Fruit and vegetable intake and cognitive function in the SU.VI.MAX 2 prospective study[1–3]

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ABSTRACT

Background: Current hypotheses suggest that intake of fruit and vegetables (FVs) protects against age-related cognitive impairment.

Objective: We examined the 13-y association between FV intake and cognitive performance in a sample of French adults.

Design: A total of 2533 subjects aged 45–60 y at baseline, who were part of the Supplementation with Antioxidant Vitamins and Minerals 2 (SU.VI.MAX 2) cohort, were selected. FV intake was estimated at baseline in participants who had completed at least six 24-h dietary records. Cognitive performance was assessed 13 y after baseline and included an evaluation of verbal memory (RI-48 cued recall, semantic, and phonemic fluency tests) and executive function (trail-making and forward and backward digit span tests). Principal components analysis was performed to account for correlations in test scores. The relation between cognitive performance and quartiles of FV intake was assessed by multivariate linear regression analyses.

Results: Intakes of FVs (*P*-trend = 0.02), fruit alone (*P*-trend = 0.04), vitamin C–rich FVs (*P*-trend = 0.03), vitamin C (*P*-trend = 0.005), and vitamin E (*P*-trend = 0.04) were positively associated with verbal memory scores. In contrast, intakes of FVs (*P*-trend = 0.006), vegetables alone (*P*-trend = 0.03), and β-carotene–rich FVs (*P*-trend = 0.02) were negatively associated with executive functioning scores.

Conclusions: FVs might have a differential effect on cognition according to groups of FVs and type of cognitive function. Further research using sensitive and reliable measures of various types of cognitive function is needed to clarify the effect of individual FV groups and nutrients. This trial is registered at clinicaltrials.gov as NCT00272428.　　*Am J Clin Nutr* 2011;94:1295–303.

INTRODUCTION

Cognitive impairment increases with age, and its prevalence is expected to rise with the population aging. Of the potentially modifiable risk factors for cognitive decline, nutrition factors have been gathering substantial public health interest (1).

Different food groups, especially fish and dietary fat, have been shown to be associated with cognition (1). In animal models, a diet supplemented with extracts of strawberries, blueberries, and spinach was shown to protect against neuronal and behavioral aging (2–4). In recent epidemiologic studies, consumption of FVs[4] as a whole was positively associated with global cognitive performance (5) and specifically with memory and executive function (6). A significant inverse relation between FV consumption and dementia was also found (7–9). However, many studies report nonsignificant effects regarding various cognitive domains (10). When considering FVs separately, findings are also inconsistent. Cognitive performance or decline was associated with FVs (5, 11) and vegetables but not fruit (12–14), fruit but not vegetables (15), or none of these subgroups (16). A more recent study even suggested a potential negative effect of vegetable intake on cognitive decline, whereas no association was shown for fruit (10). The positive effect of specific vegetables, such as green leafy (12, 13), cruciferous (5, 12, 13), and yellow vegetables (13) and carrots (5) and citrus fruit (5) on cognitive functioning has been observed.

In both epidemiologic (1, 2, 11, 17–20) and laboratory (21, 22) studies, antioxidants and folate compounds were shown to play a role in cognitive function. Dietary antioxidants may act as free radical scavengers in brain tissue protecting from selective neuronal damage or from atherogenic factors (23). In the case of folate deficiency, metabolic disturbances in the structural constituents of cerebral tissue and signaling molecules, neocortical atrophy, and hyperhomocysteinemia have been suggested (23).

Different vitamins, phytonutrients (23), or foodstuffs (24) could exert site-specific action within the brain structure. An animal study showed that a strawberry diet offered better protection against cognitive processes that depend on hippocampal

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[4] Abbreviations used: CES-D, Center for Epidemiologic Studies Depression Scale; FV, fruit and vegetable; SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals; TMT, Delis-Kaplan trail-making test.

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function, whereas a blueberry diet seemed to improve reversal learning, which depends on intact striatal functioning (24). Different concentrations in vitamin E according to brain site have also been shown (25). Results of several epidemiologic studies also suggest that the association between intake of FVs and cognition could be test-specific (6, 12, 26, 27).

The literature is currently inconsistent regarding the specific categories of FVs and type of nutrients that might have an increased effect on cognition and whether such associations are uniform across cognitive domains. We therefore examined the association between baseline FV intake and cognitive performance after 13 y through neuropsychologic tests (RI-48 cued recall test, semantic and phonemic fluency tests, TMT, and forward and backward digit span tests) in a large cohort of healthy volunteers.

SUBJECTS AND METHODS

Population

Subjects were participants in the SU.VI.MAX and SU.VI.MAX 2 studies. The SU.VI.MAX study (1994–2002; n = 12,741) is a randomized, double-blind, placebo-controlled, primary prevention trial initially designed to evaluate the effect of daily supplementation with antioxidant vitamins (E, C, and β-carotene) and minerals (selenium and zinc) at nutritional doses on the incidence of cancer and ischemic heart disease (28, 29). From the full SU.VI.MAX sample, 6850 subjects were included in the SU.VI.MAX 2 study (2007–2009), which was an observational study that investigated the effect of nutrition on the quality of aging.

