Total antioxidant capacity of diet in relation to cognitive function and decline

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ABSTRACT

Background: Epidemiologic evidence on the association of individual antioxidant vitamins and cognition is inconsistent.

Objective: We evaluated the total antioxidant capacity of diets on the basis of the ferric-reducing antioxidant power (FRAP) assay in relation to cognition in older women.

Design: Starting in 1995, we used a telephone-based cognitive assessment to evaluate cognitive function on 3 occasions at 2-y intervals in 16,010 participants aged ≥70 y in the Nurses' Health Study. In 1980, and every 4 y thereafter, we collected dietary information by using a semiquantitative food-frequency questionnaire (FFQ). For each participant, we combined FFQ data with food- and supplement-specific FRAP values to obtain FRAP scores; these data were averaged from 1980 until the initial cognitive interview to reflect long-term diets. We used multivariable-adjusted linear regression to estimate mean differences in initial cognitive function and slopes of decline across quintiles of FRAP scores.

Results: In multivariable-adjusted models, there was an association between higher total FRAP scores and better cognitive function at the first interview (*P* for trend = 0.003 for global scores with all cognitive tests combined; mean difference = 0.04 standard units; 95% CI: 0.01, 0.08 standard units, comparing the highest and lowest quintiles). A weaker association was observed for dietary FRAP scores (excluding supplements) and initial global scores (*P* for trend = 0.05). However, prospective analyses of cognitive decline indicated no associations with total or dietary FRAP scores in models adjusted for multiple potential confounders (*P* for trend = 0.3 and 0.5 for global scores, respectively).

Conclusion: We observed no clear evidence of a consistent association between the total antioxidant capacity of diets and cognition in this cohort of older women. *Am J Clin Nutr* 2010;92:1157–64.

INTRODUCTION

Oxidative stress is important in the pathogenesis of impaired cognitive function and Alzheimer disease (1–3); thus, antioxidant vitamins have been thought to confer cognitive benefits. However, epidemiologic research has yielded inconsistent results (4), and several randomized trials of antioxidant vitamin supplements showed no relation with cognition in older adults (5–10). Still, most studies focused on single-antioxidant vitamin supplements, despite the wide variety of antioxidant nutrients that are available in foods (11). In rodent studies, consumption of antioxidant-rich foods or vitamin E prevented, and even reversed, age-related deficits in neuronal signaling and cognition (12, 13); however, the strongest effects were observed in rodents that consumed fruit and vegetable extracts rather than vitamin E, which suggested that combined effects of multiple antioxidant nutrients might be more influential on cognition than a single antioxidant. Limited epidemiologic evidence also indicated that higher intakes of fruit and vegetables may be associated with slower cognitive decline in older adults (14, 15), which provided additional support for broader approaches to studying antioxidant effects on cognition. To this end, we explored the total antioxidant capacity of diets by using measurements from the ferric-reducing antioxidant power (FRAP) assay, which measures iron reduction in the presence of antioxidants (16). By coupling extensive food-frequency data with published FRAP values for >1000 US-based foods and supplements, we evaluated the associations of total FRAP scores (derived from foods and supplements) and dietary FRAP scores (derived from foods only) with cognitive function and decline in ≈16,000 older women participating in the Nurses' Health Study.

SUBJECTS AND METHODS

The Nurses' Health Study began in 1976, when 121,700 US registered nurses, aged 30–55 y, completed a mailed questionnaire about their health and lifestyles. Follow-up questionnaires were mailed biennially, and a food-frequency questionnaire (FFQ) was added in 1980. During the period 1995–2000, participants who were ≥70 y old and free of stroke were invited to participate in a telephone-based study of cognitive function. For the first interview, 93% of eligible women participated (*n* = 19,415) and 7% of eligible women refused. We conducted follow-up interviews twice, at ≈2-y intervals (after the initial interview, the median time was 1.8 y to the first follow-up and 4.2 y to the second follow-up); participation in these follow-up interviews was >90% in living women. The Institutional Re-

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view Board of Brigham and Women's Hospital (Boston, MA) approved the current study.

