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Midlife Dietary Intake of Antioxidants and Risk of Late-Life Incident Dementia

The Honolulu-Asia Aging Study

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Antioxidants have been hypothesized to protect against Alzheimer's disease, but studies conducted in late life have been inconsistent. Risk factors measured in midlife may better predict dementia in late life because they are less affected by the disease process. The authors examined the association of midlife dietary intake of antioxidants to late-life dementia and its subtypes. Data were obtained from the Honolulu-Asia Aging Study, a prospective community-based study of Japanese-American men who were aged 45–68 years in 1965–1968, when a 24-hour dietary recall was administered. The analysis included 2,459 men with complete dietary data who were dementia-free at the first assessment in 1991–1993 and were examined up to two times for dementia between 1991 and 1999. The sample included 235 incident cases of dementia (102 cases of Alzheimer's disease, 38 cases of Alzheimer's disease with contributing cerebrovascular disease, and 44 cases of vascular dementia). Relative risks by quartile of intake were calculated using Cox proportional hazards models with age as the time scale, after adjustment for sociodemographic and lifestyle factors, cardiovascular risk factors, other dietary constituents, and apolipoprotein E e4. Intakes of beta-carotene, flavonoids, and vitamins E and C were not associated with the risk of dementia or its subtypes. This analysis suggests that midlife dietary intake of antioxidants does not modify the risk of late-life dementia or its most prevalent subtypes.

Alzheimer disease; antioxidants; dementia; diet; dietary supplements

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; HAAS, Honolulu-Asia Aging Study.

Much support for the role of oxidative stress in the etiology of Alzheimer's disease and vascular dementia has emerged from the identification of several potential neurodegenerative mechanisms in experimental and clinical studies (1, 2). Oxidative stress has also been implicated in cardiovascular diseases, which in turn have been associated with the occurrence of Alzheimer's disease and vascular dementia (3, 4). Consequently, the effects of intake of antioxidants, including carotenoids (beta-carotene), ascorbic acid (vitamin C), tocopherols (vitamin E), and flavonoids, in the prevention of cognitive impairment and dementia have been investigated in a number of studies (5–17). To date, the evidence is inconsistent.

Two prospective studies previously reported a protective effect of dietary intake of antioxidants against Alzheimer's disease (13, 14), but neither study found the same benefits in supplement users (18). Most studies evaluating the relation between dietary antioxidants and cognitive function have considered late-life diet, either in cross-sectional studies (5, 12) or in prospective studies (6, 8, 10, 13, 14) or clinical trials (17, 19) with relatively short follow-up periods. However, dementia has a long latency period, and preclinical cognitively impaired persons have reduced dietary intakes in comparison with nondemented people (20). There is evidence that measurement of specific risk factors in midlife better predicts late-life cognitive impairment, because the measures are less influenced by preclinical disease (21). Thus, it is of interest to study the association between dementia and dietary patterns measured in midlife.

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The Honolulu-Asia Aging Study (HAAS) is a longitudinal study of elderly Japanese-American men in which extensive evaluations of health characteristics, including a dietary assessment, were carried out during midlife. Previously, we reported no association between dementia and antioxidant supplement intake measured within a 6-year follow-up period (15). Here we examine the association between midlife dietary intake of antioxidants and the incidence of late-life dementia and its subtypes.

MATERIALS AND METHODS

The Honolulu Heart Program is a longitudinal community-based study of coronary heart disease and stroke in Japanese-American men (22). The original sample consisted of 8,006 men of Japanese ancestry born between 1900 and 1919 who were residing on the island of Oahu, Hawaii, in 1965. The first examination in the Honolulu Heart Program (examination 1) was carried out from 1965 through 1968, after which participants were further evaluated in 1968–1970 (examination 2) and in 1971–1974 (examination 3). At all examinations, a standardized clinical evaluation of several physical and laboratory functions was conducted, and data on sociodemographic characteristics and medical history were collected by structured interview. In 1988, all surviving members of the cohort were mailed a health survey including questions on supplemental vitamin intake (participation rate = 83 percent).

As a continuation of the Honolulu Heart Program, the HAAS was established in 1991 to study neurodegenerative diseases (23). Of the initial Honolulu Heart Program cohort, 3,734 subjects (80 percent of those eligible) ranging in age from 71 to 93 years agreed to participate in the HAAS (1991–1993; examination 4). Subjects were reexamined twice for dementia after the HAAS baseline assessment in 1994–1996 (examination 5) and 1997–1999 (examination 6).

The Kuakini Medical Center Institutional Review Board reviewed and approved this study. All subjects, or their caretakers if subjects were demented, provided written informed consent.

