, which provided an approximately equal number of cases per period and thus maximized power. For these interactions, we multiplied each exposure variable (using tertile medians) by a time period indicator (years 0–8 versus 9–14).

All analyses were repeated after excluding participants who used supplements at baseline, and all data analysis was performed using SPSS version 13.0 software (SPSS Inc, Chicago, Ill).

RESULTS

When we examined a variety of health and lifestyle characteristics, we found few meaningful differences across tertiles of dietary vitamin E, vitamin C, beta carotene, and flavonoids (Table 1); however, for all four antioxidants, participants in higher tertiles of consumption were less likely to be current smokers. In addition, participants with greater flavonoid intake tended to be slightly older, and those with lower vitamin E consumption and greater intakes of vitamin C and beta carotene, on average, had slightly higher BMI.

Higher vitamin E intake was related to a lower long-term risk of dementia in both age- and multivariate-adjusted models (p-trend=0.02 for both) (Table 2). For participants in the top tertile of dietary vitamin E, we found a 24% lower risk of dementia compared to those in the bottom tertile in age-adjusted models (HR, 0.76; 95% CI, 0.60–0.96); this estimate was very similar in models adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, BMI and supplement use (HR, 0.75; 95% CI, 0.59–0.95). However, participants in the middle tertile of vitamin E intake did not have a lower risk of dementia compared to those in the bottom tertile, either in age- or multivariate-adjusted models (e.g. HR, 1.20; 95% CI, 0.97–1.49, after multivariable adjustment). For vitamin C, beta carotene, and flavonoids, we found no associations between intake level and long-term risk of dementia (p-trend=1.0 for both vitamin C and beta carotene, and p-trend=0.6 for flavonoids in multivariate models). When we excluded 644 participants who used supplements at baseline, our results for all four antioxidants remained unchanged in both age- and multivariate-adjusted models (e.g. HR=0.75; 95% CI, 0.58–0.97; p-trend=0.03, comparing extreme tertiles of vitamin E, and adjusting for potential confounders).

When we examined AD specifically, we also found a lower risk among those with greater consumption of vitamin E, which was very similar in age- and multivariate-adjusted models (e.g. p-trend=0.03 after multivariate adjustment) (Table 3). The estimated long-term risk reduction was 26% in the top tertile of vitamin E intake compared to the bottom (HR, 0.74; 95% CI, 0.56–0.97 in multivariable models), although risk was not lower when the middle versus bottom tertiles were compared (HR, 1.12; 95% CI, 0.88–1.44). Vitamin C, beta carotene, and flavonoid intakes were unrelated to AD risk (p-trend=0.8 for both vitamin C and beta carotene, and p-trend=0.5 for flavonoids in multivariable models). Again, excluding supplement users did not change the observed relations, as higher vitamin E intake remained associated with lower long-term risk of AD (p-trend=0.05 in multivariate-adjusted models), and vitamin C, beta carotene, and flavonoid intakes were not associated

with AD risk (p-trend=0.5 for both vitamin C and beta carotene, and p-trend=0.3 for flavonoids).

Finally, the effect of vitamin E on dementia risk was not modified by vitamin C intake (p-value for interaction=0.5), and antioxidant effects were not modified by education, smoking, or APOE ε4 status. Although we found a borderline significant interaction for vitamin C and APOE ε4 (p-value for interaction=0.05), this should not be over-interpreted. When we divided follow-up time into shorter (years 0–8) versus longer (years 9–14) periods (data not shown), we found no interaction between vitamin E, vitamin C, beta carotene, or flavonoids with time in relation to dementia risk (e.g. for vitamin E, p-value for interaction=0.8). All results were similar when AD risk was considered separately.

COMMENT

We found that higher dietary intake of vitamin E, but not vitamin C, beta carotene, or flavonoids, was associated with a decreased long-term risk of dementia over an average of ten years in the Rotterdam Study. These findings extend an earlier analysis in this cohort, which indicated that higher consumption of vitamins E and C might be related to lower AD risk. Despite their differences, these studies provide consistent evidence for a modest benefit of dietary vitamin E on dementia risk over the shorter and longer term.

