

Dietary Intakes of Berries and Flavonoids in Relation to Cognitive Decline

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Objective: Berries are high in flavonoids, especially anthocyanidins, and improve cognition in experimental studies. We prospectively evaluated whether greater long-term intakes of berries and flavonoids are associated with slower rates of cognitive decline in older women.

Methods: Beginning in 1980, a semiquantitative food frequency questionnaire was administered every 4 years to Nurses' Health Study participants. In 1995–2001, we began measuring cognitive function in 16,010 participants, aged ≥ 70 years; follow-up assessments were conducted twice, at 2-year intervals. To ascertain long-term diet, we averaged dietary variables from 1980 through the initial cognitive interview. Using multivariate-adjusted, mixed linear regression, we estimated mean differences in slopes of cognitive decline by long-term berry and flavonoid intakes.

Results: Greater intakes of blueberries and strawberries were associated with slower rates of cognitive decline (eg, for a global score averaging all 6 cognitive tests, for blueberries: p -trend = 0.014 and mean difference = 0.04, 95% confidence interval [CI] = 0.01–0.07, comparing extreme categories of intake; for strawberries: p -trend = 0.022 and mean difference = 0.03, 95% CI = 0.00–0.06, comparing extreme categories of intake), after adjusting for multiple potential confounders. These effect estimates were equivalent to those we found for approximately 1.5 to 2.5 years of age in our cohort, indicating that berry intake appears to delay cognitive aging by up to 2.5 years. Additionally, in further supporting evidence, greater intakes of anthocyanidins and total flavonoids were associated with slower rates of cognitive decline (p -trends = 0.015 and 0.053, respectively, for the global score).

Interpretation: Higher intake of flavonoids, particularly from berries, appears to reduce rates of cognitive decline in older adults.

ANN NEUROL 2012;72:135–143

Substantial experimental data have established that berry supplementation enhances neuronal function and survival and ameliorates age-related cognitive impairment in rodents.^{1–7} Very small trials in older persons (≤ 15 participants) have also observed improved short-term cognitive performance with flavonoid-rich fruit juices, including blueberry juice.^{8,9} Supporting these findings, berries are particularly high in a subclass of flavonoids called anthocyanidins, which can cross the blood–brain barrier and localize in areas of learning and memory (eg, hippocampus).¹⁰ Moreover, flavonoids more generally have powerful antioxidant and anti-inflammatory properties, and both oxidative stress and inflammation are thought to be important contributors to cognitive impairment; thus, increased flavonoid con-

sumption could be a potential strategy for reducing cognitive decline in older adults.^{11–13}

However, no epidemiologic studies have specifically examined berry or anthocyanidin intake and cognition, and few large-scale epidemiologic studies have explored dietary flavonoids in relation to cognitive decline in older adults. Because easily utilized databases of diverse flavonoids recently became available, we evaluated the associations of long-term dietary intake of berries and flavonoids, including anthocyanidins, with cognitive decline in a large, prospective cohort of older women in the Nurses' Health Study. Our a priori hypothesis was that greater intake of berries and flavonoids would be associated with slower rates of cognitive decline.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.23594

Received Dec 1, 2011, and in revised form Mar 16, 2012. Accepted for publication Mar 22, 2012.

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Subjects and Methods

The Nurses' Health Study began in 1976, when 121,700 female, registered nurses, aged 30 to 55 years, completed a mailed questionnaire on their health and lifestyle. Follow-up questionnaires are sent biennially; follow-up is >90%. A food frequency questionnaire was added in 1980 and updated every 4 years. During 1995–2001, women who were ≥ 70 years old and free of stroke were invited to participate in a telephone-based study of cognitive function. For the first interview, 93% percent of eligible women participated ($n = 19,415$) and 7% refused; follow-up was >90% in the second and third interviews. Median time between the first and second interviews was 1.8 years, and between the first and third interviews it was 4.2 years. The institutional review board of Brigham and Women's Hospital approved this study, and informed consent was implied by return of the mailed questionnaire and completion of the telephone cognitive interview.