Dietary assessment

We used a 61-item Willett semiquantitative FFQ (17) to assess dietary habits in 1980 and an expanded version (with ≈130 items) in 1984, 1986, and every 4 y thereafter. Foods were specified in a common unit or portion size (eg, one orange or one cup of tea) and detailed information was collected on antioxidant supplement use. Participants reported how often, on average, they consumed each food item over the previous year; there were 9 response categories ranging from almost never to ≥6 times/d. To determine each food's contribution to the FRAP, we used tables published by the Institute of Nutrition Research, University of Oslo (Oslo, Norway), which included measurements from the FRAP assay for >1000 foods obtained from the US Department of Agriculture National Food and Nutrient Analysis Program (16). When an item was not listed in the tables, we worked with nutritional experts to impute reasonable values on the basis of foods with similar antioxidant profiles; FRAP scores were assigned to all FFQ foods. The vast majority of food items contained in the top 50 foods with the highest antioxidant potential, according to the published tables, were included in our FFQ (eg, nuts, berries, fruit, vegetables, coffee, and juices). An exception was spices, which were not ascertained in our FFQ, but spices are consumed in small enough quantities that they are unlikely to contribute substantially to FRAP scores. Participants also reported information on supplement type, frequency, and dosage, which was used to estimate the FRAP contribution of supplements; FRAP values for supplements were determined by special analysis at the Institute of Nutrition Research, University of Oslo. For each participant, we multiplied the frequency of consumption of each food or supplement by the corresponding FRAP value and summed the resulting values across all dietary sources; for each dietary assessment period when relevant information was available, total FRAP scores were calculated on the basis of the contribution of foods and supplements, whereas dietary FRAP scores were calculated on the basis of the contribution of foods only. Because FRAP is correlated with total energy intake ($\rho = 0.3$ for total FRAP and $\rho = 0.4$ for dietary FRAP; $P < 0.0001$ for both), we calculated energy-adjusted FRAP scores by using the residual method (18).

In a validation study, we determined that the rank order of intakes of major food contributors to FRAP scores was ascertained well with the FFQ compared with four 1-wk dietary records collected over 1 y (19). For example, correlation coefficients between the 2 methods were 0.78 for coffee, 0.93 for tea, 0.74 for oranges, and 0.90 for red wine. The FRAP assay was validated in vitro before measurement of food- and supplement-specific FRAP values (16, 20).

Cognitive assessment

Initially, we administered the Telephone Interview of Cognitive Status (TICS), which is a telephone adaptation of the Mini-Mental State Examination; the 2 tests are highly correlated ($r = 0.94$) (21). After we established high participation rates, we gradually added 5 other tests as follows: the East Boston Memory Test (immediate and delayed recalls) (22), category fluency (23, 24), delayed recall of the TICS 10-word list, and digit span backward (25). We trained nurses who were blinded to study hypotheses to conduct all cognitive interviews. In a validation study, our cognitive battery correlated well with detailed, in-person interviews in 61 highly educated women who were ≥70 y of age ($r = 0.81$); interinterviewer reliability was also high across 10 interviewers ($r > 0.95$ for each cognitive test). Participation rates were identical across all cognitive tests and remained stable over time.

We evaluated the following 3 primary outcomes: 2 measures of general cognition and 1 measure of verbal memory [a strong predictor of developing Alzheimer disease (26–28)]. For general cognition, we considered TICS scores and global composite scores, which averaged together all 6 cognitive tests. For verbal memory, we averaged together the immediate and delayed recalls of both the East Boston Memory Test and TICS 10-word list. For constructing the global and verbal memory composite scores, we created z scores of each test because the scales of these tests were different (z scores were calculated as the difference between each participant's score and the population mean score and divided by the population SD). Composite scores were constructed only for women who completed all contributing tests.

Population for analysis

Of 19,415 participants who completed the initial cognitive interview, we excluded 3405 women who did not respond to the initial FFQ in 1980; thus, our primary analyses included 16,010 remaining women who participated in the initial FFQ and the first cognitive interview. Characteristics of women who we excluded were similar to our study population [eg, age was nearly identical (mean: 74.4 compared with 74.2 y, respectively) as was the body mass index (in kg/m^2) (mean: 26.3 compared with 26.0, respectively)].