Dementia assessment

At baseline and at follow-up, subjects were first screened for dementia using the 100-point Cognitive Abilities Screening Instrument, a combination of the Hasegawa Dementia Screening Scale, the Folstein Mini-Mental State examination, and the Modified Mini-Mental State Test (24). Case-finding at examination 4 was conducted according to a multistep procedure using the Cognitive Abilities Screening Instrument score to determine subgroups for evaluation, a process described in detail elsewhere (22, 25). The dementia evaluation included a neurologic examination, neuropsychological testing, and an informant interview about changes in cognitive function and behavior. In subjects with dementia, a brain image was made and routine blood tests were conducted. On the basis of these data, a consensus diagnosis for dementia was given by the study neurologist and two physicians with expertise in dementia, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (26). Probable or possible Alzheimer's disease was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria (27). Vascular dementia was diagnosed using the criteria of the California Alzheimer's Disease Diagnostic and Treatment Centers (28). Other dementias included those due to chronic alcohol abuse, brain tumor, subdural hematoma, Parkinson's disease, Lewy body disease, Pick's disease, trauma, vitamin B_{12} deficiency, hypothyroidism, progressive supranuclear palsy, and unknown causes.

Dietary assessment

A 24-hour dietary recall was administered to all subjects as part of examination 1 (1965–1968). This method is especially useful for estimating intakes in culturally diverse populations with a wide range of foods and eating habits (29). Dietitians trained in standardized procedures used appropriate food models and serving utensils to establish food consumption (30). According to predefined rules, the dietitians tallied foods eaten during the previous 24 hours on a precoded interview form (31). Subjects were asked whether the 24-hour recall was fairly typical or unusual (i.e., major difference due to under- or overeating or drinking). In addition, questions related to the frequencies of consumption of 26 selected food and drink items characteristic of Western or traditional Japanese diets, including tea, were asked at examinations 1 and 3. In 1996, the nutritional information (beta-carotene, vitamin C, vitamin E, and total energy intake) from the 24-hour recall was recoded and estimated for subjects with a typical diet (93.6 percent) using a modified Nutritionist IV (version 3.0) software program (N-Squared Computing, Salem, Oregon) that included over 9,700 food items with 75 nutrients. Nutrient estimates were calculated using the US Department of Agriculture nutrition data bank (32), the Canadian nutrition data bank (33), the Composition of Malaysian Foods (34), and other available recipe and cookbook files (Dr. Kamal Masaki, Pacific Health Research Institute (Honolulu, Hawaii), personal communication, 2002). Food items specific to Hawaii and to the Japanese population were added directly from data provided by the Cancer Research Center of Hawaii and the Standard Tables of Food Composition in Japan (35) or were based on the recipes provided by the US Department of Agriculture Recipe File or Hawaiian cookbooks created using the software. Important sources of antioxidants in the Hawaiian diet include sweet potato, taro, bok choy, konbu, nori, and wakame for beta-carotene; breadfruit, sweet potato, turnip, guava, lychee, mango, and pineapple for vitamin C; and macadamia nuts, sweet potato, and mango for vitamin E.

Flavonoid intake was estimated using mean intake of tea (green and black) at examinations 1 and 3 and the average content of flavonoids from 11 types of tea infusions as published by Hertog et al. (36). Information on wine drinking by type (red or white) was not available, but this is presumed to be a minor source of flavonoids in this popula-

TABLE 1. Midlife characteristics of nondemented subjects and subjects with incident dementia, Honolulu-Asia Aging Study, 1991–1999

Characteristic	Nondemented subjects (n = 2,224)		Subjects with incident dementia (n = 235)		p value*
	Median or %	IQR†	Median or %	IQR	
Age (years) at examination 1	51.2	49.0–54.1	53.9	51.0–58.1	<0.001
Age (years) at examination 4	76.3	74.2–79.3	78.9	76.1–83.3	<0.001
Years of education	12	8–12	10	8–12	0.07
Midlife smoking (%)‡					0.71
Ever smoker	34.5		32.9		
Current smoker	28.4		27.0		
Midlife alcohol intake (%)‡					0.71
No alcohol drinking	27.1		30.0		
0–15 g/day	51.1		47.6		
15–30 g/day	9.2		12.3		
≥30 g/day	12.6		10.1		
Body mass index§ at examination 1	23.9	22.0–25.8	23.8	21.6–25.7	0.85
Carrier apolipoprotein E e4 (%)‡	17.9		20.9		0.11
Dietary intake at examination 1					
Energy (kcal/day)	2,256	1,865–2,666	2,235	1,840–2,667	0.33
Beta-carotene (μg/day)	142.8	35.9–549.1	171.8	39.4–558.2	0.38
Vitamin C (mg/day)	99.8	41.9–159.5	116.0	43.2–186.9	0.10
Vitamin E (mg/day)	13.8	7.2–23.3	13.6	8.2–24.9	0.19
Flavonoids (mg/day)	4.1	2.3–6.1	4.1	2.4–6.5	0.10
Midlife supplement use (%)	57.4		53.2		0.16