Population for Analysis

Of the 19,415 women who completed the initial cognitive interview, we excluded those who did not provide dietary data ($n = 3,405$); thus, our analytic sample consisted of 16,010 women (Supplementary Fig). Women included in our analysis were similar to those who were excluded (eg, mean age = 74.2 vs 74.4 years; mean body mass index = 26.0 vs 26.3 kg/m²; 77 vs 80% with an associate's degree, 23 vs 20% with a bachelor's degree or higher, respectively).

Dietary Assessment

We used a 61-item, Willett semiquantitative food frequency questionnaire to ascertain dietary habits in 1980, and an expanded 130-item version in 1984, 1986, and every 4 years thereafter.¹⁴ Foods were specified in a common unit or portion size (eg, $\frac{1}{2}$ cup of blueberries), and participants reported how often, on average, they consumed each food over the previous year (9 response categories ranged from "almost never" to " ≥ 6 times per day"). For each participant, the consumption frequency of each food was multiplied by its flavonoid content, and values were summed across all foods. We also calculated intakes for 31 individual flavonoids representing 6 major flavonoid subclasses (anthocyanidins, flavonols, flavones, flavanones, flavan-3-ols, and polymeric flavonoids) that are commonly found in US diets. Flavonoid information was obtained using the US Department of Agriculture database, an extensive European database (EuroFIR eBASIS, <http://www.eurofir.org>), and consultation with nutritional experts. Individual flavonoid intakes were summed to estimate total flavonoid intake.

In a validation study, intakes of major flavonoid-containing foods were found to correlate highly when measurements from the food frequency questionnaire were compared to four 1-week dietary records collected over 1 year (eg, correlations were 0.93 for tea, 0.80 for apples, 0.84 for orange juice, and 0.74 for oranges).¹⁵

Cognitive Assessment

We administered 6 cognitive tests: Telephone Interview of Cognitive Status, a telephone adaptation of the Mini-Mental State Examination; East Boston Memory Test, immediate and delayed recalls; category fluency; delayed recall of the Telephone Interview of Cognitive Status 10-word list; and digit span backward.^{16–18} In a validation study, our telephone-based cognitive battery performed well compared to detailed, in-person interviews among 61 highly educated women aged ≥ 70 years old ($\rho = 0.81$ comparing the 2 modes of assessment). Interinterviewer reliability was also high across 10 interviewers, each scoring the same cognitive interview ($\rho > 0.95$ for interviewers' scoring of each cognitive test). For analysis, we evaluated 3 primary cognitive outcomes selected a priori: 2 measures of overall cognition (a global composite score averaging all tests, and the Telephone Interview of Cognitive Status) and a verbal memory composite score, averaging 4 tests of episodic memory (which is particularly affected in early Alzheimer disease).^{19–21} Because our 6 cognitive tests were each scaled differently, we used z scores to create the 2 composite measures; specifically, we calculated the difference between each participant's individual score on a given test measure and the overall mean score for our population, and then divided by the population standard deviation. To create the global score, we averaged together z scores for all 6 cognitive tests; for the verbal score, we averaged z scores for the immediate and delayed recalls of both the East Boston Memory Test and the Telephone Interview of Cognitive Status 10-word list.

Statistical Analyses

Because cognitive decline develops over many years, long-term dietary habits are likely most relevant to brain health; thus, to obtain stable measures reflecting long-term diet, we averaged berry and flavonoid intakes from each food frequency questionnaire beginning in 1980, through each participant's last dietary report prior to initial cognitive assessment.²² Based on our a priori hypothesis, we evaluated the association of berry and anthocyanidin intake with cognitive decline as our primary analysis. Because flavonoids might have cognitive benefits more generally, we also examined other flavonoid subclasses as well as total flavonoid intake. To complement these analyses, we evaluated intakes of other flavonoid-rich foods (tea, apples, oranges, and onions) because dietary recommendations are easier to make based on foods rather than nutrients.