Statistical analysis

Because cognitive decline likely develops over many years, long-term dietary habits are probably most relevant (29); thus, we averaged total FRAP scores (derived from foods and supplements) and dietary FRAP scores (derived from foods only) from 1980 through a participant's last dietary report before initial cognitive assessment. Women had an average of 5 dietary assessments during this period. Multivariable-adjusted linear regression was used to estimate mean differences in initial cognitive scores across quintiles of total and dietary FRAP scores. To evaluate cognitive decline over repeated assessments, we used linear mixed models with random intercepts and random slopes, which assumed that a participant's change in cognitive function followed that of the population mean except for random effects for initial cognitive levels (ie, random intercepts) and rates of change (ie, random slopes). In mixed models, we included main-effect terms for the exposure, covariates, and continuous time to account for relations with initial cognitive scores; the addition of interaction terms for the exposure and each covariate with continuous time was used to estimate associations with cognitive decline. We calculated 95% CIs for all models and

performed linear tests of trend by using the median values of quintiles.

We included multiple potential confounders in our models as follows: age, education, antidepressant use, smoking, physical activity, body mass index, and history of high blood pressure, myocardial infarction, and type 2 diabetes. These factors are established risk factors for cognitive decline (30–34) and were related to FRAP scores in age-adjusted analyses (**Table 1**). For analyses of dietary FRAP scores, we also included use of vitamin E supplements, vitamin C supplements, and multivitamin supplements in our models. Covariates were determined at the time of the initial cognitive interview.

We conducted several secondary analyses as well. First, we considered the possibility that cardiovascular risk factors might be potential intermediates as well as confounders; therefore, we compared our primary results to models adjusted for all potential confounders except for high blood pressure, myocardial infarction, and diabetes. In addition, we examined an interaction term for total and dietary FRAP (in quintiles) with smoking (categorized as never, former, and current) because smoking is an important contributor to oxidative stress, and effects of FRAP might depend on existing oxidative stress levels. Finally, we individually evaluated 5 major dietary contributors to FRAP scores (ie, caffeinated coffee, tea, decaffeinated coffee, oranges, and chocolate) to assess whether they were related to cognition because dietary recommendations are easier to make on the basis of foods rather than on FRAP scores. These dietary sources accounted for ≈67% of between-person variation in dietary FRAP scores over the 6 dietary assessments. All analyses were performed with SAS software (version 9; SAS, Cary, NC).

RESULTS

We examined age-adjusted characteristics of our participants at the initial cognitive interview (Table 1) and observed significant associations between total FRAP scores and multiple lifestyle factors. However, only some of these differences appeared to be qualitatively meaningful, and our large sample

TABLE 1
Age-adjusted characteristics of women at the initial cognitive interview in the Nurses' Health Study cognitive substudy by selected quintiles of total ferric-reducing antioxidant power (FRAP) scores (n = 16,010)[1]

	Quintile 1	Quintile 3	Quintile 5	P[2]
n	3202	3202	3202	
FRAP score (mmol/d)[3]	8.1 (7.0–8.9)	12.5 (12.0–13.0)	19.5 (17.8–22.6)	
Age (y)[4]	74.3 ± 2.3	74.2 ± 2.3	74.2 ± 2.3	0.04
Education (%)[5]				
RN degree	80	77	73	
Bachelor's degree	15	17	19	
Graduate degree	5	6	8	<0.0001
Alcohol intake (%)[5]				
None	62	44	44	
1–14 g/d	33	46	46	
≥15 g/d	5	10	10	<0.0001
Antidepressant use (%)[5]	5	6	6	0.05
Smoking (%)				
Never	55	45	41	
Former	39	47	50	
Current	6	8	10	<0.0001
Physical activity (MET-h)	13.5	16.7	18.2	<0.0001
BMI (%)[5]				
<22 kg/m^2	17	21	24	
22–24 kg/m^2	24	26	29	
25–29 kg/m^2	37	36	32	
≥30 kg/m^2	22	17	15	<0.0001
Vitamin E supplement use (%)[5]	32	47	76	<0.0001
Vitamin C supplement use (%)[5]				
None	85	65	22	
Seasonal	6	11	11	
Regular	9	24	67	<0.0001
Multivitamin use (%)[5]	51	64	76	<0.0001
High blood pressure (%)[5,6]	59	55	53	<0.0001
Myocardial infarction (%)[5,6]	6	6	5	0.04
Type 2 diabetes (%)[5,6]	14	10	8	<0.0001