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the Declaration of Helsinki guidelines and were approved by the Ethics Committee for Studies with Human Subjects of Paris-Cochin Hospital (no. 706 and no. 2364, respectively) and the Comité National Informatique et Liberté (no. 334641 and no. 907094, respectively). Written informed consent was obtained from all participants.

Dietary assessment

During the SU.VI.MAX study, the subjects were invited to provide a 24-h dietary record every 2 mo for a total of 6 records per year. Days of the week for these records were randomized and fixed for each subject so that each day of the week and all seasons were covered. Information was collected via computerized questionnaires with the use of the Minitel Telematic Network loaded with study-specific software. The Minitel was a small terminal widely used in France as an adjunct to the telephone. A validated instruction manual (30) was used for coding food portions. It included photographs of >250 generic items (corresponding to 1000 specific foods), with 60 images of FVs. Subjects could choose from 3 main portion sizes, 2 intermediate portion sizes, or 2 extreme portion sizes, for a total of 7 different portion sizes. A French food-composition table (31) was used to calculate nutrient contents. Because dietary intake was expressed in grams, it should be noted that 400 g is equivalent to 5 servings of FVs.

We included participants with a minimum of six 24-h records ($\geq$3 of them reported between May and October and $\geq$3 between November and April) provided in the first 2 y of follow-up. FV groups included FVs from composite dishes, excluding potatoes, legumes, and dried fruit. FVs were grouped based on their nutrient content: folate-rich FVs (superior to the median values of FV intake: 29 μg/100 g), β-carotene–rich FVs (>200 μg/100 g), vitamin C–rich FVs (>11 mg/100 g), or vitamin E–rich FVs (>410 mg/100 g). Intakes of nutrients (folates, β-carotene, and vitamins C and E) were also studied on the basis of food intake, excluding nutrient intake from supplementation.

Cognitive assessment

As part of the SU.VI.MAX 2 study, all participants were invited to undergo a check-up that included a neuropsychological evaluation carried out by trained neuropsychologists. Episodic memory was evaluated with the RI-48 cued recall test (32)—a delayed recall test based on a list of 48 words belonging to 12 different categories. This test was designed to limit "ceiling" effects encountered in some list-learning tests. The score is the number of words retrieved (maximum score: 48) (32). Lexical-semantic memory was assessed by verbal fluency tests, including a semantic fluency test that consisted of naming as many animals as possible and a phonemic fluency test consisting of citing words beginning with the letter "P." The total score was based on the number of correct words produced during a 2-min period for each test (33).

Mental flexibility was assessed with the TMT, which consists of connecting numbers and letters alternating between the 2 series. The score was the time (in s) needed to complete the test (34). Working memory was assessed with the forward and backward digit span tests. Subjects were asked to repeat 2 sequences of digits—forward or backward. The number of digits increased by 1 until the participant failed 2 consecutive trials of the same digit span. One point was assigned for each correct sequence repeated, with a maximum score of 14 points for digit span forward and for backward (35).

Covariate assessment

Age, sex, physical activity (irregular, <1 h walking/d, or $\geq$1 h walking/d), smoking status (never smoker, former smoker, or current smoker), and education level (primary, secondary or university level) were provided at enrollment. At the first follow-up (1995–1996), anthropometric measurements were obtained. Weight was measured with an electronic scale while subjects were wearing indoor clothing and no shoes. Height was measured under the same conditions with a wall-mounted stadiometer. Intakes of total energy, alcohol, food (fish, vegetable fat, and animal fat), and specific nutrients (saturated fatty acids, $n-3$ fatty acids, and $n-6$ fatty acids) were provided by 24-h dietary records in the first 2 y of follow-up. During follow-up, cases of cardio- or cerebrovascular disease were reviewed and validated by an independent expert committee. Depressive symptoms were assessed during cognitive evaluation with the French version of the CES-D (36).

Statistical methods

We selected subjects with available dietary and cognitive evaluation and who were 45–60 y of age at baseline. Subjects with missing values for any of the covariates were excluded.

Included and excluded subjects were compared by using the chi-square test or the nonparametric Wilcoxon's rank-sum test. BMI was calculated as the ratio of weight (in kg) to height^2 (in m).

The TMT was log-transformed to improve normality. Principal components analysis was carried out to produce factors that are independent linear combinations of the cognitive test scores, thereby maximizing the explained variance. Factors were rotated through an orthogonal transformation. The number of retained factors was determined according to 2 criteria: eigenvalues >1 and Cattel's Scree test (plot of the total variance related to each factor). Factors were labeled according to the tests with the strongest correlation. A 0.1-point difference in the cognitive factor between the first and fourth quartiles corresponded to one-tenth of the SD.

