RESEARCH ARTICLE

Long-term Dietary Flavonoid Intake and Subjective Cognitive Decline in US Men and Women

Tian-Shin Yeh, MD, PhD, Changzheng Yuan, ScD, Alberto Ascherio, MD, DrPH, Bernard A. Rosner, PhD, Walter C. Willett, MD, DrPH, and Deborah Blacker, MD, ScD

Neurology® 2021;97:e1041-e1056. doi:10.1212/WNL.0000000000012454

Correspondence
Dr. Willett
walter.willett@channing.harvard.edu

Abstract

Objective

To prospectively examine the associations between long-term dietary flavonoids and subjective cognitive decline (SCD).

Methods

We followed 49,493 women from the Nurses' Health Study (NHS) (1984–2006) and 27,842 men from the Health Professionals Follow-Up Study (HPFS) (1986–2002). Poisson regression was used to evaluate the associations between dietary flavonoids (flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, polymeric flavonoids, and proanthocyanidins) and subsequent SCD. For the NHS, long-term average dietary intake was calculated from 7 repeated semiquantitative food frequency questionnaires (SFFQs), and SCD was assessed in 2012 and 2014. For the HPFS, average dietary intake was calculated from 5 repeated SFFQs, and SCD was assessed in 2008 and 2012.

Results

Higher intake of total flavonoids was associated with lower odds of SCD after adjustment for age, total energy intake, major nondietary factors, and specific dietary factors. In a comparison of the highest vs the lowest quintiles of total flavonoid intake, the pooled multivariable-adjusted odds ratio (OR) of 3-unit increments in SCD was 0.81 (95% confidence interval [CI] 0.76, 0.89). In the pooled results, the strongest associations were observed for flavones (OR 0.62 [95% CI 0.57, 0.68]), flavanones (0.64 [0.58, 0.68])], and anthocyanins (0.76 [0.72, 0.84]) (p trend <0.001 for all groups). The dose-response curve was steepest for flavones, followed by anthocyanins. Many flavonoid-rich foods such as strawberries, oranges, grapefruits, citrus juices, apples/pears, celery, peppers, and bananas, were significantly associated with lower odds of SCD.

Conclusion

Our findings support a benefit of higher flavonoid intakes for maintaining cognitive function in US men and women.

MORE ONLINE

CME Course
NPub.org/cmelist

From the Departments of Epidemiology (T.-S.Y., A.A., W.W., D.B.), Nutrition (T.-S.Y., A.A., W.W., C.Y.), and Biostatistics (B.R.), Harvard T.H. Chan School of Public Health, Harvard University; Channing Division of Network Medicine (T.-S.Y., A.A., W.W., C.Y., B.R.), Brigham and Women's Hospital and Harvard Medical School, Boston, MA; School of Public Health (C.Y.), Zhejiang University, Hangzhou, China; Department of Medicine (B.R.), Harvard Medical School; and Department of Psychiatry (D.B.), Massachusetts General Hospital, Harvard Medical School, Boston.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **HPFS** = Health Professionals Follow-Up Study; **NHS** = Nurses' Health Study; **OR** = odds ratio; **SCD** = subjective cognitive decline; **SFFQ** = semiquantitative food frequency questionnaire; **SU.VI.MAX** = Supplementation en Vitamines et Mineraux Antioxydants; **USDA** = US Department of Agriculture.

The world is experiencing rapid aging, and the global prevalence of age-related cognitive decline and dementia is expected to rise substantially.[1] The functional disability of cognitive decline and dementia[2] not only affects patients but also greatly burdens family and society.[1] Effective treatments for dementia are still lacking, highlighting the importance of preventive strategies. Subjective cognitive decline (SCD)—when self-perceived cognitive decline is present but objective cognitive impairments cannot be detected—may occur before clinically apparent mild cognitive impairment and dementia.[3] The cerebral pathologies that contribute to dementia may develop for years or even decades before SCD.[4] The long preclinical phase of dementia may be a critical window for prevention.[5] Among the modifiable risk factors for cognitive decline, diet has received growing attention.[6]

Flavonoids are a group of naturally occurring phytochemicals found in plants[7] and have long been considered to be powerful antioxidants.[8] Considering the likely role of oxidative stress in age-related cognitive decline,[9] flavonoids have been proposed as potentially effective agents for preventing deterioration of cognitive function.[10] Although some small, short-term intervention trials have provided some evidence to support the beneficial role of flavonoids in cognitive decline,[11,12] epidemiologic studies have remained inconclusive.[13-20] Furthermore, whether different flavonoid subclasses and specific foods contributing to flavonoid intake possess distinct relationships with cognitive function is unclear. Therefore, we investigated the relationships between intake of flavonoids and subsequent SCD using comprehensive repeated dietary assessments from >20 years of follow-up in 2 large prospective cohorts of men and women.