[1] RN, registered nurse; MET-h, metabolic equivalent hour (ie, the amount of energy expended during 1 h of sitting). Total FRAP scores were averaged from 1980 until the initial cognitive interview.

[2] Derived from multinomial logistic regression models, with the ordinal variable for the total FRAP score (in quintiles) included as the response variable and predictors included as either categorical or continuous variables. All models included age as a continuous variable.

[3] Values are medians; interquartile ranges in parentheses.

[4] Values are means ± SDs.

[5] Percentages of nonmissing values.

[6] Refers to a history of the condition indicated.

size, in part, might explain why some differences reached statistical significance. Still, women with greater total FRAP scores were more likely to be supplement users (as expected), slightly more likely to be smokers, and slightly less likely to be obese or have type 2 diabetes than were women with lower total FRAP scores. In addition, physical activity levels were greater across increasing quintiles of total FRAP scores. Patterns were very similar for dietary FRAP scores (results not shown).

We observed that higher total FRAP scores (derived from supplements and foods) were related to better cognitive function at the initial interview for all 3 outcomes when age and education were controlled for (P for trend = 0.04 for TICS scores, 0.0002 for global scores, and 0.003 for verbal scores; **Table 2**). For example, women in the highest quintile of total FRAP scores had initial global scores that were 0.06 standard units higher than those in the lowest quintile of total FRAP scores (95% CI: 0.03, 0.09 standard units). These trends were attenuated when we additionally adjusted for antidepressant use, smoking, physical activity, body mass index, and history of high blood pressure, myocardial infarction, and type 2 diabetes. In particular, significant associations remained for global scores (P for trend = 0.003; mean difference: 0.04 standard units; 95% CI: 0.01, 0.08 standard units, comparing highest and lowest quintiles) and verbal scores (P for trend = 0.02; mean difference: 0.04 standard units; 95% CI: 0.01, 0.08 standard units) but not for TICS scores (P for trend = 0.1; mean difference: 0.10 standard units; 95% CI: −0.04, 0.23 standard units).

For cognitive decline, there were no significant associations with total FRAP scores in models adjusted for age and education (P for trend = 0.3 for global scores; **Table 3**). For example, women in the highest quintile of total FRAP scores had a similar slope of decline for global scores compared with that of women in the lowest quintile (mean difference: 0.00 standard units/y; 95% CI: −0.01, 0.01 standard units/y). Results were similar when we included antidepressant use, smoking, physical activity, body mass index, high blood pressure, myocardial infarction, and type 2 diabetes in our models (P for trend = 0.3 for global scores; mean difference: 0.00 standard units/y; 95% CI: −0.01, 0.00 standard units/y, comparing extreme quintiles).

When we considered dietary FRAP scores (from food sources only), we observed that higher scores were associated with 2 out of 3 cognitive measures at the initial interview in age- and education- adjusted models (P for trend = 0.002 for global scores and 0.03 for verbal scores; **Table 4**). For example, participants in the highest quintile of dietary FRAP scores had global scores that were 0.04 standard units higher than those in the lowest quintile (95% CI: 0.01, 0.07 standard units). Similar to the results for total FRAP scores, these trends were attenuated when we adjusted for antidepressant use, smoking, physical activity, body mass index, use of vitamin E supplements, vitamin C supplements, and multivitamin supplements, high blood pressure, myocardial infarction, and type 2 diabetes. Specifically, the association became borderline significant for global scores (P for trend = 0.05; mean difference: 0.02 standard units; 95% CI: −0.01, 0.06 standard units, comparing extreme quintiles) but was no longer significant for verbal scores (P for trend = 0.2; mean difference 0.01 standard units; 95% CI: −0.02, 0.05 standard units).