Multivariable-adjusted, mixed linear regression was utilized to estimate mean differences in rates of cognitive decline over approximately 4 years, across categories of berry and other flavonoid-rich food consumption (sensible categories were determined based on the distribution of intake for each food) and quintiles of flavonoid intakes. Flavonoid variables were energy adjusted using the residual method.²³ We used repeated-measures modeling with random intercepts and slopes, which permits description of individual cognitive trajectories over time and provides explicit tests regarding the relation of exposures to rates of cognitive decline. To construct our mixed models, we included terms for the exposure, covariates, and continuous

time to account for associations with initial cognitive scores, and added interaction terms for the exposure and covariates with continuous time to estimate relations with cognitive decline. We calculated 95% confidence intervals (CIs) and performed linear tests of trend using continuous variables composed of the median values of exposure categories.

We considered multiple potential confounders: age (continuous), education (associate's degree, bachelor's degree, graduate degree), antidepressant use (yes, no), smoking (never, past, current), physical activity (metabolic equivalent h/wk in quintiles, missing), body mass index (<22, 22–24, 25–30, >30kg/m²), history of high blood pressure (yes, no), history of high cholesterol (yes, no), history of type 2 diabetes (yes, no), history of myocardial infarction (yes, no), total caloric intake (kcal/day in quintiles), and dietary factors including fish intake (≤3 servings/mo, 1 serving/wk, 2–4 servings/wk, ≥5 servings/wk, missing), alcohol intake (none, 0–14g/day, >15g/day, missing), and overall dietary scores (the Alternative Healthy Eating Index and Alternative Mediterranean Diet, in quintiles). We were particularly concerned that socioeconomic status might confound associations with berries, as they tend to be relatively high-priced fruits; thus, we considered adjustments for marital status (yes, no), husband's highest level of educational attainment (high school degree or less, college degree, graduate school, missing), mother's occupation when nurse was age 16 years (upper white collar, lower white collar and skilled manual, unskilled manual, farming, other/missing), father's occupation when nurse was age 16 years (upper white collar, lower white collar and skilled manual, unskilled manual, farming, other/missing), and several variables based on the census tract of a participant's residence, geocoded to the 2000 US Census, including median annual household income (quintiles) and median home value (quintiles). Covariate status was determined at the time of initial cognitive interview.

In our model building, we evaluated initial models that were adjusted for age and education only, and then carefully considered adjustment for numerous other potential confounding factors listed above. In particular, we built several sets of models adjusting for age and education plus the following covariates in successive models: (1) antidepressant use; (2) lifestyle factors (smoking, physical activity, body mass index, alcohol intake); (3) cardiovascular factors (history of high blood pressure, high cholesterol, type 2 diabetes, and myocardial infarction); (4) dietary factors (total energy intake, fish intake, and dietary patterns); and (5) socioeconomic status (marital status, husband's highest level of educational attainment, mother's occupation when nurse was age 16 years, father's occupation when nurse was age 16 years, annual household income, and median home value). Effect estimates were very similar in all of these models, and we therefore chose to develop a parsimonious model including: age, education, alcohol intake (except in flavonoid analyses where red wine contributed to the exposure), physical activity, body mass index, total caloric intake, and annual household income. These covariates were selected because they were related to berry intake (Table 1) and were either significantly associated with cognitive decline in our participants,

or were key a priori risk factors for cognitive decline based on the literature.

In secondary analyses, we evaluated effect modification by smoking status, because smoking greatly increases oxidative stress, and berries and flavonoids could affect cognition through antioxidant mechanisms. We also repeated our analyses while excluding women in the bottom 10% of the score distribution on our initial cognitive tests, as these women may have been experiencing early stages of dementia that also caused them to reduce their intake of healthy foods, such as blueberries and strawberries.

All statistical analyses were performed in SAS version 9 (SAS Institute, Cary, NC).

Results

Blueberries and strawberries were the primary foods contributing to anthocyanidin intake in our cohort, whereas tea, apples, and oranges were the top contributors to other flavonoid subclasses and total flavonoid intake (Fig). In total, tea, apples, oranges, berries, and onions accounted for >80% of between-person variation in total flavonoid consumption in this cohort. We observed few meaningful differences in participants' characteristics at the initial cognitive interview across categories of blueberry and strawberry intake (see Table 1). However, women with the highest blueberry or strawberry intakes had somewhat higher physical activity levels and annual household income compared to those with the lowest berry intakes; as expected, total caloric intake and fish intake were both greater across increasing quintiles of berry intake. Similarly, participant characteristics did not differ markedly across categories of total flavonoid intake either (data not shown in table).