Descriptive results from chi-square tests or nonparametric Kruskal-Wallis tests are reported as percentages or means ± SDs across quartiles of FV intake. Multivariate linear regression models were used to estimate the predictive value of quartiles of FV and nutrient intakes from food for specific cognitive domains. The same analysis was also performed for each of the 6 cognitive tests. All analyses were adjusted for potential confounders of the association between FVs and cognition, identified in the literature, ie, sex, age at cognitive evaluation, BMI, educational level, supplementation group (intervention compared with placebo), energy intake (excluding alcohol to avoid overfitting), alcohol use, smoking status, physical activity, and CES-D scores (1). In addition to these variables, 2 models were used to adjust for dietary confounders shown in the literature to be associated with cognition (1). The food intake model was adjusted for fish, vegetable fat, and animal fat and the respective FV groups (eg, the fruit intake model was adjusted for vegetable intake and vice versa); the nutrient intake model was adjusted for saturated fatty acids, $n-3$ fatty acids, $n-6$ fatty acids, and respective FV nutrients (eg, the folate intake model was adjusted for β-carotene and vitamins C and E).

Regression analysis was performed to evaluate the association between various levels of adherence to recommendations (<4.5, 4.5–5.5, or >5.5 servings FVs/d) and cognitive factors. Sensitivity analyses were performed after exclusion of subjects who developed cardio- or cerebrovascular disease during SU.VI.MAX follow-up. All tests of statistical significance were 2-sided, and the type I error was set at 5%. Statistical analyses were performed by using SAS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the sample

Of the 6850 adults included in the SU.VI.MAX 2 study, 2533 individuals aged 45–60 y at baseline with available dietary and cognitive evaluation and without missing data on covariates were included in the current analysis (**Figure 1**). Subjects were more often male ($P < 0.0001$), were less often smokers ($P = 0.042$), had lower CES-D scores ($P < 0.0001$), and had better scores at all cognitive tests ($P < 0.01$ for each test) than did those who were excluded because of missing dietary records. In the included subjects, the mean scores were as follows: RI-48 cued recall test = 26.56 ± 6.01, semantic fluency test = 29.95 ± 8.15, phonemic fluency test = 22.98 ± 6.58, TMT = 91.43 ± 38.19, forward digit span test = 6.09 ± 1.14, and backward digit span test = 4.70 ± 1.27.

In our full sample, participants consumed slightly >5 servings FVs/d (424.5 ± 172.9 g/d). Characteristics of the population according to FV quartiles of intake are presented in **Table 1**. Across increasing FV quartiles, the subjects were older, were more physically active, were less often smokers, had greater energy intakes, and consumed less alcohol. In addition, subjects had greater energy intakes and, as expected, had a higher intake of all FV subgroups and food nutrients with increasing FV quartiles. β-Carotene and vitamin C status increased across increasing FV quartiles, whereas α-tocopherol status was not modified. Fruit intake was positively associated with vegetable intake ($P < 0.0001$). In energy-adjusted models, subjects with a higher FV intake consumed more added vegetable fat and less

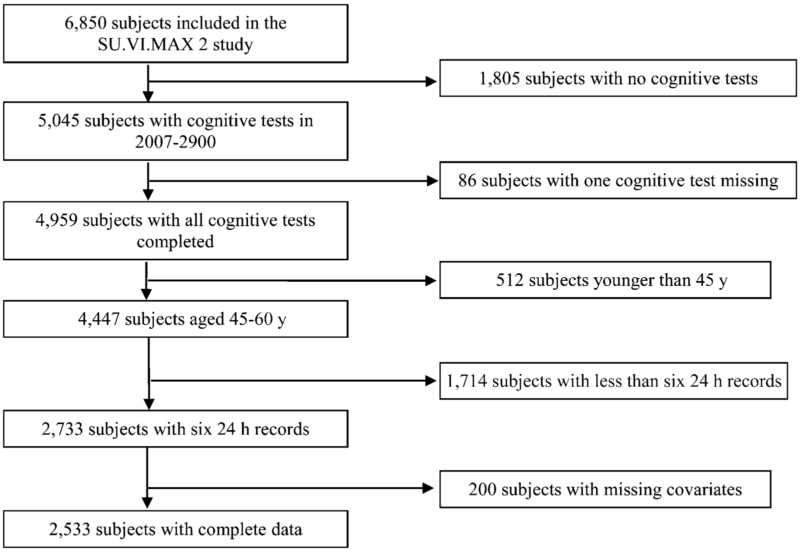

FIGURE 1. Flow chart of subjects from the SU.VI.MAX 2 study cohort (2007–2009) included in the current analysis. SU.VI.MAX 2, Supplementation with Antioxidant Vitamins and Minerals 2.