Furthermore, dietary FRAP scores were not associated with cognitive decline in models adjusted for age and education (P for trend = 0.3 for global scores; mean difference: 0.01 standard units/y; 95% CI: 0.00, 0.01 standard units/y, comparing highest and lowest quintiles), and these results were essentially unchanged after adjustment for multiple potential confounders (P for trend = 0.5 for global scores; mean difference: 0.00 standard units/y; 95% CI: 0.00, 0.01 standard units/y, comparing extreme quintiles; **Table 5**).

In secondary analyses, results were generally similar when we excluded diabetes and cardiovascular risk factors from our multivariate models because they might be intermediates. Greater total FRAP scores were associated with better cognitive performance at the initial interview for global scores (P for trend = 0.01; mean difference: 0.04 standard units; 95% CI: 0.01, 0.08

TABLE 2
Mean differences in initial cognitive function by quintiles of total ferric-reducing antioxidant power (FRAP) scores[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend[2]
n	3202	3202	3202	3202	3202	
FRAP score (mmol/d)[3]	8.1 (7.0–8.9)	10.6 (10.1–11.1)	12.5 (12.0–13.0)	14.9 (14.2–15.7)	19.5 (17.8–22.6)	
TICS						
Model 1[4]	0.00[5]	0.13 (−0.01, 0.26)[6]	0.05 (−0.08, 0.18)	0.18 (0.05, 0.31)	0.14 (0.01, 0.27)	0.04
Model 2[7]	0.00	0.10 (−0.03, 0.23)	0.00 (−0.13, 0.14)	0.13 (0.00, 0.26)	0.10 (−0.04, 0.23)	0.1
Global						
Model 1[4]	0.00	0.03 (0.00, 0.06)	0.03 (0.00, 0.06)	0.06 (0.02, 0.09)	0.06 (0.03, 0.09)	0.0002
Model 2[7]	0.00	0.02 (−0.01, 0.05)	0.02 (−0.01, 0.05)	0.04 (0.01, 0.07)	0.04 (0.01, 0.08)	0.003
Verbal						
Model 1[2]	0.00	0.02 (−0.01, 0.06)	0.02 (−0.01, 0.06)	0.05 (0.01, 0.08)	0.05 (0.01, 0.09)	0.003
Model 2[7]	0.00	0.02 (−0.02, 0.05)	0.01 (−0.02, 0.05)	0.03 (0.00, 0.07)	0.04 (0.01, 0.08)	0.02

[1] TICS, Telephone Interview of Cognitive Status. Total FRAP scores were averaged from 1980 until the initial cognitive interview. Results were obtained from multivariable-adjusted linear regression models.

[2] Calculated in separate multivariable-adjusted linear regression models by using the median intake of each quintile as a continuous variable.

[3] All values are medians; interquartile ranges in parentheses.

[4] Adjusted for age (continuous) and education (registered nurse, bachelor's degree, and graduate degree).

[5] Mean difference (all such values); reference.

[6] Mean difference; 95% CI in parentheses (all such values).

[7] Adjusted for age, education, antidepressant use (yes or no), smoking (never, former, or current), physical activity (in quintiles, missing), BMI (in kg/m^2; <22, 22–24, 25–29, ≥30, or missing), high blood pressure (yes or no), myocardial infarction (yes or no), and type 2 diabetes (yes or no).

TABLE 3
Mean differences in slopes of cognitive decline over 3 interviews by quintiles of total ferric-reducing antioxidant power (FRAP) scores[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[2]
n	3202	3202	3202	3202	3202	
FRAP score (mmol/d)[3]	8.1 (7.0–8.9)	10.6 (10.1–11.1)	12.5 (12.0–13.0)	14.9 (14.2–15.7)	19.5 (17.8–22.6)	
TICS						
Model 1[4]	0.00[5]	0.00 (−0.04, 0.04)[6]	0.02 (−0.02, 0.06)	0.01 (−0.03, 0.05)	−0.02 (−0.06, 0.02)	0.3
Model 2[7]	0.00	0.00 (−0.04, 0.04)	0.01 (−0.03, 0.05)	0.00 (−0.04, 0.04)	−0.02 (−0.06, 0.02)	0.2
Global						
Model 1[4]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.3
Model 2[7]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.00)	0.3
Verbal						
Model 1[4]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	−0.01 (−0.02, 0.00)	0.2
Model 2[7]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	−0.01 (−0.02, 0.00)	0.2