Methods

Standard Protocol Approvals, Registrations, and Participant Consents

The study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital. Informed consent was obtained from all participants.

Study Design

The Nurses' Health Study (NHS) began in 1976 in the United States with 121,701 female registered nurses aged 30 to 55 years. Participants have been followed up via biennial questionnaires that included information on potential risk factors and newly diagnosed diseases. Dietary information was collected in 1980, 1984, and 1986 and then every 4 years with the semiquantitative food frequency questionnaire (SFFQ) that has been validated in multiple studies.[21] Starting in 2012, 49,693 women completed questions on SCD. Follow-up rates have been ≈90% for each 2-year cycle.

The Health Professionals Follow-up Study (HPFS) began in 1986 with 51,529 male US health professionals 40 to 75 years of age. Detailed questionnaires have been sent biennially to participants to update information on lifestyle risk factors and medical history.[22] Starting in 1986 and continuing every 4 years, participants have been asked to complete the SFFQ.

Assessment of Dietary Flavonoid Intake

Dietary assessments were done with the SFFQs (available at online through Channing Division of Network Medicine, Brigham and Women's Hospital). Participants were asked how often, on average, they consumed each food of a standard portion size in the previous year. For the NHS, follow-up began in 1984 when the first comprehensive SFFQ was administered with 131 items. Average intakes of total flavonoids, flavonoids subclasses, other nutrients/foods, and total energy were calculated from 7 repeated SFFQs collected in 1984, 1986, and every 4 years until 2006. This approach can reduce within-participant variation and best represent long-term diet.[23] For the HPFS, dietary data have been updated every 4 years since 1986 with the SFFQ. Average dietary intake was calculated from the 5 repeated SFFQs collected in 1986 and every 4 years until 2002.

A database for the assessment of different flavonoid subclasses intakes was constructed as previously described, using the US Department of Agriculture (USDA) database and a European database (EuroFIR eBASIS) as main sources.[24] In short, the intake of different flavonoid subclasses was calculated by multiplying the flavonoid content of each food by its consumption frequency. We focused on the following 6 subclasses, which are commonly consumed in the Western diet: flavonols (isorhamnetin, kaempferol, quercetin, and myricetin), flavones (apigenin and luteolin), flavanones (eriodictyol, hesperetin, and naringenin), flavan-3-ol monomers (catechins, epicatechins, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, and gallocatechins), anthocyanins (cyanidin, delphinidin, malvidin, pelargonin, peonidin, and petunidin), and polymers (proanthocyanidins, theaflavins, and thearubigins). The sum of all subclasses was defined as total flavonoids. Proanthocyanidins, the sum of monomers and polymers of the repetitive flavonol units,[25] were also examined, given their possible neuroprotective

effects.[26] Intakes of total flavonoids, flavonoid subclasses, and major flavonoid-containing foods measured by the SFFQ were generally highly correlated with weighed dietary records (e.g., correlations were 0.80 for apples, 0.84 for orange juice, and 0.93 for tea).[27]

Assessment of SCD

SCD was assessed twice by mailed or online questionnaires (2012 and 2014 for the NHS, 2008 and 2012 for the HPFS). In our prior work,[28] we used the term subjective cognitive function, but we have updated the terminology in keeping with changes in the field (our outcome assessment met the definition of SCD as self-reported and persistent deterioration in cognitive function).[29] The SCD scores for the HPFS were based on 6 yes/no questions on the recent change in general memory, executive function, attention, and visuospatial skills: (1) "Do you have more trouble than usual remembering recent events?" (2) "Do you have more trouble than usual remembering a short list of items, such as a shopping list?" (3) "Do you have trouble remembering things from one second to the next?" (4) "Do you have any difficulty in understanding things or following spoken instructions?" (5) "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?" (6) "Do you have trouble finding your way around familiar streets?" The SCD scores for the NHS included 1 additional question: "Have you recently experienced any change in your ability to remember things?"[30] Equal value was assigned to each question, 1 point for every "yes." The average of the 2 SCD scores was used to reduce random errors. For participants who completed only 1 of the 2 SCD questionnaires, that 1 assessment was then used as their SCD score. We stopped updating dietary data 6 years before SCD assessment to minimize reverse causation, that is, the possible effects of altered cognitive function on diet.