After adjustment for age and education, greater consumption of blueberries was highly associated with slower decline in the global score (p -trend = 0.010), the verbal score (p -trend = 0.016), and the Telephone Interview of Cognitive Status (p -trend = 0.027; Table 2). The mean difference in rate of global decline was 0.04 standard units over the follow-up period (95% CI = 0.01–0.07) comparing women who ate ≥1 serving of blueberries per week to those who ate <1 serving per month. Similarly, greater intake of strawberries was related to slower decline in the global and verbal scores when we adjusted for age and education (p -trends = 0.021 and 0.014, respectively); for example, women who ate ≥2 servings of strawberries per week had an average decline in the global score that was 0.03 standard units less over follow-up compared to women who ate <1 serving per week (95% CI = 0.00–0.06). To help interpret the mean differences, we found that 1 year of age in our population was associated with a mean decline of 0.02

TABLE 1: Baseline Characteristics of Women in the Nurses' Health Study by Categories of Berry Intake^a

Characteristic	Blueberry Intake			Strawberry Intake		
	<1 Serving/ mo, 35.2%	1–3 Servings/ mo, 44.8%	≥1 Serving/ wk, 20.0%	<1 Serving/ wk, 44.5%	1 Serving/ wk, 33.9%	≥2 Servings/ wk, 21.6%
Mean age, yr	74.4	74.2	74.2	74.3	74.2	74.3
Education, %						
Associate's degree	80.6	76.9	73.1	79.4	76.5	75.0
Bachelor's degree	14.1	16.8	18.8	15.1	16.8	17.6
Graduate degree	5.3	6.3	8.1	5.5	6.7	7.4
Antidepressant use, %	6.3	5.6	5.7	5.8	5.7	6.3
Smoking, %						
Never	44.9	47.1	49.5	43.9	49.2	49.1
Past	45.1	45.8	45.3	46.6	43.9	45.5
Current	10.0	7.1	5.2	9.5	6.9	5.4
Median physical activity, metabolic equivalent h/wk ^b	7.9	10.2	11.6	8.4	10.5	11.0
Body mass index, %						
<22kg/m ²	23.2	19.5	20.0	22.9	19.6	18.7
22–24kg/m ²	26.4	27.6	25.7	27.2	26.4	26.7
25–30kg/m ²	32.5	35.8	37.1	33.3	36.1	36.2
≥30kg/m ²	17.9	17.1	17.2	16.6	17.9	18.4
High blood pressure, % ^c	55.7	55.1	54.1	55.8	53.8	55.7
High cholesterol, % ^c	65.8	65.8	63.3	66.4	64.0	65.0
Type 2 diabetes, % ^c	9.4	10.0	9.9	9.0	10.2	10.7
Myocardial infarction, % ^c	5.8	6.0	5.8	6.4	5.1	6.0
Mean caloric intake, kcal/day	1,619.9	1,721.5	1,816.1	1,636.7	1,731.2	1,803.5
Fish intake, %						
≤3 servings/month	12.4	5.8	3.8	9.7	6.6	5.4
1 serving/week	24.0	16.9	12.7	22.5	16.6	13.3
2–4 servings/week	55.3	64.1	60.8	58.6	62.9	60.1
≥5 servings/week	8.3	13.2	22.7	9.2	13.9	21.2
Alcohol intake, %						
None	54.5	47.7	44.0	51.4	47.3	48.1
0–14g/day	36.4	43.7	47.8	38.9	44.1	44.9
≥15g/day	9.1	8.6	8.2	9.7	8.6	7.0
Mean score on the Alternative Healthy Eating Index, points	39.3	43.0	46.6	40.1	43.3	45.8

TABLE 1 (Continued)