The brain is a site of high metabolic activity, which makes it vulnerable to oxidative damage, and slow accumulation of such damage over a lifetime may contribute to the development of dementia. In particular, when beta-amyloid (a hallmark AD pathology) accumulates in the brain, an inflammatory response is likely evoked that produces nitric oxide radicals and downstream neurodegenerative effects[1]. Vitamin E is a powerful, fat-soluble antioxidant that may help to inhibit dementia pathogenesis. In experimental studies, vitamin E has been shown to attenuate toxic effects of beta-amyloid and improve cognitive performance in rodents[3–8]. Although optimal timing for antioxidant benefits is unclear, existing evidence indicates that antioxidants affect early stages of dementia[16–18]. Still, the on-going accumulation of beta-amyloid in AD may imply a sustained contribution of oxidative damage, and thus continued benefits of vitamin E intake throughout pathogenesis.

In contrast to our previous study, the current findings do not include an inverse association between vitamin C and dementia risk. However, this result was modest in our shorter-term analysis (HR, 0.66; 95% CI, 0.44–1.00)[14], and therefore chance is the most likely explanation. Alternatively, vitamin C intake could be important exclusively at later stages of dementia development, but this is less likely because previous studies suggest that antioxidants influence early stages of dementia pathogenesis[16–18]. Another possibility is that reverse causation biased our initial finding (i.e. the presence of sub-clinical dementia in cases diagnosed shortly after baseline could have resulted in decreasing intake of vitamin C); yet, if this type of bias occurred, we would expect to observe similar effects for beta carotene, as both antioxidants are derived from “healthy” fruits and vegetables. Furthermore, we did not replicate our previous findings of interactions between vitamins E and C, or between any of the antioxidants and smoking; these too were likely due to chance. On balance, an important perspective may be the contrast between these differences and consistent vitamin E findings over time – evidence that supports a causal link between vitamin E intake and dementia risk.

Previous observational studies of dietary antioxidants and dementia risk have yielded inconsistent results based on relatively short or very long follow-up periods. In the Chicago Health and Aging Project (CHAP), greater intake of vitamin E, but not vitamin C or beta carotene, was associated with substantial reductions in AD risk over a mean follow-up of

two years (OR, 0.30; 95% CI, 0.10–0.92, adjusted for potential confounders)[11]. The PAQUID cohort found that higher intake of flavonoids (and not vitamin C) was related to decreased risk of dementia over a five-year span. In contrast, the Washington Heights-Inwood Columbia Aging Project (WHICAP) found no relations for vitamin E, vitamin C, or carotenes with AD over an average follow-up of four years, although confidence intervals were wide and vitamin E intake appeared to be very low[13]. In a much longer study, the Honolulu Asia Aging Study (HAAS) found no associations for vitamin E, vitamin C, beta carotene, or flavonoids with dementia risk over a 30-year period (e.g. for vitamin E: HR, 1.33; 95% CI, 0.90–1.96, in multivariate-adjusted models comparing extreme quartiles)[31]; however, 30% of participants were lost to follow-up, which could have contributed to these null findings. Furthermore, the ascertainment of dietary antioxidants thirty years prior to diagnosis of incident dementia may be too remote to detect associations. Overall, more research is clearly needed to assess points at which antioxidant intake might be most relevant to dementia risk.

In our study, dietary intakes of antioxidants were comparable to, if not greater than, those of existing studies. For vitamin E, our participants had similar intake (mean=13.9 mg/day) compared to those in HAAS (mean=13.8 mg/day), but considerably higher intake than CHAP (median=5.7 mg/day) or WHICAP (mean=4.0 mg/day). Vitamin C and beta carotene levels were relatively consistent across cohorts (the exception was low beta carotene levels in HAAS), and flavonoid intake was considerably higher in our cohort (mean=28.5 mg/day) compared to PAQUID (mean=14.1 mg/day) and HAAS (mean=4.1 mg/day). Thus, dietary antioxidant levels appear to be sufficient compared to previously-studied populations, such that low dietary exposure is unlikely to explain our null findings for three out of four antioxidants.

Several meaningful differences distinguish the implications of our study from those of previous clinical trials involving vitamin E and dementia. First, we provide population-based estimates of incident dementia risk over a decade, as opposed to trials that examined short-term risk of dementia progression in clinic-based populations. Second, our study focused on food-based antioxidants in the context of a Western-type diet, with intakes several-fold lower than supplementation levels in trials. Finally, we studied a variety of antioxidants and total vitamin E (including all 8 forms), whereas trials have evaluated single-form, alpha-tocopherol supplements. Thus, our study provides additional information, beyond that of clinical trials, on diet-based antioxidants and long-term risk of incident dementia at levels consistent with a Western-type diet.