TABLE 1
Baseline characteristics of the population by quartile of FV intake in the SU.VI.MAX and SU.VI.MAX 2 studies, 1994–2009[1]

	Q1 (*n* = 634)	Q2 (*n* = 633)	Q3 (*n* = 634)	Q4 (*n* = 632)	*P*[2]
Men (%)	54.9	54.8	54.9	54.9	1
Age at clinical evaluation (y)	64.6 ± 4.4[3]	65.0 ± 4.6	65.9 ± 4.6	66.2 ± 4.6	<0.0001
BMI (kg/m^2)	24.1 ± 3.2	23.9 ± 2.9	24.0 ± 3.0	23.9 ± 3.0	0.53
Physical activity (%)					
Irregular	27.0	24.5	21.0	18.4	
<1 h walking/d	28.7	29.2	32.7	27.4	0.0008
≥1 h walking/d	44.3	46.3	46.4	54.3	
Smoking status (%)					
Never-smoker	44.79	50.24	53.15	55.54	
Former smoker	40.06	38.55	38.64	39.24	<0.0001
Current smoker	15.14	11.22	8.2	5.22	
Educational level (%)					
Primary school	24.3	21.0	19.1	20.6	
High school	40.5	37.1	41.2	41.0	0.13
University or equivalent	35.2	41.9	39.8	38.5	
CES-D	8.4 ± 7.0	8.7 ± 7.6	8.4 ± 7.0	8.8 ± 7.4	0.44
Intervention group, 1994–2002	49.4	56.1	54.7	53.8	0.09
Food intake					
Energy (kcal/d)[4]	1992.6 ± 555.2	2192.2 ± 545.3	2271.4 ± 543.5	2455.3 ± 611.0	<0.0001
Alcohol (g/d)	24.3 ± 23.4	22.8 ± 20.2	20.4 ± 19.6	17.2 ± 18.0	<0.0001
FV (g/d)	231.8 ± 54.0	353.1 ± 29.7	459.1 ± 37.3	654.5 ± 134.9	<0.0001
Fruit (g/d)	90.3 ± 46.6	158.7 ± 53.1	225.7 ± 62.4	353.5 ± 127.3	<0.0001
Vegetables (g/d)	141.5 ± 46.1	194.4 ± 51.9	233.3 ± 60.1	301.0 ± 88.6	<0.0001
Folate-rich FVs (g/d)	106.5 ± 37.9	155.4 ± 41.8	194.1 ± 50.8	268.1 ± 80.3	<0.0001
β-Carotene–rich FVs (g/d)	121.1 ± 40.4	172.7 ± 44.4	208.9 ± 54.1	272.2 ± 79.7	<0.0001
Vitamin C–rich FVs (g/d)	90.3 ± 36.5	134.1 ± 42.7	169.7 ± 53.4	238.4 ± 84.8	<0.0001
Vitamin E–rich FVs (g/d)	124.1 ± 41.2	197.0 ± 43.4	262.6 ± 55.8	379.5 ± 115.7	<0.0001
Nutrient intake					
Folate (μg/d)	250.8 ± 68.6	304.2 ± 64.5	343.8 ± 74.7	410.0 ± 91.7	<0.0001
β-Carotene (μg/d)	2.6 ± 1.4	3.7 ± 1.6	4.4 ± 1.9	5.6 ± 2.6	<0.0001
Vitamin C (mg/d)	67.7 ± 32.0	88.1 ± 32.9	104.2 ± 34.5	134.7 ± 42.8	<0.0001
Vitamin E (mg/d)	10.1 ± 3.5	12.4 ± 3.7	13.7 ± 4.1	16.0 ± 5.4	<0.0001
Plasma antioxidant concentrations					
β-Carotene (μmol/L)[5]	0.5 ± 0.4	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.5	<0.0001
Vitamin C (μg/mL)[6]	9.1 ± 5.1	9.6 ± 5.7	10.2 ± 4.2	10.6 ± 3.6	<0.0001
α-Tocopherol (μmol/L)[5]	31.6 ± 7.9	31.9 ± 8.1	32.0 ± 7.8	31.9 ± 8.1	0.92

[1] CES-D, Center for Epidemiologic Studies–Depression Scale; FV, fruit and vegetable; Q, quartile; SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.

[2] Based on the chi-square test (categorical variables) and the Kruskal-Wallis test (continuous variables).

[3] Mean ± SD (all such values).

[4] Excluding energy from alcohol.

[5] Analysis carried out in a subgroup of individuals for whom biomarker was available: *n* = 536 (Q1), 550 (Q2), 557 (Q3), and 536 (Q4).

[6] Analysis carried out in a subgroup of individuals for whom biomarker was available: *n* = 498 (Q1), 486 (Q2), 466 (Q3), and 446 (Q4).

added animal fat, sweetened foods, and soda drinks than did those with a lower intake (data not shown).