* p values were adjusted for age at examination 1 (education), education (age), or both (all other characteristics).
† IQR, interquartile range.
‡ Information on smoking was missing for 13 subjects in the incident dementia group and for 105 in the nondemented cohort; information on alcohol intake was missing for eight subjects in the incident dementia group and 63 in the nondemented cohort; information on apolipoprotein E e4 was missing for 20 subjects in the nondemented cohort.
§ Weight (kg)/height $(m)^2$.

tion. Tea intake has been reported to be one of the main sources of flavonoids in the diet (37).

Covariates and potential confounders

We considered covariates and potential confounders that were assessed during midlife from 1965 through 1974. Variables measured at examination 1 included age, years of education, body mass index, total energy intake, physical activity, blood pressure, and cholesterol concentration. Systolic and diastolic blood pressure values corresponded to the mean of three measurements made on the left arm while the subject was seated. Serum total cholesterol was measured in previously frozen blood specimens collected from subjects in a nonfasting state using Auto-Analyzer methods (38). An index of physical activity was calculated by summing the products of five levels of habitual activity in a day by corresponding intensity factor (39). Cholesterol and physical activity index were categorized into tertiles.

Variables for other characteristics, including midlife cigarette smoking and alcohol consumption, were based on information collected from examinations 1–3. Cigarette smoking status was categorized as never smoker, past smoker, and current smoker; alcohol intake was categorized as no alcohol, <15 g/day, 15–30 g/day, and ≥30 g/day. Supplemental vitamin intake (yes/no) corresponded to either intake of vitamins A, C, and E, as listed in the mailed questionnaire, or intake at examination 4. History of cardiovascular disease, including coronary heart disease and stroke events, was derived by continuous surveillance of hospital discharge and death records on Oahu from 1965 through 1997. Events were categorized relative to examination 4, as no event prior to examination 4 and no event after examination 4. Apolipoprotein E (APOE) genotyping was obtained by standard DNA amplification and restriction isotyping (40). Because few subjects were homozygous for the e4 allele, all carriers of APOE e4 were combined, and the variable was coded as a binary variable (presence/absence of APOE e4). Con-

TABLE 2. Relative risk of dementia and its subtypes associated with midlife intakes of specific antioxidants, Honolulu-Asia Aging Study, 1991–1999

	Quartile of energy-adjusted intake*							
	First (referent)	Second		Third		Fourth	
		RR†	95% CI†	RR	95% CI	RR	95% CI
			Beta-carotene				
Dementia							
No. of cases	53 (8.6)‡		59 (9.6)		64 (10.4)		59 (9.6)
RR§	1.00	1.12	0.77, 1.62	1.20	0.83, 1.73	1.07	0.74, 1.56
Multivariate RR¶	1.00	1.11	0.76, 1.62	1.13	0.78, 1.64	1.08	0.74, 1.57
Alzheimer's disease							
No. of cases	25 (4.3)		25 (4.3)		29 (5.0)		23 (4.0)
RR§	1.00	1.02	0.58, 1.77	1.12	0.65, 1.92	0.90	0.51, 1.59
Multivariate RR¶	1.00	0.99	0.57, 1.74	1.05	0.61, 1.82	0.86	0.49, 1.53
Alzheimer's disease with and without cerebrovascular disease							
No. of cases	35 (5.9)		34 (5.8)		36 (6.1)		35 (5.9)
RR§	1.00	0.99	0.62, 1.59	1.02	0.64, 1.63	0.98	0.61, 1.57
Multivariate RR¶	1.00	0.98	0.61, 1.58	0.98	0.61, 1.58	0.98	0.61, 1.57
Vascular dementia							
No. of cases	9 (1.6)		12 (2.1)		14 (2.5)		9 (1.6)
RR§	1.00	1.27	0.54, 3.02	1.58	0.68, 3.66	0.95	0.38, 2.39
Multivariate RR¶	1.00	1.22	0.49, 3.02	1.35	0.55, 3.29	1.24	0.47, 3.25
			Vitamin C				
Dementia							
No. of cases	58 (9.4)		43 (7.0)		59 (9.6)		75 (12.2)
RR§	1.00	0.73	0.49, 1.09	0.98	0.68, 1.41	1.17	0.83, 1.65
Multivariate RR¶	1.00	0.75	0.50, 1.12	0.96	0.66, 1.40	1.25	0.87, 1.78
Alzheimer's disease							
No. of cases	26 (4.5)		19 (3.2)		24 (4.1)		33 (5.8)
RR§	1.00	0.71	0.39, 1.29	0.88	0.50, 1.54	1.09	0.65, 1.84
Multivariate RR¶	1.00	0.62	0.34, 1.14	0.83	0.47, 1.47	1.06	0.62, 1.80
Alzheimer's disease with and without cerebrovascular disease							
No. of cases	33 (5.6)		27 (4.5)		34 (5.8)		46 (7.9)
RR§	1.00	0.79	0.47, 1.33	0.98	0.61, 1.60	1.22	0.78, 1.92
Multivariate RR¶	1.00	0.73	0.43, 1.22	0.93	0.57, 1.53	1.24	0.78, 1.98
Vascular dementia							
No. of cases	11 (1.9)		9 (1.6)		9 (1.6)		15 (2.7)
RR§	1.00	0.79	0.32, 1.91	0.79	0.33, 1.92	1.32	0.60, 2.89
Multivariate RR¶	1.00	0.97	0.38, 2.46	0.72	0.28, 1.84	1.42	0.61, 3.27

