American Journal of Epidemiology

Vol. 144, No. 3
Printed in U.S.A.

A BRIEF ORIGINAL CONTRIBUTION

Dietary Antioxidants and Cognitive Function in a Population-based Sample of Older Persons

The Rotterdam Study

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Antioxidants have been implicated in processes related to atherosclerosis, aging, and selective neuronal damage, all of which may ultimately affect cognitive function. In a sample of older persons, the authors examined the cross-sectional relation between cognitive function and dietary intake of β-carotene and vitamins C and E. The data were derived from 5,182 community participants aged 55–95 years in the population-based Rotterdam Study in the period 1990 to 1993. Dietary intake was estimated from a semiquantitative food frequency questionnaire and categorized into five levels of intake. Cognitive function was measured with the 30-point Mini-Mental State Examination (MMSE) and characterized as unimpaired (>25 points) or impaired (≤25 points). Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for cognitive impairment. After adjustment for age, education, sex, smoking, total caloric intake, and intake of other antioxidants, a lower intake of β-carotene was associated with impaired cognitive function (<0.9 mg vs. ≥ 2.1 mg intake, OR = 1.9, 95% CI 1.2–3.1; p for trend < 0.04). There was no association between cognitive function and intake of vitamins C and E. These cross-sectional observations are compatible with the view that β-carotene-rich foods may protect against cognitive impairment in older people. The finding could also reflect unmeasured confounding, measurement error, or a change in food habits that *resulted from* rather than *preceded* the onset of cognitive impairment. *Am J Epidemiol* 1996;144:275–80.

aged; antioxidants; cognition disorders

Cognitive impairment, or an acquired deficit in memory function, problem solving, orientation, and abstraction, reduces an individual's ability to function independently and is a major component of age-related dementing disease. As the population of older persons increases, we can expect the numbers of cognitively impaired older individuals to increase. Evidence is accumulating that cerebrovascular lesions make an important contribution to cognitive impairment (1–4). Data from clinical and epidemiologic studies suggest that antioxidants may reduce the risk for cerebrovascular disease (5–8). These findings are supported by studies that show that the progression of cardiovascular lesions may be accelerated by oxidative damage brought about by free radical reactions (9, 10). Free radical damage has also been implicated in processes related to aging and selective nerve cell damage, both of which may contribute to cognitive impairment (11). On the basis of this evidence, we hypothesized that antioxidants may also protect against cognitive impairment.

Most previous studies that have examined the relation between cognitive impairment and dietary or plasma levels of antioxidants have been based on samples of demented individuals and controls or on samples of healthy volunteers (12–15). The present study examines the relation between cognitive function and dietary intake of antioxidants in a population-based sample of older persons living in the community.

MATERIALS AND METHODS

Data are from the Rotterdam Study, which has been described in detail elsewhere (16). Briefly, the study

Received for publication June 27, 1995, and accepted for publication January 5, 1996.

Abbreviations: CAMCOG, neuropsychologic component of the Cambridge Examination of Mental Disorders in the Elderly; CI, confidence interval; MMSE, Mini-Mental State Examination.

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cohort includes all inhabitants in the Rotterdam suburb of Ommoord aged 55 years or older who lived in the district for at least one year at enrollment. The baseline data were collected between 1990 and 1993 in a home interview and two follow-up visits at a research center. Of the 10,275 eligible subjects, 7,983 (78 percent) were interviewed at home, and of these 7,006 (88 percent) visited the research center twice. During the home visit, trained interviewers administered a questionnaire covering, among other subjects, sociodemographic background, medical history, and medication use. At the end of the visit, a dietary questionnaire was left behind, to be filled in by the respondent and brought to the research center. At the center, subjects underwent clinical examinations and additional interviews, including further assessment of dietary intake, screening, and evaluation for dementia. Dementia was detected in 474 subjects using a three-stage procedure that included neuropsychologic testing and a clinical exam (17).

As part of the protocol, the dietary interviews were not administered to individuals who were thought to be unable to reliably recall past dietary intake, including nursing home residents ($n = 479$) and persons who scored poorly (<80 points) on the CAMCOG ($n = 122$), the neuropsychologic component of the Cambridge Examination of Mental Disorders in the Elderly, a standardized protocol used in the second stage of case-finding for dementia (18). In addition, the 277 respondents in the pilot phase of the study were not offered the dietary questionnaire and 482 did not receive the questionnaire due to logistical reasons. After these exclusions, 5,646 persons were offered the dietary questionnaire. A further 212 interviews were excluded from the sample due to logical inconsistencies, resulting in 5,434 completed questionnaires. The conduct of the study was approved by the Medical Ethics Committee of the Erasmus University.