Validity of SCD assessment has been documented by its strong association with both concurrent objective cognitive function[30] and subsequent cognitive decline,[30] especially for those with a high level of education.[31] The strong association between *APOE* ε4 genotype and our SCD score in both the NHS and HPFS further strengthened the validity of this score.[28] In addition, risk factors for dementia such as heavy smoking, cardiovascular disease (CVD), high blood pressure, high blood cholesterol, depression, and type 2 diabetes were all related to low subsequent SCD scores.

Covariates

Information on covariates of interest was collected prospectively in the NHS and HPFS baseline and follow-up questionnaires. Covariates of interest included age, body mass index (kilograms per meters squared), physical activity (metabolic equivalents-hours per week), race (White, Black, other), multivitamin use (yes/no), smoking status (pack-years), alcohol consumption, diabetes, high blood pressure, elevated cholesterol, CVD (stroke, myocardial infarction, angina, or coronary artery surgery), cancer (prostate, colon/rectum, melanoma, lymphoma, leukemia, or other cancer), family history of dementia, and depression (defined as antidepressant use or self-reported depression). For the NHS, information on postmenopausal status and hormone replacement therapy use, parity (nulliparous, 1–2, >2), education (registered nursing degrees, bachelor degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), and Census tract income ($50,000/y, $50,000/y–$69,999/y, or $70,000/y) was available; for the HPFS, information on profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian) was obtained.

Population for Analysis

For both the NHS and HPFS, we excluded individuals with >70 food items blank, those with extreme energy intakes (<600 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men), and participants who developed Parkinson disease before SCD assessments because they may also experience cognitive impairment. The final analysis included 49,493 women with a mean age of 48 years at baseline in 1984 and 27,842 men with a mean age of 51 years at enrollment in 1986 (efigure 1 available from Dryad [doi.org/10.5061/dryad.p5hqbzkpj]).

Statistical Analysis

Age-standardized characteristics of participants were calculated according to quintiles of total flavonoid intakes. Because of the distribution and nature of the SCD scores, Poisson regression was used to evaluate the associations between flavonoid intakes and flavonoid-containing foods with SCD. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Because ≥3 positive SCD questions have been used to indicate poor cognitive function,[30] ORs (95% CIs) for 3-unit increments in SCD were calculated. To be consistent with the time frame of dietary assessments, average covariate information from 1984 to 2006 was used for the NHS; information from 1986 to 2002 was used for the HPFS. Because the relationship between age and SCD was nonlinear, a quadratic term and a linear term for age were included in the model, and age-adjusted associations were calculated. In multivariate analyses, age, total energy intake, race, smoking history, physical activity level, body mass index, intakes of alcohol, family history of dementia, missing indicator for SCD measurement if 1 of the 2 assessments was missing, number of dietary assessments during the follow-up period, and multivitamin use were included as covariates. For the NHS, the following variables were also included: parity, postmenopausal status and hormone replacement therapy use, Census tract income, education, and husband's education; for the HPFS, profession was included. Hypertension, diabetes, elevated cholesterol, and CVD were not adjusted for in our primary analysis because these variables may be mediators on the causal pathway, although results remained similar when these variables were included. To examine whether the associations were independent of other nutrients/antioxidants, we further adjusted for total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid in the final model. Missing indicators were included in the model for variables

Table 1 Characteristics[a] of NHS and HPFS Participants by Quintiles of Total Flavonoid Intake