Table continues

founding factors with less than 5 percent missing values had missing values replaced with dummy variables, when variables were discrete, or were given the mean value of the distribution of the study population when continuous.

Study population

Of the 3,734 men in the HAAS at baseline, 226 were demented and were excluded from subsequent analyses. Of the remaining subjects, 1,049 could not be included because of either atypical diet (n = 226, 6.4 percent), death between examination 4 and examination 5 (n = 516, 14.7 percent), or nonresponse to examination 5 (n = 307, 8.8 percent); this left 2,459 subjects for analysis. Compared with subjects from the study sample, those with an atypical diet were similar in terms of age, education, and body mass index at examination 1 and intake of supplemental vitamins. Those who died between examinations 4 and 5 (mean age at death = 83.2 years) were, at examination 1, on average older (55.3 years vs. 52.4 years; $p < 0.05$) and less educated (9.9 years vs. 10.8 years; $p < 0.001$), had a lower energy intake (2,254 kcal/day vs. 2,307 kcal/day; $p < 0.05$), and comprised fewer supple-

TABLE 2. Continued

	Quartile of energy-adjusted intake*							
	First (referent)	Second		Third		Fourth		
		RR	95% CI	RR	95% CI	RR	95% CI	
Vitamin E								
Dementia								
No. of cases	48 (7.8)	67 (10.9)		59 (9.6)		61 (9.9)		
RR§	1.00	1.57	1.08, 2.28	1.34	0.91, 1.96	1.41	0.96, 2.06	
Multivariate RR¶	1.00	1.47	1.01, 2.14	1.27	0.86, 1.88	1.33	0.90, 1.96	
Alzheimer's disease								
No. of cases	21 (3.6)	31 (5.4)		21 (3.6)		29 (5.0)		
RR§	1.00	1.81	1.04, 3.16	1.20	0.65, 2.20	1.63	0.92, 2.87	
Multivariate RR¶	1.00	1.84	1.04, 3.25	1.19	0.64, 2.22	1.58	0.87, 2.85	
Alzheimer's disease with and without cerebrovascular disease								
No. of cases	25 (4.2)	43 (7.3)		30 (5.1)		42 (7.1)		
RR§	1.00	2.03	1.24, 3.33	1.39	0.82, 2.38	1.89	1.15, 3.12	
Multivariate RR¶	1.00	1.92	1.16, 3.18	1.35	0.78, 2.31	1.78	1.06, 2.98	
Vascular dementia								
No. of cases	11 (1.9)	10 (1.8)		14 (2.5)		9 (1.6)		
RR§	1.00	1.02	0.43, 2.41	1.37	0.62, 3.02	0.91	0.38, 2.20	
Multivariate RR¶	1.00	1.11	0.44, 2.78	1.42	0.61, 3.35	1.07	0.41, 2.78	
Flavonoids								
Dementia								
No. of cases	48 (7.8)	57 (9.3)		49 (8.0)		81 (13.2)		
RR§	1.00	1.27	0.87, 1.87	0.89	0.59, 1.32	1.17	0.82, 1.68	
Multivariate RR¶	1.00	1.35	0.92, 1.99	0.95	0.63, 1.43	1.36	0.95, 1.96	
Alzheimer's disease								
No. of cases	21 (3.6)	19 (3.3)		18 (3.1)		44 (7.6)		
RR§	1.00	0.95	0.51, 1.77	0.72	0.38, 1.35	1.43	0.84, 2.42	
Multivariate RR¶	1.00	0.97	0.52, 1.81	0.72	0.38, 1.36	1.56	0.92, 2.67	
Alzheimer's disease with and without cerebrovascular disease								
No. of cases	30 (5.0)	25 (4.3)		28 (4.7)		57 (9.7)		
RR§	1.00	0.89	0.52, 1.52	0.79	0.47, 1.32	1.28	0.82, 2.01	
Multivariate RR¶	1.00	0.93	0.54, 1.58	0.83	0.49, 1.42	1.43	0.91, 2.26	
Vascular dementia								
No. of cases	13 (2.3)	9 (1.6)		14 (2.4)		8 (1.5)		
RR§	1.00	0.73	0.31, 1.71	0.99	0.47, 2.11	0.51	0.21, 1.22	
Multivariate RR¶	1.00	0.78	0.32, 1.89	1.14	0.50, 2.59	0.73	0.29, 1.84	