[1] TICS, Telephone Interview of Cognitive Status. Total FRAP scores were averaged from 1980 until the initial cognitive interview. Results were obtained from multivariable-adjusted mixed linear regression models that included terms for continuous time, exposure, and covariates and interaction terms for exposure and each covariate with continuous time.
[2] Calculated in separate multivariable-adjusted linear regression models by using the median intake of each quintile as a continuous variable.
[3] All values are medians; interquartile ranges in parentheses.
[4] Adjusted for age (continuous) and education (registered nurse, bachelor's degree, and graduate degree).
[5] Mean difference (all such values); reference.
[6] Mean difference; 95% CI in parentheses (all such values).
[7] Adjusted for age, education, antidepressant use (yes or no), smoking (never, former, or current), physical activity (in quintiles, missing), BMI (in kg/m^2; <22, 22–24, 25–29, ≥30, or missing), high blood pressure (yes or no), myocardial infarction (yes or no), and type 2 diabetes (yes or no).

standard units, comparing extreme quintiles), and there were no significant associations between total FRAP scores and cognitive decline (*P* for trend for global scores = 0.2) (results not shown in tables). For dietary FRAP scores, there was a significant relation with initial global scores (*P* for trend = 0.02; mean difference: 0.03 standard units; 95% CI: 0.00, 0.06 standard units, comparing extreme quintiles), but not with cognitive decline on any of the outcome measures (*P* for trend for global scores = 0.4).

In addition, there was a slight indication that smoking status might have modified the association of total FRAP scores with initial cognitive scores (*P* for interaction = 0.09 for the global score) and cognitive decline (*P* for interaction = 0.07 for the global score), with the strongest associations generally observed in non-smokers. However, there was no effect modification by smoking for the relation of dietary FRAP scores with initial cognition (*P* for trend for global scores = 0.4) or cognitive decline (*P* for trend for global scores = 0.3).

Finally, none of the 5 major food contributors to dietary FRAP scores showed significant associations with initial cognitive performance; eg, global scores were not related to intakes of caffeinated coffee (*P* for trend = 0.9), tea (*P* for trend = 0.2),

TABLE 4
Mean differences in initial cognitive function by quintiles of dietary ferric-reducing antioxidant power (FRAP) scores[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[2]
n	3202	3202	3202	3202	3202	
FRAP score (mmol/d)[3]	7.5 (6.3–8.5)	9.9 (9.2–10.6)	11.5 (10.2–12.2)	12.8 (10.7–14.1)	12.9 (10.8–15.6)	
TICS						
Model 1[4]	0.00[5]	0.10 (−0.03, 0.23)[6]	0.12 (−0.01, 0.26)	0.16 (0.03, 0.30)	0.11 (−0.02, 0.24)	0.08
Model 2[7]	0.00	0.06 (−0.07, 0.19)	0.07 (−0.07, 0.20)	0.09 (−0.04, 0.22)	0.06 (−0.07, 0.19)	0.3
Global						
Model 1[4]	0.00	0.02 (−0.01, 0.05)	0.03 (0.00, 0.06)	0.05 (0.02, 0.09)	0.04 (0.01, 0.07)	0.002
Model 2[7]	0.00	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.04)	0.03 (0.00, 0.07)	0.02 (−0.01, 0.06)	0.05
Verbal						
Model 1[4]	0.00	0.01 (−0.03, 0.04)	0.02 (−0.02, 0.06)	0.05 (0.01, 0.08)	0.03 (−0.01, 0.06)	0.03
Model 2[7]	0.00	0.00 (−0.04, 0.04)	0.00 (−0.03, 0.04)	0.03 (−0.01, 0.06)	0.01 (−0.02, 0.05)	0.2