Cognitive performance factors

Two major cognitive factors were extracted with principal components analysis, accounting for 61% of the total initial variance in cognitive performance. The factor-loading matrix is presented in **Table 2**. The first factor accounted for 42% of the variance and was highly correlated with the RI-48 cued recall test and the semantic and phonemic fluency tests. This factor assessed verbal memory and was therefore named accordingly. The second factor accounted for 19% of the variance and was highly correlated with the forward and backward digit span tests measuring working memory and, to a lesser extent, with the TMT measuring mental flexibility. Hence, this factor pertained to executive function and was named accordingly.

Association between FV intake and cognitive function

The association between intake of FV and verbal memory is shown in **Table 3**. In the food intake model, subjects with a higher consumption of FVs as a whole, and of fruit and vitamin C–rich FVs, had better cognitive performance for verbal memory. In these models, the lowest quartile of consumption likely drove most of the observed associations. In the nutrient

TABLE 2
Factor loading matrix from principal components analysis

	Factor 1	Factor 2
Verbal memory		
Episodic memory: RI-48 cued recall test	0.74	−0.07
Lexical-semantic memory: semantic fluency test	0.80	0.19
Lexical-semantic memory: phonemic fluency test	0.68	0.31
Executive function		
Mental flexibility: trail-making test	−0.44	−0.50
Working memory: forward digit span test	0.04	0.85
Working memory: backward digit span test	0.14	0.84

intake model, dietary intakes of vitamins C and E were positively associated with verbal memory, whereas no association with folate or β-carotene was found. Although better performances were observed in subjects with greater intakes of folate-rich FVs, β-carotene–rich FVs, and folate, the associations did not remain significant after adjustment for relevant food and nutrient categories. When considered individually, intake of vitamin C was significantly associated with the RI-48 cued recall test (*P*-trend = 0.02) and the phonemic fluency test (*P*-trend = 0.002), whereas the association with the semantic fluency test was not significant (*P*-trend = 0.13). Intakes of FVs and fruit were not associated with these 3 tests, with one exception: fruit intake was significantly associated with the RI-48 cued recall test (*P*-trend = 0.02).

The associations between intake of FVs and executive function are shown in **Table 4**. In the food intake model, subjects with a higher consumption of FVs as a whole, vegetables, and β-carotene–rich FVs had lower executive functioning scores. In the nutrient intake model, vitamin E was

TABLE 3
Linear regression analysis showing the association between quartile of FV intake and related nutrient intake and verbal memory assessed 13 y after baseline in 2533 individuals[1]

	Q1	Q2	Q3	Q4	*P*-trend
Food model					
FVs					
Model 1[2]	−0.18 ± 0.04	−0.01 ± 0.04	0.01 ± 0.04	−0.01 ± 0.04	0.005
Model 2[3]	−0.16 ± 0.04	−0.01 ± 0.04	0.01 ± 0.04	−0.01 ± 0.05	0.02
Fruit					
Model 1[2]	−0.14 ± 0.04	−0.03 ± 0.04	−0.03 ± 0.04	0.01 ± 0.04	0.02
Model 3[4]	−0.12 ± 0.04	−0.03 ± 0.04	−0.03 ± 0.04	0.01 ± 0.05	0.04
Vegetables					
Model 1[2]	−0.13 ± 0.04	−0.02 ± 0.04	−0.03 ± 0.04	−0.02 ± 0.04	0.08
Model 3[4]	−0.11 ± 0.05	−0.01 ± 0.04	−0.03 ± 0.04	−0.03 ± 0.05	0.25
Folate-rich FVs					
Model 1[2]	−0.14 ± 0.04	−0.04 ± 0.04	−0.03 ± 0.04	0.00 ± 0.04	0.02
Model 3[4]	−0.10 ± 0.04	−0.04 ± 0.04	−0.03 ± 0.04	−0.01 ± 0.05	0.18
β-Carotene–rich FVs					
Model 1[2]	−0.15 ± 0.04	−0.03 ± 0.04	−0.01 ± 0.04	−0.01 ± 0.04	0.02
Model 3[4]	−0.12 ± 0.05	−0.02 ± 0.04	−0.01 ± 0.04	−0.03 ± 0.05	0.14
Vitamin C–rich FVs					
Model 1[2]	−0.12 ± 0.04	−0.10 ± 0.04	−0.01 ± 0.04	0.02 ± 0.04	0.004
Model 3[4]	−0.10 ± 0.04	−0.09 ± 0.04	0.00 ± 0.04	0.01 ± 0.04	0.03
Vitamin E–rich FVs					
Model 1[2]	−0.12 ± 0.04	−0.05 ± 0.04	0.00 ± 0.04	−0.04 ± 0.04	0.11
Model 3[4]	−0.08 ± 0.04	−0.04 ± 0.04	0.00 ± 0.04	−0.06 ± 0.05	0.59
Nutrient model[5]					
Folate					
Model 1[2]	−0.18 ± 0.05	−0.06 ± 0.04	0.02 ± 0.04	0.03 ± 0.05	0.002
Model 4[6]	−0.13 ± 0.05	−0.05 ± 0.04	0.00 ± 0.04	−0.03 ± 0.05	0.16
β-Carotene					
Model 1[2]	−0.05 ± 0.04	−0.09 ± 0.04	−0.03 ± 0.04	−0.03 ± 0.04	0.52
Model 4[6]	−0.02 ± 0.04	−0.08 ± 0.04	−0.04 ± 0.04	−0.06 ± 0.04	0.67
Vitamin C					
Model 1[2]	−0.15 ± 0.04	−0.08 ± 0.04	−0.02 ± 0.04	0.05 ± 0.04	0.0003
Model 4[6]	−0.14 ± 0.05	−0.08 ± 0.04	−0.02 ± 0.04	0.04 ± 0.05	0.005
Vitamin E					
Model 1[2]	−0.12 ± 0.04	−0.14 ± 0.04	0.02 ± 0.04	0.03 ± 0.04	0.002
Model 4[6]	−0.11 ± 0.05	−0.14 ± 0.04	0.01 ± 0.04	0.03 ± 0.06	0.04