Several limitations of this study should be considered. First, this is an observational study and therefore residual confounding could explain the associations we observed. Although we cannot dismiss this possibility, we adjusted our statistical models for various health and lifestyle factors, which made little difference in our results compared to adjustment for age alone. We were particularly concerned about possible confounding by polyunsaturated fat intake; however, this is unlikely to have occurred because we previously showed that polyunsaturated fat was not associated with dementia risk in the Rotterdam Study[32]. In addition, any participants who changed dietary or supplement habits with respect to antioxidants over the long follow-up period would tend to bias our results toward the null. However, since we would expect such attenuation to affect observed relations for all four antioxidants, our consistent findings for vitamin E over shorter- and longer-term follow-up suggest that these changes did not influence our results substantially.

In summary, we found that higher consumption of vitamin E from foods was modestly associated with long-term risk of dementia in this cohort of older adults in the Netherlands.

Future studies should continue to evaluate dietary intake of antioxidants in relation to dementia risk, including different points at which antioxidant intake might modulate risk.

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Table 1

Baseline characteristics of the study population across tertiles of dietary vitamin E, vitamin C, beta carotene, and flavonoids (n=5,395)

	Vitamin E			Vitamin C			Beta carotene			Flavonoids		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Age, in years [a]	68.1	67.6	67.5	67.7	68.1	67.4	67.9	67.8	67.4	66.9	67.8	68.4
Education, %												
Low	36	34	34	36	34	34	38	33	34	38	34	33
Intermediate	28	28	29	29	28	29	28	30	27	27	29	29
High	36	38	37	35	38	37	34	37	39	35	37	38
Alcohol, %												
None	20	20	22	22	19	21	22	19	21	21	20	21
<1 drink/week	20	21	23	22	22	21	20	23	21	22	21	22
≥1 drink/week –	27	27	30	24	29	31	27	28	30	24	29	31
<1 drink/day												
1–3 drinks/day	28	29	23	28	27	25	27	27	26	28	27	25
≥4 drinks/day	5	3	2	4	3	2	4	3	2	5	3	1
Smoking, %												
Never	32	35	35	32	34	36	32	35	35	29	36	37
Former	41	42	45	39	44	45	41	41	46	38	42	48
Current	27	23	20	29	22	19	27	24	19	33	22	15
BMI, kg/m^2 [a]	26.5	26.3	26.2	26.2	26.3	26.5	26.2	26.3	26.6	26.3	26.3	26.4
Total energy intake, kJ/day [a]	8350	8451	8295	8376	8413	8308	8357	8500	8239	8348	8484	8264
APOE ε4 carriers, %	28	27	28	29	27	28	28	27	28	28	29	26
Supplement use, % [b]	11	12	13	12	12	11	12	11	13	12	12	12

[a] Indicates mean values.

[b] Supplement use includes antioxidant supplements (multivitamins or single supplements for vitamins E or C, beta carotene, or flavonoids) and omega-3 supplements. Since only 19 people indicated use of omega-3 supplements at baseline, percentages for supplement use essentially reflect antioxidant supplement use.

Table 2

Adjusted hazard ratios (HR) of incident dementia across tertiles of dietary vitamin E, vitamin C, beta carotene, and flavonoids