Measurement and definition of variables

Dietary intake was assessed with a 170-item semiquantitative food frequency questionnaire, which is a modified version of a previously validated questionnaire (19). The questionnaire was administered in two stages. In the first stage, respondents checked off the foods they usually ate (at least twice a month) in the last year. This took place at home. The second stage was completed during the second visit to the research center. After a review of the checked food items, a dietitian asked the respondent how much and how often each food item was consumed. Average daily dietary nutrient intake was calculated by multiplying the frequency and amount consumed for each food item by its nutrient content listed in an automated version of the Dutch Food Composition Table (20). Data on consumption of vitamin supplements was collected by the dietitian at the center and at the home interview when respondents were asked to show all vials of medication used in the past week.

We examined the relation between cognitive function and intakes of the major dietary antioxidants, β-carotene and vitamins C and E. For the analysis, absolute intake was classified into five equally spaced categories to create the maximum contrast between low and high intake. To do this, the lowest category was set at the amount that fell around the 15th percentile of intake for the nutrient (a round number was selected). Thereafter, four categories at equally spaced intervals were created. Because so few respondents ($n = 292$ for vitamin C, $n = 69$ for vitamin E, and $n = 31$ for β-carotene) reported that they took single nutrient vitamin supplements, users were put in the highest category of intake. Users of multivitamin supplements ($n = 315$) were not recategorized; use of these supplements (yes/no) was considered as a separate variable.

Cognitive function was tested with the 30-point Mini-Mental State Examination (MMSE) (21) administered during the first center visit. The MMSE contains 20 items covering orientation, memory, attention, language, and visuospatial construction. It is widely used in epidemiologic studies to characterize global cognitive functioning or to screen for dementia (22, 23). For the analyses, the MMSE was dichotomized using a cut-off of 25 points (i.e., MMSE score of ≤ 25 vs. >25 points). Scores of ≤ 25 points have been shown to be indicative of cognitive impairment (23).

The following variables were considered as potential confounders: age (in years), level of education, sex, smoking status, total caloric intake, and intake of other antioxidants. Education was classified into the following levels: primary, junior vocational or academic, and higher vocational or academic training. Smoking history was obtained by questionnaire; participants were categorized as current, former, or never smokers. Total caloric intake was computed from the food frequency questionnaire as described above. This variable and intake of other antioxidants were expressed as continuous variables.

Subclinical and clinical cardiovascular disease were considered to be possible mediators of the relation between cognitive function and diet. Information on cardiovascular disease was collected with a standard questionnaire administered at the home interview. For this study, an individual was considered to have cardiovascular disease when one or more of the following were present: history of myocardial infarction that led to one or more hospital admissions, history of stroke

confirmed by a physician, or presence of angina pectoris or intermittent claudication, as defined in the London School of Hygiene questionnaire (24). The ankle-brachial index was used a measure of subclinical atherosclerosis (25). This index was obtained by dividing the systolic blood pressure of the right and left posterior tibial arteries by the brachial pressure. The ankle pressure was measured with a Doppler probe (Huntleigh 500 D Huntleigh Technology, Bedfordshire, England) and a random-zero sphygmomanometer. If the left and right leg ankle-brachial index differed, the lesser value was used. Subjects were grouped into quartiles of ankle-brachial index, and the 490 subjects with missing values were grouped into a fifth category for the multivariate analyses.

Data analysis

Complete data on nutrient intake and confounding variables were available on 5,182 respondents. Compared with those without dietary data, individuals with dietary data tended to be younger, to have more education, and to score better on the MMSE, as would be expected given the exclusion criteria. The exclusion criteria eliminated all but 11 mildly demented individuals from the sample, one of whom had a MMSE score of >25 points. Removal of this group of mildly demented individuals did not change the results.

The Mantel-Haenszel chi-square test (for categorical variables) or analysis of variance (for continuous ones) was used to evaluate the age- and education-adjusted relation of potential confounding and mediating variables to nutrient intake and to the dichotomized MMSE variable. Logistic regression was used to estimate the odds ratio (95 percent confidence intervals) for cognitive impairment associated with categories of dietary intake. Three models are shown. Model 1 shows the results adjusted for age and education. Model 2 includes those variables along with sex, smoking, total caloric intake, and intake of the other antioxidants. Model 3 includes the putative mediating variables, cardiovascular disease and ankle-brachial index, and all of the confounding variables in model 2. Tests of interaction did not suggest that the relation between intake of any of the antioxidants and cognitive function differed by age, sex, or smoking status. Inclusion of a variable designating multivitamin supplement use did not change the results presented here. The 1990 release of the BMDP statistical package was used for the analysis (26).

RESULTS

The mean age of the participants was 67.6 years (standard deviation, 7.7 years) (range, 55–95 years). Fifty-nine percent of the sample was female, 20.4 percent had a primary school education, 21.4 percent currently smoked, and 15.3 percent reported a history of clinical cardiovascular disease. Seven percent had a score of ≤25 points on the MMSE (table 1).