[1] TICS, Telephone Interview of Cognitive Status. Dietary FRAP scores were averaged from 1980 until the initial cognitive interview. Results were obtained from multivariable-adjusted linear regression models.
[2] Calculated in separate multivariable-adjusted linear regression models by using the median intake of each quintile as a continuous variable.
[3] All values are medians; interquartile ranges in parentheses.
[4] Adjusted for age (continuous) and education (registered nurse, bachelor's degree, and graduate degree).
[5] Mean difference (all such values); reference.
[6] Mean difference; 95% CI in parentheses (all such values).
[7] Adjusted for age, education, antidepressant use (yes or no), smoking (never, former, or current), physical activity (in quintiles, missing), BMI (in kg/m^2; <22, 22–24, 25–29, ≥30, or missing), vitamin E supplement use (yes, no, or missing), vitamin C supplement use (yes, regular; yes, seasonal; no; or missing), multivitamin supplement use (yes, no, or missing), high blood pressure (yes or no), myocardial infarction (yes or no), and type 2 diabetes (yes or no).

TABLE 5
Mean differences in slopes of cognitive decline over 3 cognitive interviews by quintiles of dietary ferric-reducing antioxidant power (FRAP) scores[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[2]
n	3202	3202	3202	3202	3202	
FRAP score (mmol/d)[3]	7.5 (6.3–8.5)	9.9 (9.2–10.6)	11.5 (10.2–12.2)	12.8 (10.7–14.1)	12.9 (10.8–15.6)	
TICS						
Model 1[4]	0.00[5]	0.04 (0.00, 0.08)[6]	0.03 (−0.01, 0.07)	0.03 (−0.01, 0.07)	0.03 (−0.01, 0.07)	0.3
Model 2[7]	0.00	0.03 (−0.01, 0.07)	0.03 (−0.01, 0.07)	0.02 (−0.02, 0.06)	0.02 (−0.02, 0.06)	0.6
Global						
Model 1[4]	0.00	0.01 (0.00, 0.01)	0.00 (0.00, 0.01)	0.00 (−0.01, 0.01)	0.01 (0.00, 0.01)	0.3
Model 2[7]	0.00	0.00 (0.00, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (0.00, 0.01)	0.5
Verbal						
Model 1[4]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.8
Model 2[7]	0.00	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	1.0

[1] TICS, Telephone Interview of Cognitive Status. Dietary FRAP scores were averaged from 1980 until the initial cognitive interview. Results were obtained from multivariable-adjusted mixed linear regression models that included terms for continuous time, exposure, and covariates and interaction terms for exposure and each covariate with continuous time.

[2] Calculated in separate multivariable-adjusted mixed linear regression models by using the median intake of each quintile as a continuous variable.

[3] All values are medians; interquartile ranges in parentheses.

[4] Adjusted for age (continuous) and education (registered nurse, bachelor's degree, and graduate degree).

[5] Mean difference (all such values); reference.

[6] Mean difference; 95% CI in parentheses (all such values).

[7] Adjusted for age, education, antidepressant use (yes or no), smoking (never, former, or current), physical activity (in quintiles, missing), BMI (in kg/m^2; $<$22, 22–24, 25–29, $\geq$30, or missing), vitamin E supplement use (yes, no, or missing), vitamin C supplement use (yes, regular; yes, seasonal; no; or missing), multivitamin supplement use (yes, no, or missing), high blood pressure (yes or no), myocardial infarction (yes or no), and type 2 diabetes (yes or no).

decaffeinated coffee (*P* for trend = 0.5), oranges (*P* for trend = 0.9), or chocolate (*P* for trend = 0.9) in multivariate models adjusted for potential confounders. Results were also null for cognitive decline (eg, for the global score, *P* for trends ranged from 0.1 for tea intake to 0.9 for decaffeinated coffee intake).

DISCUSSION

In this cohort, we showed little relation between FRAP and cognitive health, with significant associations between total FRAP scores and initial cognitive function on some cognitive outcomes, only a borderline association with dietary FRAP scores and initial cognition on one of 3 outcomes, and no relations between FRAP scores and cognitive decline over 4 y. In addition, major food contributors to FRAP scores were unrelated to cognition in this study. Thus, overall, these results do not provide consistent evidence of an association between total antioxidant capacity of diets and cognition in older adults.