Tertiles	Median intake	Total population (n=5,395)			Excluding antioxidant and omega-3 supplement users (n=4,751)		
		No. of dementia cases	Age-adjusted	Multivariate-adjusted [a]	No. of dementia cases	Age-adjusted	Multivariate-adjusted [b]
Vitamin E (in mg/day)							
1	9.0	164	1.00 (ref)	1.00 (ref)	149	1.00 (ref)	1.00 (ref)
2	13.5	181	1.16 (0.94, 1.43)	1.20 (0.97, 1.49)	147	1.05 (0.84, 1.32)	1.11 (0.88, 1.40)
3	18.5	120	0.76 (0.60, 0.96)	0.75 (0.59, 0.95)	111	0.76 (0.60, 0.97)	0.75 (0.58, 0.97)
			p-trend=0.02	p-trend=0.02		p-trend=0.03	p-trend=0.03
Vitamin C (in mg/day)							
1	80	151	1.00 (ref)	1.00 (ref)	132	1.00 (ref)	1.00 (ref)
2	121	158	0.97 (0.77, 1.21)	0.96 (0.77, 1.21)	140	0.96 (0.75, 1.21)	0.94 (0.74, 1.20)
3	174	156	1.04 (0.83, 1.30)	0.99 (0.79, 1.25)	135	1.00 (0.79, 1.27)	0.95 (0.74, 1.21)
			p-trend=0.7	p-trend=1.0		p-trend=1.0	p-trend=0.7
Beta carotene (in μg/day)							
1	1710	152	1.00 (ref)	1.00 (ref)	129	1.00 (ref)	1.00 (ref)
2	2627	159	1.03 (0.82, 1.28)	1.09 (0.86, 1.37)	139	1.06 (0.83, 1.35)	1.11 (0.87, 1.43)
3	3779	154	1.11 (0.89, 1.39)	1.18 (0.94, 1.49)	139	1.18 (0.93, 1.50)	1.27 (0.99, 1.63)
			p-trend=0.7	p-trend=1.0		p-trend=1.0	p-trend=0.7
Flavonoids (in mg/day)							
1	16.9	136	1.00 (ref)	1.00 (ref)	114	1.00 (ref)	1.00 (ref)
2	27.6	169	1.14 (0.91, 1.43)	1.14 (0.91, 1.44)	148	1.18 (0.93, 1.51)	1.18 (0.92, 1.52)
3	39.3	160	1.03 (0.82, 1.30)	1.06 (0.84, 1.34)	145	1.12 (0.87, 1.43)	1.14 (0.88, 1.46)
			p-trend=0.8	p-trend=0.6		p-trend=0.4	p-trend=0.3

[a] Models are adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, BMI, and supplement use.

[b] Models are adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, and BMI.

Table 3

Adjusted hazard ratios (HR) of incident Alzheimer's disease (AD) across tertiles of dietary vitamin E, vitamin C, beta carotene, and flavonoids

Tertiles	Median intake	Total population (n=5,395)			Excluding antioxidant and omega-3 supplement users (n=4,751)		
		No. of AD cases	Age-adjusted	Multivariate-adjusted [a]	No. of AD cases	Age-adjusted	Multivariate-adjusted [b]
Vitamin E (in mg/day)							
1	9.0	131	1.00 (ref)	1.00 (ref)	117	1.00 (ref)	1.00 (ref)
2	13.5	137	1.10 (0.86, 1.40)	1.12 (0.88, 1.44)	107	0.97 (0.75, 1.27)	1.02 (0.78, 1.34)
3	18.5	97	0.77 (0.59, 1.00)	0.74 (0.56, 0.97)	89	0.78 (0.59, 1.03)	0.75 (0.57, 1.00)
			p-trend=0.05	p-trend=0.03		p-trend=0.07	p-trend=0.05
Vitamin C (in mg/day)							
1	80	118	1.00 (ref)	1.00 (ref)	101	1.00 (ref)	1.00 (ref)
2	121	129	1.01 (0.79, 1.30)	1.01 (0.78, 1.30)	112	1.00 (0.76, 1.30)	0.98 (0.74, 1.29)
3	174	118	1.01 (0.78, 1.30)	0.96 (0.74, 1.25)	100	0.97 (0.73, 1.28)	0.91 (0.69, 1.21)
			p-trend=1.0	p-trend=0.8		p-trend=0.8	p-trend=0.5
Beta carotene (in µg/day)							
1	1710	126	1.00 (ref)	1.00 (ref)	103	1.00 (ref)	1.00 (ref)
2	2627	123	0.95 (0.74, 1.22)	1.02 (0.79, 1.31)	107	1.02 (0.78, 1.34)	1.08 (0.82, 1.42)
3	3779	116	1.01 (0.79, 1.31)	1.07 (0.83, 1.39)	103	1.10 (0.84, 1.45)	1.18 (0.89, 1.57)
			p-trend=1.0	p-trend=0.8		p-trend=0.8	p-trend=0.5
Flavonoids (in mg/day)							
1	16.9	109	1.00 (ref)	1.00 (ref)	90	1.00 (ref)	1.00 (ref)
2	27.6	127	1.07 (0.83, 1.38)	1.11 (0.85, 1.44)	108	1.09 (0.83, 1.45)	1.13 (0.85, 1.51)
3	39.3	129	1.04 (0.81, 1.34)	1.09 (0.84, 1.42)	115	1.12 (0.85, 1.47)	1.16 (0.87, 1.54)
			p-trend=0.8	p-trend=0.5		p-trend=0.4	p-trend=0.3

[a] Models are adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, BMI, and supplement use.

[b] Models are adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, and BMI.