* Median energy-adjusted intakes for the first, second, third, and fourth quartiles, respectively, corresponded to 16, 71, 296, and 1,101 μg/day for beta-carotene; 23, 69, 128, and 219 mg/day for vitamin C, 3.8, 10.7, 18.0, and 29.9 mg/day for vitamin E; and 2.0, 2.9, 4.5, and 8.2 mg/day for flavonoids.

† RR, relative risk; CI, confidence interval.

‡ Numbers in parentheses, percentage.

§ RRs were adjusted for age and education.

¶ Multivariate RRs were adjusted for age, education, smoking status, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, and apolipoprotein E e4.

ment users (48 percent vs. 57 percent; $p < 0.001$). Nonresponders to examination 5 were also older at examination 1 (52.9 years vs. 52.4 years; $p < 0.01$), had lower intakes of beta-carotene (423 μg/day vs. 480 μg/day; $p < 0.05$) and vitamin C (108 mg/day vs. 119 mg/day; $p < 0.05$), and comprised fewer supplement users (50 percent vs. 57 percent; $p < 0.05$).

Statistical analysis

Over 30.2 years of follow-up (range, 25.7–33.0 years), 2,224 subjects remained cognitively normal and 235 developed dementia; this included 102 cases of Alzheimer's disease, 38 cases of Alzheimer's disease with contributing cerebrovascular disease, 44 cases of vascular dementia, and

TABLE 3. Relative risk of dementia and its subtypes associated with *z* score sums of midlife energy-adjusted antioxidant intakes, Honolulu-Asia Aging Study, 1991–1999

	z score sum				
	Sum ≤ 1.5 (referent)	–1.5 < sum ≤ 1.5		Sum > 1.5	
		RR*	95% CI*	RR	95% CI
Dementia					
No. of cases	37 (8.4)†	124 (8.5)		74 (13.4)	
RR‡	1.00	1.04	0.72, 1.50	1.53	1.03, 2.27
Multivariate RR§	1.00	0.99	0.68, 1.44	1.44	0.96, 2.17
Alzheimer's disease					
No. of cases	15 (3.6)	54 (3.9)		33 (6.3)	
RR‡	1.00	1.18	0.66, 2.10	1.74	0.94, 3.23
Multivariate RR§	1.00	1.05	0.58, 1.89	1.58	0.84, 2.97
Alzheimer's disease with and without cerebrovascular disease					
No. of cases	18 (4.2)	76 (5.4)		46 (8.7)	
RR‡	1.00	1.36	0.81, 2.28	1.99	1.14, 3.45
Multivariate RR§	1.00	1.23	0.73, 2.09	1.82	1.04, 3.21
Vascular dementia					
No. of cases	10 (2.4)	25 (1.8)		9 (1.8)	
RR‡	1.00	0.77	0.37, 1.61	0.72	0.29, 1.78
Multivariate RR§	1.00	0.78	0.36, 1.72	0.86	0.33, 2.26

* RR, relative risk; CI, confidence interval.
† Numbers in parentheses, percentage.
‡ RRs were adjusted for age and education.
§ Multivariate RRs were adjusted for age, education, smoking status, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, and apolipoprotein E e4.

51 cases due to other causes. Comparisons between incident dementia cases and the nondemented were conducted using Kruskal-Wallis tests for continuous variables and chi-squared tests for categorical variables, after adjustment for age and education. Associations between intakes of specific antioxidants and outcomes were assessed after adjustment for total energy intake using the residual method (41). Intakes of antioxidants were log-transformed to normalize their distribution. Quartiles of energy-adjusted antioxidant intakes, based on their distribution in the study sample, were used to estimate the risks in the second, third, and fourth quartiles relative to the first (low intake). A combined antioxidant index was also created by summing z scores of energy-adjusted values of beta-carotene, vitamins C and E, and flavonoids, after verifying that associations between antioxidants and dementia were linear. This procedure assigns the same weight to every antioxidant and does not account for any potential prooxidant activity that could result from the interaction among antioxidants. Values of specific log-transformed antioxidant z scores ranged from –12.0 to 2.4, with 0 as the mean and 1 as the standard deviation, negative values indicating lower intakes of antioxidants. Values of the combined antioxidant index ranged from –17.7 to 5.1, with 0 as the mean and 2.2 as the standard deviation. *Z*-score sums were coded into three categories using ±1.5 as the cutoff point. Subjects with a high intake comprised 22.2 percent of the group; subjects with a low intake comprised 19.6 percent and constituted the reference group.