Characteristic	Blueberry Intake			Strawberry Intake		
	<1 Serving/ mo, 35.2%	1–3 Servings/ mo, 44.8%	≥1 Serving/ wk, 20.0%	<1 Serving/ wk, 44.5%	1 Serving/ wk, 33.9%	≥2 Servings/ wk, 21.6%
Husband's education, %						
High school degree or less	58.0	50.1	45.5	54.1	50.8	49.3
College degree	25.5	28.5	29.7	26.6	28.5	28.6
Graduate school	16.5	21.4	24.8	19.3	20.7	22.1
Father's occupation when nurse was age 16 years, %						
Upper white collar	23.9	25.7	26.1	24.3	25.4	26.4
Lower white collar and skilled manual	59.4	58.2	59.2	59.7	58.4	57.7
Unskilled manual	3.4	3.4	3.3	3.6	3.4	3.0
Farming	13.3	12.7	11.4	12.4	12.8	12.9
Median annual household income, US dollars	\$53,607.0	\$56,484.0	\$59,635.0	\$55,645.5	\$55,785.0	\$57,912.5
Mean baseline cognitive scores ^d						
Global score, standard units	−0.03	0.02	−0.01	−0.02	0.02	−0.03
Verbal memory score, standard units	−0.03	0.01	−0.01	−0.03	0.01	−0.02
Telephone Interview of Cognitive Status, points	33.7	33.9	33.8	33.7	33.9	33.7

^aPercentages are of nonmissing values.

^bOne metabolic equivalent hour is proportional to the amount of energy spent sitting quietly for 1 hour.

^cRefers to a history of 1 of these conditions.

^dThe global score is calculated by standardizing scores (using *z* scores) on all 6 cognitive tests in our battery, and averaging them together. The verbal memory score is calculated similarly, but using only 4 tests of verbal memory. The Telephone Interview of Cognitive Status is scored from 0 to 41 points.

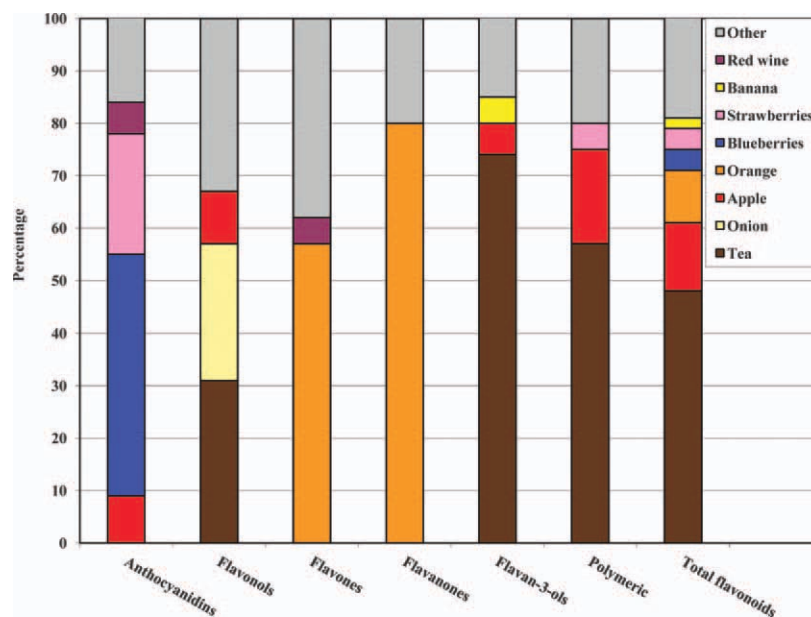


FIGURE: Top food contributors to 6 flavonoid subclasses (anthocyanidins, flavonols, flavones, flavanones, flavan-3-ols, and polymeric flavonoids) and total flavonoid intake in the Nurses' Health Study. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

TABLE 2: Mean Differences (95% CI) in Rates of Cognitive Decline over 4 Years of Follow-up, across Categories of Berry Intake^{a,b}