We explored a novel method for assessing total antioxidant capacity of diets by using FRAP scores, a combination of food-frequency data, and food- and supplement-specific FRAP values. An important advantage of this method was that the antioxidant capacity of both supplements and food sources were considered together in one metric. In addition, FRAP scores captured the effects of the wide variety of antioxidant nutrients available in foods, including those nutrients that were not well characterized or well measured and, thus, understudied (eg, flavonoids). Another advantage of using FRAP scores over single-nutrient dietary analyses was the ability to capture possible interactions among antioxidant nutrients in foods because the FRAP values were food specific. Finally, the use of FRAP scores eliminated issues of multiple comparisons that are inherent in analyzing multiple individual nutrient exposures.

To our knowledge, this is the first study to explore FRAP scores in relation to cognitive outcomes in later life. Our null results concurred with several randomized trials of antioxidant supplements and cognition (5–10) and observations from the Zutphen Elderly Study (35) and the Cognitive Change in Women Study (an ancillary study to the Women's Health Initiative) (36); still, 2 additional studies (37, 38) identified inverse associations between dietary antioxidants and cognitive decline. Furthermore, 2 studies showed that greater intakes of fruit and vegetables were related to less cognitive decline (14, 15); however, these studies showed the strongest effects for green, leafy vegetables, which suggested that these observations could be due to other nutrients (eg, folate). In this context, our study provided additional insight into research on antioxidants and cognition by using a more comprehensive and integrated approach to studying antioxidants than did previous studies.

Several limitations should be considered when interpreting our results. First, dietary FRAP scores were only modestly associated with plasma measurements of total antioxidant capacity in 2 previous studies (39, 40); however, most feeding studies showed that consumption of antioxidant-rich foods is significantly related to plasma FRAP measurements taken immediately after ingestion (41). Thus, plasma FRAP measurements may not provide an appropriate gold standard for dietary FRAP scores on the basis of long-term diets, which might explain the modest associations that were previously observed between FFQ-derived FRAP scores and plasma FRAP measurements. Moreover, 3 studies reported significant associations of higher dietary FRAP scores with lower levels of components of the metabolic syndrome (42), higher concentrations of adiponectin (43), and a lower risk of mortality (44). In our cohort, the median dietary FRAP score of 11.5 mmol/d was higher than the median for the study of metabolic syndrome (6.9 mmol/d), which is the only one of these studies to include the FRAP contributions of coffee and tea. Thus, dietary FRAP scores at the level reported in our cohort appeared to contain biologically meaningful information for predicting health-related outcomes, although their relation

to antioxidant status in the body has not been definitively established.

A second limitation is that our self-reported food-frequency data contain some random measurement errors, which would tend to bias our results toward the null (45). We used validated assessments for dietary intake (19), and an important advantage of averaging FRAP scores over multiple dietary reports is the reduction of random measurement errors (46); thus, our estimates of FRAP are likely as valid as possible under the circumstances. In addition, we previously identified relations between various dietary factors and cognition in this cohort (14, 32), which established our ability to detect diet-related associations in this group.

Finally, we could have had insufficient distribution of FRAP scores to identify associations with cognition in this cohort. Yet, the difference in the medians of total FRAP scores between extreme quintiles (11 mmol/d) was equivalent to the amount of FRAP contained in ≈5–6 cups of coffee or tea, which represent the top 2 dietary contributors to FRAP in our participants. The same comparison for dietary FRAP scores was equivalent to 3–4 cups of coffee or tea. Thus, we believe the exposure distribution was sufficiently broad to allow a meaningful contrast of FRAP scores.

In conclusion, the total antioxidant capacity of diets assessed by FFQ-based FRAP scores did not appear to be substantially related to cognitive health in older women. Nonetheless, because oxidative stress remains a compelling biologic hypothesis in the pathogenesis of cognitive decline, further research is needed to evaluate alternative approaches to assessing antioxidant status and its role in preventing cognitive decline.

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