Cox proportional hazards regression with delayed entry and age as the time scale was used to identify and adjust for confounding variables (42). The age of onset was assigned at the midpoint of the interval between the last examination without dementia and the first follow-up examination with dementia. Subjects who died or did not participate in subsequent follow-up examinations were censored as of the time of their last evaluation. The proportional hazards assumptions were tested graphically and by including the interaction of time with covariates. In addition to age and education, associations between specific antioxidants and different outcomes were adjusted for smoking status, alcohol intake, body mass index, physical activity, total energy intake, year of birth (coded in tertiles), cholesterol concentration, systolic and diastolic blood pressures, history of cardiovascular disease, supplemental vitamin intake, and APOE e4. Effect modification of risk of dementia by smoking habits, body mass index, total energy intake, and APOE e4 was investigated in stratified analysis. Analyses were performed using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Subjects included in the analyses were, on average, aged 52.4 years (standard deviation, 4.2) at enrollment in 1965–1968 and aged 77.4 years (standard deviation, 4.1) at the first dementia assessment. Compared with subjects who remained free of dementia, those who developed dementia were, on average, older (79.3 years (standard deviation, 4.8) vs. 76.7 years (standard deviation, 3.9); $p < 0.001$) at the HAAS baseline. There was no difference in education, body mass index, or intakes of energy and antioxidants between the two groups, and distributions of smoking status, alcohol intake, APOE e4, and supplemental vitamin use were similar (table 1).

Intakes of beta-carotene, vitamin C, and flavonoids were not associated with the risk of dementia and its subtypes (table 2). Slightly increased risks of dementia and Alzheimer's disease were observed for the second quartile of energy-adjusted intake of vitamin E in both models as compared with a low intake (multivariate relative risks were 1.47 (95 percent confidence interval (CI): 1.01, 2.14) and 1.84 (95 percent CI: 1.04, 3.25), respectively), but no significant associations were observed for the third or fourth quartile (table 2). Significantly higher risks of Alzheimer's disease with and without contributing cerebrovascular disease were observed for the second and fourth quartiles of energy-adjusted intakes of vitamin E (multivariate relative risks were 1.92 (95 percent CI: 1.16, 3.18) and 1.78 (95 percent CI: 1.06, 2.98), respectively), but no association was observed for the third quartile. Energy-adjusted intake of vitamin E was not related to the incidence of vascular dementia. No significant trends were noted between quartiles of energy-adjusted intakes of antioxidants and risk of disease. Furthermore, no interaction was found between antioxidant intake and smoking habits, body mass index, total energy intake, or the APOE e4 allele (data not shown).

After controlling for age and education, a marginally significant increased risk of dementia was observed in subjects with a high total intake of antioxidants compared with a low intake; this relation was weakened in the fully adjusted model (table 3). Compared with a low intake of antioxidants, intermediate and high intakes were not associated with the risk of Alzheimer's disease. In subjects with Alzheimer's disease with and without contributing cerebrovascular disease, the association between a high intake of antioxidants and risk was significant (multivariate relative risk = 1.82, 95 percent CI: 1.04, 3.21). However, no association was observed between an intermediate intake and the risk of Alzheimer's disease with and without contributing cerebrovascular disease. Finally, total antioxidant intake was not related to the incidence of vascular dementia.

DISCUSSION

Although some results were contrary to our expectations, the present analysis suggests that overall there is no association between midlife dietary intake of antioxidants and the incidence of dementia and its subtypes in late life.

These findings contribute uniquely to the body of prospectively collected data on antioxidants and the risk of dementia. Our results are based on a large community-based sample of elderly Japanese-American men that has been followed extensively for research purposes for more than 30 years. Dietary intake was estimated during midlife, which makes it less likely that eating behavior was altered by preclinical changes related to dementia. Furthermore, the exposure of several potential confounders involving dietary patterns and cognitive function was documented throughout midlife, up to the end of the follow-up period.

Limitations of these analyses must be recognized. Of all eligible subjects, 29.9 percent could not be included in the study sample because they either died or did not participate in the first follow-up. Distributions of antioxidants across quartiles of intake were not different between deceased or nonresponding subjects and subjects included in the analyses. However, we cannot exclude the possibility that persons not included in the analysis had a higher risk of dementia than those who were included.