Score	Blueberries			<i>p</i> -trend
	<1 Serving/ mo, 35.2%	1–3 Servings/mo, 44.8%	≥1 Serving/wk, 20.0%	
Global score				
Model 1 ^c	0.00	0.02 (–0.01 to 0.04)	0.04 (0.01 to 0.07)	0.010
Model 2 ^d	0.00	0.02 (–0.01 to 0.04)	0.04 (0.01 to 0.07)	0.014
Verbal memory score				
Model 1 ^c	0.00	0.02 (–0.01 to 0.05)	0.05 (0.01 to 0.09)	0.016
Model 2 ^d	0.00	0.02 (–0.01 to 0.06)	0.05 (0.01 to 0.09)	0.022
Telephone Interview of Cognitive Status				
Model 1 ^c	0.00	0.11 (–0.01 to 0.22)	0.16 (0.02 to 0.31)	0.027
Model 2 ^d	0.00	0.11 (–0.01 to 0.23)	0.17 (0.03 to 0.32)	0.022
Score	Strawberries			<i>p</i> -trend
	<1 Serving/ wk, 44.5%	1 Serving/wk, 33.9%	≥2 Servings/wk, 21.6%	
Global score				
Model 1 ^c	0.00	0.00 (–0.03 to 0.02)	0.03 (0.00 to 0.06)	0.021
Model 2 ^d	0.00	0.00 (–0.03 to 0.02)	0.03 (0.00 to 0.06)	0.022
Verbal memory score				
Model 1 ^c	0.00	0.00 (–0.03 to 0.03)	0.04 (0.01 to 0.08)	0.014
Model 2 ^d	0.00	0.00 (–0.04 to 0.03)	0.04 (0.01 to 0.08)	0.015
Telephone Interview of Cognitive Status				
Model 1 ^c	0.00	0.01 (–0.10 to 0.13)	0.08 (–0.05 to 0.21)	0.24
Model 2 ^d	0.00	0.01 (–0.11 to 0.13)	0.09 (–0.05 to 0.22)	0.22

^aTo help interpret these mean differences, we found that 1 year of age is associated with a mean decline of 0.02 standard units on the global score, 0.02 standard units on the verbal memory score, and 0.10 points on the Telephone Interview of Cognitive Status; thus, the mean differences that we observed for extreme categories of berry intake were equivalent to approximately 1.5 to 2.5 years of aging.

^bThe global score is calculated by standardizing scores (using *z* scores) on all 6 cognitive tests in our battery, and averaging them together. The verbal memory score is calculated similarly, but using only 4 tests of verbal memory. The Telephone Interview of Cognitive Status is scored from 0 to 41 points.

^cAdjusted for age and education.

^dAdjusted for age, education, alcohol intake, physical activity, body mass index, total caloric intake, and annual household income. CI = confidence interval.

standard units on the global score over the follow-up period; thus, the mean differences that we observed comparing extreme categories of blueberry and strawberry intakes were equivalent to approximately 1.5 to 2.5 years of cognitive aging. In other words, women with higher berry intake appeared to have delayed cognitive aging by up to 2.5 years. These trends all remained similar upon adjustment for multiple potential confounders, including annual household income.

We also found that greater intake of anthocyanidins was related to cognitive decline (eg, *p*-trend = 0.015 for the global score), after adjusting for multiple potential confounders (results not shown in tables). For example, the mean difference in global score decline over the follow-up period was 0.03 standard units (95% CI = –0.01 to 0.06) comparing extreme quintiles of anthocyanidin intake. We observed a modest association for flavonols as well (eg, for the global score, *p*-trend = 0.052,

TABLE 3: Mean Differences (95% CI) in Rates of Cognitive Decline over 4 Years of Follow-up, across Quintiles of Total Flavonoid Intake^{a,b}