A lower intake of vitamin E was associated with higher age (education adjusted), lower education (age adjusted), and was more common among women than men (age and education adjusted) (data not shown). Older subjects and women had a lower intake of β-carotene, while older subjects and men had a lower intake of vitamin C. After adjustment for age and education, current smokers had significantly lower intakes of β-carotene and vitamin C and former smokers had higher intakes of vitamin E. Finally, compared with unimpaired subjects, cognitively impaired subjects were older and more poorly educated.

TABLE 1. Description of the analytical sample studied for cognitive impairment associated with dietary intake of antioxidants, the Rotterdam Study, 1990–1993

Characteristic		Range
Age (years), mean (SD*) (*n* = 5,182)	67. 6 (7.7)	55–95
Sex		
Males (*n* = 2,114) (%)	40.8	
Females (*n* = 3,068) (%)	59.2	
Educational level		
Primary education (*n* = 1,058) (%)	20.4	
Junior vocational or academic (*n* = 2,225) (%)	42.9	
Higher vocational or academic (*n* = 1,899) (%)	36.6	
Smoking status		
Never (*n* = 1,926) (%)	37.2	
Former (*n* = 2,146) (%)	41.4	
Current (*n* = 1,110) (%)	21.4	
Cardiovascular disease†		
Present (*n* = 793) (%)	15.3	
Cognitive status‡ (*n* = 5,182) (points)		
MMSE	28	18–30
CAMCOG	91	80–104
Nutrient intake (*n* = 5,182)		
Calories (kcal/day)	1,921	1,612–2,258
β-carotene (mg/day)	1.4	1.1–1.8
Vitamin C (mg/day)	113.2	84.1–147.0
Vitamin E (mg/day)	12.9	9.3–17.2

* SD, standard deviation.

† Includes history of myocardial infarction, stroke, presence of angina pectoris, or intermittent claudication.

‡ MMSE, Mini-Mental State Examination (21); CAMCOG, neuropsychologic component of the Cambridge Examination of Mental Disorders in the Elderly (18).

After adjustment for age, education, sex, smoking, total calorie intake, and intake of other antioxidants, an inverse association between intake of β-carotene and cognitive function was observed (p for trend < 0.04) (table 2). The odds for performing poorly on the MMSE in the lowest (<0.9 mg) relative to the highest intake of β-carotene (≥2.1 mg) was 1.91 (95 percent CI 1.18–3.10). There was no reduction in the odds ratio for cognitive impairment after adjustment for cardiovascular disease and the ankle-brachial index (table 2, model 3). The associations of cognitive function to intake of vitamins C and E were not significant. The results did not change after controlling for the total amount of fat or percent of energy derived from fat, in place of total calorie intake.

DISCUSSION

We investigated the cross-sectional relation of cognitive impairment to dietary intake β-carotene and vitamins C and E in a population-based study of community-dwelling men and women. Because this is, to our knowledge, the first study to investigate the relation of dietary antioxidants to cognitive function in such a sample, direct comparisons with other studies are difficult. Most previous studies either were based on healthy samples or compared demented individuals to healthy controls (12–15). These latter studies are difficult to interpret because the nutritional status of demented persons may depend upon the care that they receive. Preliminary findings (27) from the cohort of Japanese men studied in the Honolulu Asia Aging Study (an extension of the Honolulu Heart Study) suggested a significant protective effect on cognitive function of vitamin C and vitamin E supplement use measured 4 years prior to and concurrently with the measurement of cognitive function.

The relation between antioxidant status and vascular events, an important risk factor for cognitive impairment (1–4, 9), has been studied in prospective studies and randomized trials. Preliminary data from the Nurses Health Study (28) and the Massachusetts Elderly Cohort Study (29) show a protective effect of dietary β-carotene against stroke. In the Prospective Basel Study of pharmaceutical company employees (7), an association between poor levels of plasma carotene and higher mortality from stroke was shown. Preliminary results from a randomized trial among physicians with chronic stable angina (30) suggest a 54 percent reduction in risk of major vascular events can be achieved with supplementation of β-carotene. In contrast, there was no association between β-carotene and the risk for stroke in the randomized Finnish Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (31). The Finnish study as well as the Nurses Health Study also found no significant relation between vitamin E intake and the risk for stroke.