[1] All values are adjusted means ± SEMs. FV, fruit and vegetable; Q, quartile.

[2] Adjusted for sex, age at clinical evaluation, BMI, educational level, intervention group, energy intake (excluding alcohol), alcohol use, smoking status, physical activity, and Center for Epidemiologic Studies–Depression Scale score.

[3] Adjusted as for model 1 plus intakes of vegetable fat, animal fat, and fish.

[4] Adjusted as for model 1 plus all relevant FV intake groups.

[5] Nutrient model includes nutrients from food only.

[6] Adjusted as for model 1 plus saturated fatty acids, n−3 fatty acids, n−6 fatty acids, and all relevant nutrient groups.

TABLE 4

Linear regression analysis showing the association between quartile of FV intake and related nutrient intake and executive function assessed 13 y after baseline in 2533 individuals[1]

	Q1	Q2	Q3	Q4	*P*-trend
Food model					
FVs					
Model 1[2]	0.04 ± 0.04	−0.03 ± 0.04	0.01 ± 0.04	−0.07 ± 0.05	0.13
Model 2[3]	0.08 ± 0.04	−0.02 ± 0.04	0.01 ± 0.04	−0.12 ± 0.05	0.006
Fruit					
Model 1[2]	0.02 ± 0.04	−0.03 ± 0.04	0.01 ± 0.04	−0.06 ± 0.04	0.28
Model 3[4]	0.02 ± 0.04	−0.03 ± 0.04	0.01 ± 0.04	−0.06 ± 0.05	0.36
Vegetables					
Model 1[2]	0.01 ± 0.04	−0.01 ± 0.04	0.01 ± 0.04	−0.05 ± 0.04	0.38
Model 3[4]	0.06 ± 0.05	−0.01 ± 0.04	0.00 ± 0.04	−0.10 ± 0.05	0.03
Folate-rich FVs					
Model 1[2]	0.00 ± 0.04	−0.01 ± 0.04	−0.01 ± 0.04	−0.03 ± 0.04	0.63
Model 3[4]	0.02 ± 0.05	−0.02 ± 0.04	−0.01 ± 0.04	−0.06 ± 0.05	0.30
β-Carotene–rich FVs					
Model 1[2]	0.02 ± 0.04	0.00 ± 0.04	−0.03 ± 0.04	−0.03 ± 0.04	0.29
Model 3[4]	0.06 ± 0.05	0.01 ± 0.04	−0.05 ± 0.04	−0.08 ± 0.05	0.02
Vitamin C–rich FVs					
Model 1[2]	0.01 ± 0.04	−0.06 ± 0.04	0.05 ± 0.04	−0.05 ± 0.04	0.71
Model 3[4]	0.01 ± 0.04	−0.06 ± 0.04	0.05 ± 0.04	−0.07 ± 0.05	0.47
Vitamin E–rich FVs					
Model 1[2]	0.04 ± 0.04	−0.06 ± 0.04	0.02 ± 0.04	−0.04 ± 0.04	0.40
Model 3[4]	0.05 ± 0.04	−0.06 ± 0.04	0.02 ± 0.04	−0.07 ± 0.05	0.14
Nutrient model[5]					
Folate					
Model 1[1]	−0.01 ± 0.05	0.01 ± 0.04	−0.04 ± 0.04	−0.00 ± 0.05	0.84
Model 4[6]	0.03 ± 0.05	0.02 ± 0.04	−0.06 ± 0.04	−0.04 ± 0.05	0.32
β-Carotene					
Model 1[2]	0.03 ± 0.04	−0.04 ± 0.04	0.00 ± 0.04	−0.04 ± 0.04	0.37
Model 4[6]	0.03 ± 0.04	−0.03 ± 0.04	0.00 ± 0.04	−0.05 ± 0.04	0.32
Vitamin C					
Model 1[2]	−0.07 ± 0.04	0.02 ± 0.04	−0.01 ± 0.04	0.01 ± 0.04	0.28
Model 4[6]	−0.08 ± 0.05	0.01 ± 0.04	−0.00 ± 0.04	0.03 ± 0.05	0.15
Vitamin E					
Model 1[2]	−0.06 ± 0.05	−0.07 ± 0.04	0.00 ± 0.04	0.09 ± 0.04	0.01
Model 4[6]	−0.01 ± 0.05	−0.05 ± 0.04	−0.01 ± 0.04	0.03 ± 0.06	0.53

[1] All values are adjusted means ± SEMs. FV, fruit and vegetable; Q, quartile.