Flavonoid Intake/Score	Quintiles of Total Flavonoid Intake					<i>p</i> -trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Median flavonoid intake, mg/day	145.4	220.5	297.7	412.0	684.1	
Global composite score						
Model 1 ^c	0.00	0.01 (−0.02 to 0.05)	0.01 (−0.02 to 0.05)	0.02 (−0.01 to 0.05)	0.04 (0.00 to 0.07)	0.029
Model 2 ^d	0.00	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)	0.02 (−0.02 to 0.05)	0.03 (0.00 to 0.07)	0.053
Verbal memory composite score						
Model 1 ^c	0.00	0.03 (−0.02 to 0.07)	0.04 (−0.01 to 0.08)	0.04 (0.00 to 0.09)	0.05 (0.01 to 0.09)	0.028
Model 2 ^d	0.00	0.02 (−0.02 to 0.07)	0.03 (−0.01 to 0.08)	0.04 (0.00 to 0.08)	0.05 (0.00 to 0.09)	0.040
Telephone Interview of Cognitive Status						
Model 1 ^c	0.00	0.08 (−0.08 to 0.24)	0.02 (−0.14 to 0.18)	0.04 (−0.11 to 0.20)	0.18 (0.02 to 0.33)	0.041
Model 2 ^d	0.00	0.06 (−0.09 to 0.22)	0.00 (−0.16 to 0.16)	0.03 (−0.13 to 0.19)	0.15 (−0.01 to 0.31)	0.072

^aTo help interpret these mean differences, we found that 1 year of age is associated with a mean decline of 0.02 standard units on the global score, 0.02 standard units on the verbal memory score, and 0.10 points on the Telephone Interview of Cognitive Status; thus, the mean differences that we observed for extreme quintiles of total flavonoid intake were equivalent to approximately 1.5 to 2.5 years of aging.

^bThe global score is calculated by standardizing scores (using *z* Scores) on all 6 cognitive tests in our battery, and averaging them together. The verbal memory score is calculated similarly, but using only 4 tests of verbal memory. The telephone Interview of Cognitive Status is scored from 0 to 41 points.

^cAdjusted for age and education.

^dAdjusted for age, education, physical activity, body mass index, total caloric intake, and annual household income.

mean difference = 0.03, 95% CI = 0.00–0.07 comparing extreme quintiles of flavonol intake). Overall, qualitatively, we found suggestions of reduced cognitive decline with higher flavonoid intake across most flavonoid subclasses.

Consistent with these results, higher total flavonoid intake was associated with slower rates of cognitive decline for all 3 of our primary outcome measures in age- and education-adjusted models (eg, *p*-trend = 0.029 for the global score; Table 3). For example, women in the highest quintile of total flavonoid intake had an average decline in the global score that was 0.04 standard units less over the follow-up period (95% CI = 0.00–0.07) compared to women in the lowest quintile. These results were very similar when we additionally adjusted for multiple potential confounders, and mean differences in decline were equivalent to 1.5 to 2.5 years of cognitive aging. When we examined other important food contribu-

tors to flavonoid intake, consumption of tea, apples, onions, and oranges was not related to cognitive decline (eg, for the global score, for tea: *p*-trend = 0.23, mean difference = 0.02, 95% CI = −0.02 to 0.06 comparing extreme categories of intake; for apples: *p*-trend = 0.84, mean difference = 0.01, 95% CI = −0.03 to 0.04 comparing extreme categories of intake; for onions: *p*-trend = 0.095, mean difference = 0.02, 95% CI = −0.02 to 0.06 comparing extreme categories of intake; and for oranges: *p*-trend = 0.69, mean difference = 0.01, 95% CI = −0.02 to 0.04 comparing extreme categories of intake; results not shown in tables).

Finally, in secondary analyses, smoking status did not modify the associations of berries, flavonoids, and cognitive decline, and results were nearly identical when we excluded women with the lowest cognitive scores at our initial cognitive interview (results not shown in tables).

Discussion

Higher, long-term consumption of berries, anthocyanidins, and total dietary flavonoids were related to significantly slower rates of cognitive decline in this cohort of older women, even after careful consideration of confounding by socioeconomic status. We report the first epidemiologic evidence that greater intakes of blueberries and strawberries (top food contributors to anthocyanidin intake) were highly associated with slower rates of cognitive decline, consistent with a large body of experimental data supporting cognitive benefits of berries. The magnitude of associations that we identified for berries and flavonoids were equivalent to the cognitive differences that we observed in women up to 2.5 years apart in age; that is, women with higher intake of berries and total flavonoids appeared to have delayed cognitive aging by as much as 2.5 years.