Our results are also limited because nutrient intakes were determined from a single 24-hour dietary recall that may not be representative of usual food selection. In this study, dietary information was assessed by skilled dietitians who used several quantity estimation tools. Only subjects with recalls typical of their usual diet were considered. Because of subjects' relatively young age at examination 1, the time period for which they were questioned (the preceding 24 hours), and the use of skilled interviewers, the accuracy of data on dietary intake should have been high (43). Furthermore, the existence of midlife long-term eating patterns has been demonstrated in this population by the reproducibility of dietary frequency data over a 6-year period (between examination 1 and examination 3) (30). Finally, considering the large sample size of our study population, a single day of recall may have been adequate for determination of the average intake of antioxidants (43).

Previous prospective analyses have yielded inconsistent results. Dietary assessments were collected closer in time to the onset of dementia, and not all studies were corrected for important confounding factors. In the Rotterdam Study (13), wherein dietary intake was estimated with a semiquantitative food frequency questionnaire in subjects aged 68 years, on average, high intake of vitamins C and E was found to be associated with lower risks of Alzheimer's disease after 6 years of follow-up. A suggestion of a protective effect of vitamin E against Alzheimer's disease was also reported in the Chicago Health and Aging Project after 3.9 years of follow-up (14). However, these latter results were based on dietary data collected with a self-administered food frequency questionnaire 2.3 years before the dementia assessment in subjects aged 73 years, on average. In contrast, total intake of vitamins C and E was not associated with the risk of Alzheimer's disease in the Washington Heights-Inwood Columbia Aging Project after 4.0 years of follow-up (16). In that study, dietary data were measured using a semiquantitative food frequency questionnaire administered between baseline and the first annual follow-up visit by telephone in subjects aged 75 years, on average. As in our cohort (15), no association with use of supplemental vitamins was observed in these three studies. Finally, a protective association between flavonoid intake and dementia was found in the

PAQUID Study after a 5-year follow-up period (10). Dietary data were estimated using a simple nutritional questionnaire in subjects aged 76 years, on average.

Inconsistent findings were also reported in the few trials investigating the effects of antioxidant vitamins on cognitive function and dementia. Compared with placebo, treatment with vitamin E for 2 years in 341 persons with probable Alzheimer's disease of moderate severity was beneficial in slowing the progression of disease, but no improvement in cognitive test scores was noticed (17). In the MRC/BHF Heart Protection Study, which included 20,536 persons allocated to receive either antioxidant vitamin supplementation (vitamins E and C and beta-carotene) or placebo, no treatment differences were found in the percentage of persons defined as cognitively impaired or in mean cognitive scores after 5 years of treatment (19). In addition, no difference was observed in the number of persons who developed dementia during follow-up.

In this study, we did not observe any protective effect from midlife intakes of beta-carotene, vitamin C, and flavonoids against dementia and its subtypes. Even though higher vitamin E intake appeared to increase the risk of dementia, particularly Alzheimer's disease with and without contributing cerebrovascular disease, these associations were inconsistent across quartiles of intakes or were of marginal statistical significance. The significant finding of an increased risk of dementia with the combined antioxidant index may be more difficult to interpret, because this index was computed using all four antioxidants and assigning them the same weight. A possible explanation for this phenomenon could be the antioxidant paradox, which says that when antioxidants interact with one another they become prooxidants (44). According to this concept, a diet too high in antioxidants would favor oxidative stress. However, the fact that we did not observe any association between high supplement intakes of vitamins C and E and the incidence of dementia and subtypes does not support this argument (15). This discrepancy could also be attributed to chance.

In summary, no association was found in this study between midlife dietary intakes of beta-carotene, vitamin C, and flavonoids and the risk of late-onset dementia and its subtypes. The relation between vitamin E and risk of dementia needs further investigation.