[2] Adjusted for sex, age at clinical evaluation, BMI, educational level, intervention group, energy intake (excluding alcohol), alcohol use, smoking status, physical activity, and Center for Epidemiologic Studies–Depression Scale score.

[3] Adjusted as for model 1 plus intakes of vegetable fat, animal fat, and fish.

[4] Adjusted as for model 1 plus all relevant FV intake groups.

[5] Nutrient model includes nutrients from food only.

[6] Adjusted as for model 1 plus saturated fatty acids, n−3 fatty acids, n−6 fatty acids, and all relevant nutrient groups.

positively associated with executive function. Furthermore, none of the food or nutrient categories was associated with scores on the backward digit span test or the TMT (all *P*-trend > 0.05). Only the forward digit span test was significantly negatively associated with FVs (*P*-trend = 0.0003), vegetables (*P*-trend = 0.008), β-carotene–rich FVs (*P*-trend = 0.04), and vitamin E–rich FVs (*P*-trend = 0.01).

Different levels of adherence to recommendations (<4.5 servings FVs/d, 4.5–5.5 servings/d, or >5.5 servings/d) showed a positive linear association with verbal memory (*P*-trend = 0.045) and a near significant negative association in the case of executive function (*P*-trend = 0.051). Exclusion of subjects who developed vascular disease during follow-up (*n* = 111) did not modify the results, apart from the association between intake of fruit and verbal memory score, which did not remain significant after full adjustment (*P* = 0.10).

DISCUSSION

In this large prospective study, a long-term association was observed between consumption of FVs and cognitive performance. Specifically, higher intakes of FVs, fruit, vitamin C–rich FVs, and vitamins C and E at baseline were associated with better verbal memory assessed 13 y after inclusion. On the other hand, higher intakes of FVs, vegetables, and β-carotene–rich FVs were associated with poorer executive function, particularly regarding performance on the forward digit span test.

Associations with overall FV intake

FV intake was positively associated with verbal memory scores but negatively associated with executive function scores. Whereas no other studies have reported the latter, evidence from the literature is mixed. Some studies suggest a protective effect of FV intake on global cognitive performance (5) and on memory and executive function (6), whereas others indicate nonsignificant effects of FV intake on memory, information processing speed, and cognitive flexibility (10); general cognition, verbal memory, category fluency, and working memory (12); or perceptual speed and attention (13). Overall, measurement limitations, as well as the type of cognitive function measured, amounts of FV intake, or the types of FVs consumed might have led to the differences in the observed results.

Associations with FV groups

Our results indicated a positive association between fruit intake and verbal memory, but no association for executive function. Some cross-sectional studies showed that fruit intake (5, 11, 15), and intake of citrus fruit in particular (5), was positively associated with cognitive function; however, findings as a whole are inconsistent (10, 16).

In our study, no association between intake of vegetables, β-carotene–rich FVs, and verbal memory could be found, but an inverse association with executive function was observed. Most of the evidence from the literature shows either a protective effect (5, 11, 14, 15) or no effect (12, 16) of intake of vegetables on cognitive function. Our findings, however, are consistent with a recent study documenting an association between higher vegetable intake and lower information processing speed and worse cognitive flexibility (10). No difference in dietary profiles was observed between consumers of FVs, and no effect of education was observed, as previously suggested (10). β-Carotene content could be an important factor, because β-carotene–poor FVs were not associated with executive function ($P = 0.21$). However, no association with β-carotene was found in the nutrient model, and no data in the literature suggest a potential harmful effect of β-carotene intake (11, 18, 19). A potential explanation for this inverse association pertains to pesticide content in vegetables because exposure to toxins is known to increase cognitive impairment risk (37). In addition, it should be noted that the negative association was found only with the forward digit span test, which was administered first. Test order has been shown to affect the outcome of cognitive tests (38–41). There might be increased levels of discomfort when beginning psychological testing known to induce anxiety (33), especially so in FV consumers who are known to be particularly health conscious (42, 43).