Very small trials have indicated that berry supplementation can enhance cognitive function over 12 weeks in older adults with early cognitive impairments.^{8,9} In a study of older men ($N = 342$), total flavonoid consumption was related to a lower risk of cognitive impairment, although findings were not statistically significant (comparing the top versus bottom tertiles: odds ratio = 0.86, 95% CI = 0.39–1.89).²⁴ However, this study had limited power to detect associations between flavonoids and cognition due to its modest size. A larger study in France ($N = 1,640$) identified a relation between greater flavonoid intake and slower cognitive decline over a 10-year period (p -trend = 0.05 in models adjusted for age, sex, and education).²⁵ These results were attenuated and became nonsignificant upon adjustment for smoking, body mass index, and fruit and vegetable intake; however, the inclusion of fruit and vegetable intake probably represents overadjustment, because these foods contain flavonoids, and therefore the adjusted results are difficult to interpret. In all of these studies, no specific information on long-term dietary habits was available; as previously noted, long-term diet is likely to be most relevant for cognitive decline. In our data, correlations were modest across repeated measures of berry intake ($\rho = 0.2$ – 0.3), which probably reflects true within-person changes in berry consumption over time (eg, due to changes in berry availability by year and region^{26,27}) and also reflects some amount of random measurement error. By averaging reported intakes over multiple dietary assessments, we account for within-person changes in intake and also reduce random measurement error (as has been previously documented by our group²⁸). Thus, for biologic and statistical reasons, existing epidemiologic data probably underestimate any relation between flavonoids and cognition.

Substantial biologic evidence supports our finding that berry and flavonoid intake may be related to cognition. Berry-derived anthocyanidins are uniquely and specifically capable of both crossing the blood–brain barrier and localizing in brain regions involved in learning and memory (eg, the hippocampus).¹⁰ In multiple studies of rats, blueberry or strawberry supplementation significantly reduced age-related declines in neuronal signaling and cognitive behavior, and supplementation at older ages reversed neuronal and cognitive decline.²⁹ More generally, several flavonoids have been shown to inhibit the c-jun N-terminal kinases, apoptosis signal-regulating kinase-1, and p38 pathways, which can lead to reductions in neuroinflammation and enhanced neuronal viability. In addition, flavonoid-rich foods can activate extracellular receptor kinase and protein kinase B/Akt pathways, which are thought to enhance memory and cognition. Overall, although flavonoids are traditionally regarded as beneficial because of their antioxidant properties, the discovery of these various molecular targets suggests that flavonoids may act through multiple mechanisms; this might explain why, other than a specific effect of anthocyanidins, we largely observed that greater overall flavonoid intake appeared more important than any single flavonoid subclass or flavonoid-rich food.

Our study has limitations. First, this is an observational study, and we cannot rule out the possibility that residual confounding explains observed associations. However, we adjusted for a large variety of health and lifestyle factors, as well as socioeconomic and dietary variables, and observed very little change in our effect estimates before and after adjustment, which suggests that residual confounding is unlikely to further influence our findings meaningfully. Second, the self-reported dietary information contains some random misclassification; however, this would tend to bias our results toward the null and therefore cause an underestimation of the relation between flavonoids and cognition. Finally, we identified associations between higher berry and flavonoid intake and slower cognitive decline in an all-female cohort, and therefore our results could be limited in their generalizability to men. Yet, few existing studies have reported substantial sex differences in dietary risk factors for cognitive decline and dementia, suggesting that limited generalizability is probably not a large concern in our study. Nonetheless, future studies should consider men in analyses of berries, flavonoids, and cognitive decline.

In conclusion, we found that higher consumption of berries and anthocyanidins, as well as total flavonoids, is associated with a slower progression of cognitive decline in older women. These findings potentially have

substantial public health implications, as increasing berry intake represents a fairly simple dietary modification to test in older adults for maintaining cognition.

Acknowledgments

This study was funded by grants from the NIH National Cancer Institute (P01 CA87969) and the California Strawberry Commission. E.E.D. received a postdoctoral fellowship from the NIH National Institute on Aging (F32 AG031633) to carry out this work.

Potential Conflicts of Interest

Nothing to report.

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