In our study, β-carotene appeared to be protective against cognitive impairment. It has been hypothe-

TABLE 2. Risk for cognitive impairment* associated with dietary intake of antioxidants, the Rotterdam Study, 1990–1993

Dietary intake	Model 1†			Model 2‡			Model 3§		
	No.	OR‖	95% CI‖	OR	95% CI	p trend	OR	95% CI	p trend
β-carotene (mg/day)									
<0.9	949	1.67	1.03–2.48	1.91	1.18–3.10	<0.04	1.90	1.17–3.08	<0.04
0.9–<1.3	1,115	1.47	1.07–2.62	1.61	1.04–2.47		1.60	1.04–2.47	
1.3–<1.7	1,120	1.50	0.97–2.22	1.60	1.04–2.44		1.59	1.04–2.43	
1.7–<2.1	898	1.60	0.99–2.27	1.65	1.06–2.56		1.62	1.03–2.53	
≥2.1	1,101	1.00		1.00			1.00		
Vitamin C (mg/day)									
<70	728	1.17	0.82–1.68	1.13	0.77–1.66	<0.8	1.14	0.78–1.67	<0.8
70–<100	1,121	0.84	0.60–1.19	0.83	0.58–1.18		0.83	0.58–1.19	
100–<130	1,294	1.08	0.79–1.48	1.06	0.77–1.46		1.07	0.78–1.48	
130–<160	804	1.22	0.87–1.72	1.21	0.85–1.71		1.21	0.86–1.72	
≥160	1,236	1.00		1.00			1.00		
Vitamin E (mg/day)									
<7.5	686	0.88	0.57–1.35	0.92	0.56–1.51	<0.08	0.95	0.58–1.56	<0.8
7.5–<11.5	1,372	1.07	0.75–1.53	1.12	0.75–1.66		1.13	0.76–1.67	
11.5–<15.5	1,362	1.18	0.83–1.68	1.25	0.86–1.81		1.25	0.86–1.82	
15.5–<19.5	876	1.19	0.81–1.74	1.22	0.83–1.80		1.22	0.83–1.80	
≥19.5	887	1.00		1.00			1.00		

* Cognitive impairment is a score of ≤25 on the Mini-Mental State Examination (21).
† Adjusted for age and education.
‡ Also adjusted for sex, smoking, total energy intake, and intake of other antioxidants.
§ Also adjusted for the presence of cardiovascular disease and for the ankle-brachial index.
‖ OR, odds ratio; CI, confidence interval.

sized that β-carotene as well as other antioxidants may reduce the progression of atherosclerosis. In this context, in vitro experiments have shown that β-carotene most effectively quenches oxygen species under conditions of low oxygen tension, such as in tissues, and in particular those damaged by ischemia (32). However, in this study, statistical control for the presence of cardiovascular disease and the ankle-brachial index, as a measure of subclinical atherosclerosis, did not reduce the risk estimate for cognitive impairment associated with low β-carotene intake.

There are several design issues that should be taken into account when interpreting our results. First, this is a cross-sectional study. The design does not allow us to establish whether a low intake of β-carotene (or any other nutrient) preceded or was the result of impaired cognition. Second, the reliability of the dietary data collected from cognitively impaired subjects may be compromised. We tried to address this latter problem by excluding from the sample nursing home residents, individuals who scored poorly on the CAMCOG (including most demented subjects), and questionnaires with logical inconsistencies. Thus, we eliminated the most severely cognitively impaired and those most likely to have changed their dietary intake as a result of their condition. However, incipient dementia may also change dietary habits. Finally, although we controlled for major putative and known confounders, we cannot exclude the possibility that unmeasured confounding factors related both to antioxidant status and to the risk for cognitive impairment could explain our results.

Other factors could have impaired our ability to detect an association between cognitive function and intake of vitamin C and E. We do not know the extent to which changes in life-style and disease alter food habits of older persons so that food frequency questionnaires no longer capture longer-term dietary intake patterns. Such a measurement error would tend to make it more difficult to detect an effect of antioxidants on cognitive function if these effects are long-term. In addition, the ability to detect existing relations may be affected by the range of dietary intake and differences in the validity and reliability with which the content of various nutrients are measured in food, intake is measured in the questionnaire, and intake is reported by respondents (33). Finally, by design, the sample included individuals who functioned relatively well. Because the MMSE has a low ceiling effect, the distribution of scores in the sample was narrow. Additionally, a global measure of cognitive function, such as the MMSE, may not have been sensitive enough to pick up specific or subtle cognitive deficits due to impairment caused by atherosclerotic processes or selective neuronal damage (34).

In summary, these cross-sectional observations on the association of the dietary intake of β-carotene and cognitive function could reflect a biologic effect of β-carotene. However, a strong dose-response in risk by level of intake was not observed. The finding could also reflect unmeasured confounding, measurement error, or a change in food habits that *results from* rather than *precedes* the onset of cognitive impairment. A prospective study design is needed to clarify the temporal relation between antioxidants and cognitive function.

ACKNOWLEDGMENTS

This study was supported by grants from the NESTOR programme for research on the elderly (supported by the Netherlands Ministries of Health and Education), the Netherlands Heart Foundation, the Netherlands Prevention Fund, the European Community Concerted Action on the Epidemiology of Dementia (EURODEM), and the Municipality of Rotterdam.

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