Our study suggests that fruit might have a stronger effect on cognition than on vegetables. Although one study observed an effect of fruit but not vegetables on the onset of cognitive impairment (15), most studies have reported the opposite effect (12–14, 16). Antioxidant content might be better preserved in fruit than in vegetables, which often require cooking. In addition, the bottom quartile of consumption was lower in the case of fruit than vegetables, which may have contributed to the observed association. Indeed, the association between verbal memory and intake of FVs and fruit alone appeared to be mostly driven by low consumers. Verbal memory performance in low FV consumers would therefore derive a particular benefit from an increase in FV and fruit intakes.

Associations with nutrients

Vitamin C–rich FVs and vitamins C and E showed protective associations with cognition, particularly with verbal memory. In some cross-sectional studies, impaired cognitive function was associated with low dietary intakes of vitamins C and E (11, 14). However, no association with vitamins C or E was found in other cross-sectional (18) or prospective (19) studies with vitamin C and E intakes similar to those reported in our study. Vitamin C protects against oxidative stress–induced cellular damage in brain tissue by scavenging reactive oxygen species (23, 44). Vitamin E functions as an essential lipid-soluble antioxidant, scavenging hydroperoxyl radicals in a lipid milieu, and plays a major role in protecting erythrocyte membranes and nerve tissue (44). The lack of an association with vitamin E–rich FV might be due to the fact that FV are not major sources of vitamin E in the diet. Furthermore, we showed no association for β-carotene or folate, which does not help clarify evidence from the literature. Data show either a positive (11, 18) or no (19) association for β-carotene and either a positive (11) or a negative (14) association in the case of folates. Differences between studies might be related to varying plasma nutrient concentrations between subjects.

Difference between cognitive domains

In our study, fruit intake seemed to affect verbal memory, a cognitive domain particularly vulnerable to pathologic aging and Alzheimer disease, and to have no effect on executive function; vegetable intake seemed to have no influence on verbal memory and a negative influence on executive function. Such cognitive domain-specific discrepancies have been observed previously. For example, in another analysis of the SU.VI.MAX 2 study, adherence to nutritional recommendations was associated with verbal memory, but not with tests measuring executive function (45). In another study, subjects consuming fewer FVs had a higher risk of poor executive function than of poor memory (6). In addition, vegetable intake has been negatively associated with information processing speed and cognitive flexibility, whereas no association was found for memory (10). Finally, in rodents exposed to ^{56}Fe irradiation (leading to deterioration of motor and cognitive abilities), a strawberry diet offered better protection against spatial deficits, a hippocampus-mediated behavior, whereas a blueberry diet seemed to improve reverse learning, a behavior more strongly dependent on intact striatal function (24). Different foods or individual components from various sources might thus exert region-specific actions within brain structures (24). Hence, because of their disparate nutrient compositions, FVs may differentially affect cognitive functions.

Strengths and limitations

The strengths of this study include its large sample of community-dwelling subjects and its prospective design. Dietary data reflected midlife exposure because they were collected when the participants were aged 45–60 y, which was 13 y before the assessment of cognitive functions. The use of repeated 24-h dietary records accounting for seasonal variability resulted in relatively accurate dietary data, especially concerning nutrient intake (12, 13) in well-educated subjects (46). In our study, cognitive functioning was assessed by using a validated neuropsychological battery of sensitive tests with a diminished possibility for floor or ceiling effects. The main limitation of our study was the absence of cognitive function assessment at baseline. Furthermore, generalizability of the findings is somewhat limited because participants in a long-term cohort initially recruited for a randomized controlled trial are likely to be particularly health conscious and have high functional capacity levels. A healthy dietary and behavioral pattern observed in our study and often associated with FV intake could have also confounded the relations (47, 48). As mentioned previously, a presentation order effect of cognitive tests (38–41) may have occurred, leading to the inverse relation between FVs and executive function. Finally, although a wide range of covariates were assessed during follow-up, we cannot exclude the possibility that other important confounders were omitted (49), depending on the type of cognitive function in question (50). In particular, FV components not assessed in this study, such as polyphenols or enzymatic cofactors, may also be involved in the association between FVs and cognition (1, 51). From a public health perspective, the clinical significance of our findings could be evaluated according to educational level, which has consistently been shown to have an inverse association with cognitive function (26). In this study, differences in means of verbal memory and executive functioning were 0.70 and 0.63, respectively, between those with high and low levels of education. Thus, a difference of 0.15 in verbal memory between the first and fourth quartiles of FV intake may be considered relatively low at the individual level, but this difference is probably important at the population level.

Conclusions

This study documented a long-term association between consumption of FVs in midlife and cognitive performance assessed 13 y after baseline. Higher intakes of FVs, fruit alone, vitamin C–rich FVs, and vitamins C and E were associated with better verbal memory. On the other hand, higher intakes of FVs, vegetables alone, and β-carotene–rich FVs were associated with poorer executive function and, in particular, with poor performance on the forward digit span test. Encouragement of the consumption of fruit and vitamins C and E, particularly among low consumers, is important in nutritional interventions aimed at delaying the cognitive aging process. Further research is required to better elucidate the complex associations between different groups of FVs and specific cognitive domains.

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