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REFERENCES

1. Markesbery WR, Carney JM. Oxidative alterations in Alzheimer's disease. Brain Pathol 1999;9:133–46.
2. Diaz MN, Frei B, Vita JA, et al. Antioxidants and atherosclerotic heart disease. N Engl J Med 1997;337:408–16.
3. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141–5.
4. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. Stroke 2002;33:1152–62.
5. Jama JW, Launer LJ, Witteman JC, et al. Dietary antioxidants and cognitive function in a population-based sample of older persons. Am J Epidemiol 1996;144:275–80.
6. Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145:33–41.
7. Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:121–6.
8. Paleologos M, Cumming RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. Am J Epidemiol 1998; 148:45–50.
9. Mendelsohn AB, Belle SH, Stoehr GP, et al. Use of antioxidant supplements and its association with cognitive function in a rural elderly cohort: The MoVIES Project. Am J Epidemiol 1998;148:38–44.
10. Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol 2000;16:357–63.
11. Masaki KH, Losonczy KG, Izmirlian G, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 2000;54:1265–72.
12. Peacock JM, Folsom AR, Knopman DS, et al. Dietary antioxidant intake and cognitive performance in middle-aged adults. Public Health Nutr 2000;3:337–43.
13. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002; 287:3223–9.
14. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 2002;287:3230–7.
15. Laurin D, Foley DJ, Masaki KH, et al. Vitamin E and C supplements and risk of dementia. JAMA 2002;288:2266–8.
16. Luchsinger JA, Tang M-X, Shea S, et al. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 2003;60: 203–8.
17. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 1997;336:1216–22.
18. Foley DJ, White LR. Dietary intake of antioxidants and risk of Alzheimer disease: food for thought. JAMA 2002;287:3261–3.
19. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:23–33.
20. Rivière S, Gillette-Guyonnet S, Andrieu S, et al. Cognitive function and caregiver burden: predictive factors for eating behaviour disorders in Alzheimer's disease. Int J Geriatr Psychiatry 2002;17:950–5.
21. Launer LJ, Masaki K, Petrovitch H, et al. The association between midlife blood pressure levels and late-life cognitive function: The Honolulu-Asia Aging Study. JAMA 1995;274: 1846–51.
22. Syme SL, Marmot MG, Kagan A, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: introduction. Am J Epidemiol 1975;102:477–80.

23. White L, Petrovitch H, Ross GW, et al. Prevalence of dementia in older Japanese-American men in Hawaii: The Honolulu-Asia Aging Study. JAMA 1996;276:955–60.
24. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr 1994;6:45–58.
25. Havlik RJ, Izmirlian G, Petrovitch H, et al. APOE-ε4 predicts incident Alzheimer's disease in Japanese-American men: The Honolulu-Asia Aging Study. Neurology 2000;54:1526–9.
26. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, third edition, revised. Washington, DC: American Psychiatric Association, 1987.
27. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984; 34:939–44.
28. Chiu HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473–80.
29. Buzzard IM, Sievert YA. Research priorities and recommendations for dietary assessment methodology: First International Conference on Dietary Assessment Methods. Am J Clin Nutr 1994;59(suppl):275S–80S.
30. Hankin JH, Nomura A, Rhoads GG. Dietary patterns among men of Japanese ancestry in Hawaii. Cancer Res 1975;35: 3259–64.
31. Tillotson JL, Kato H, Nichaman MZ, et al. Epidemiology of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: methodology for comparison of diet. Am J Clin Nutr 1973;26:177–84.
32. Nutrient Data Laboratory, Agricultural Research Service, US Department of Agriculture. USDA National Nutrient Database for Standard Reference, release 16-1. Washington, DC: US Department of Agriculture, 2004. (World Wide Web URL: http://www.nal.usda.gov/fnic/foodcomp).
33. Health Products and Food Branch, Health Canada. Canadian Nutrient File, 2001b. Ottawa, Ontario, Canada: Health Canada, 2001. (World Wide Web URL: http://www.hc-sc.gc.ca/food-aliment/ns-sc/nr-rn/surveillance/cnf-fcen/e_index.html).
34. Nutrition Society Malaysia. Malaysian Foods Composition Database. Kuala Lumpur, Malaysia: Division of Human Nutrition, Institute for Medical Research, 2004. (World Wide Web URL: http://www.nutriweb.org.my/searchfood.php).
35. Resources Council, Japan Science and Technology Agency. Standard Tables of Food Composition in Japan. 5th rev. ed. Kawaguchi City, Japan: Japan Science and Technology Agency, 1992.
36. Hertog MG, Hollman PC, van de Putte B. Content of potentially anticarcinogenic flavonoids of tea infusions, wines, and fruit juices. J Agric Food Chem 1993;41:1242–6.
37. Hertog MG, Feskens EJ, Hollman PC, et al. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. Lancet 1993;342:1007–11.
38. Nichaman MZ, Hamilton HB, Kagan A, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: distribution of biochemical risk factors. Am J Epidemiol 1975;102:491–501.
39. Abbott RD, Rodriguez BL, Burchfiel CM, et al. Physical activity in older middle-aged men and reduced risk of stroke: The Honolulu Heart Program. Am J Epidemiol 1994;139:881–93.
40. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 1990;31:545–8.
41. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
42. Commenges D, Letenneur L, Joly P, et al. Modelling age-specific risk: application to dementia. Stat Med 1998;17:1973–88.
43. Buzzard M. 24-hour dietary recall and food record methods. In: Willett W, ed. Nutritional epidemiology. 2nd ed. New York, NY: Oxford University Press, 1998:50–73.
44. Halliwell B. The antioxidant paradox. Lancet 2000;355:1179–80.