	Quintile of total flavonoid intake				
	1	2	3	4	5
NHS (49,493 women)					
Age at study baseline, mean (SD), y	47.4 (6.4)	48.3 (6.5)	48.8 (6.6)	48.8 (6.7)	48.5 (6.7)
Total energy intake, mean (SD), kcal/d	1,697 (424)	1,749 (414)	1,769 (421)	1,758 (416)	1,699 (409)
Total flavonoids, mean (SD), mg/d	143 (32)	217 (18)	284 (22)	382 (38)	699 (251)
Flavonols, mean (SD), mg/d	10.5 (3.9)	13.4 (4.0)	15.7 (4.2)	19.0 (4.6)	28.2 (8.5)
Flavones, mean (SD), mg/d	1.6 (0.8)	2.1 (0.9)	2.4 (1.0)	2.5 (1.1)	2.3 (1.1)
Flavanones, mean (SD), mg/d	28.0 (19.0)	40.3 (22.6)	45.2 (25.0)	46.8 (26.5)	44.6 (28.3)
Flavan-3-ols, mean (SD), mg/d	13.4 (5.4)	22.1 (6.9)	32.6 (9.5)	52.7 (14.2)	126.1 (60.5)
Total anthocyanins, mean (SD), mg/d	8.3 (5.1)	13.2 (7.2)	16.8 (9.9)	19.2 (13.2)	18.6 (15.7)
Polymeric flavonoids, mean (SD), mg/d	80 (25)	125 (28)	169 (37)	243 (62)	527 (326)
Proanthocyanidins, mean (SD), mg/d	75 (23)	106 (27)	128 (34)	146 (44)	177 (57)
Alcohol, mean (SD), g/d	6.7 (10.0)	6.0 (8.3)	5.8 (8.2)	5.5 (7.7)	4.8 (7.3)
BMI, mean (SD), kg/m^2	26.5 (4.9)	26.2 (4.7)	26.1 (4.6)	25.9 (4.5)	25.9 (4.6)
Physical activity, mean (SD), MET-h/wk	14.8 (13.4)	18.0 (15.0)	19.8 (16.8)	20.8 (17.9)	19.4 (16.6)
Smoking pack-years, n (%)					
Never smoked	3,861 (39.0)	4,566 (46.1)	4,765 (48.1)	4,832 (48.8)	4,999 (50.5)
≤4 pack-y	866 (8.7)	1,083 (10.9)	1,136 (11.5)	1,251 (12.6)	1,082 (10.9)
5–24 pack-y	2,099 (21.2)	2,375 (24.0)	2,327 (23.5)	2,269 (22.9)	2,154 (21.8)
≥25 pack-y	2,921 (29.5)	1,720 (17.4)	1,493 (15.1)	1,374 (13.9)	1,518 (15.3)
Missing	152 (1.5)	153 (1.5)	179 (1.8)	173 (1.7)	145 (1.5)
Depression, n (%)	2,029 (20.5)	1,930 (19.5)	1,871 (18.9)	1,911 (19.3)	1,831 (18.5)
Postmenopausal status, n (%)					
Premenopause	40 (0.4)	40 (0.4)	29 (0.3)	49 (0.5)	45 (0.5)
Postmenopause and never use hormone	2,237 (22.6)	2,029 (20.5)	1,908 (19.3)	1,990 (20.1)	2,199 (22.2)
Postmenopause and ever use hormone	7,137 (72.1)	7,353 (74.3)	7,533 (76.1)	7,434 (75.1)	7,166 (72.4)
Missing	485 (4.9)	475 (4.8)	430 (4.3)	426 (4.3)	488 (4.9)
Parity, n (%)					
Nulliparous	454 (4.6)	551 (5.6)	495 (5.0)	535 (5.4)	540 (5.5)
1–2	641 (6.5)	658 (6.6)	663 (6.7)	666 (6.7)	666 (6.7)
≥3	8,624 (87.1)	8,526 (86.2)	8,564 (86.5)	8,514 (86.0)	8,503 (85.9)
Missing	180 (1.8)	162 (1.6)	178 (1.8)	184 (1.9)	189 (1.9)
Dietary intake, mean (SD), servings/d					
Sweets/desserts	1.3 (0.9)	1.3 (0.9)	1.2 (0.8)	1.2 (0.9)	1.2 (0.9)
Whole grain	1.2 (0.8)	1.4 (0.8)	1.5 (0.8)	1.5 (0.8)	1.4 (0.8)
Refined grain	1.6 (0.9)	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)
Sugar-sweetened beverages	0.3 (0.5)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.2 (0.4)
Total carotenoids, μg/d	13,174 (4,580)	14,796 (4,753)	15,714 (5,025)	16,278 (5,436)	15,772 (5,431)

Continued

Table 1 Characteristics[a] of NHS and HPFS Participants by Quintiles of Total Flavonoid Intake *(continued)*

	Quintile of total flavonoid intake				
	1	2	3	4	5
HPFS (27,842 men)					
Age at study baseline, mean (SD), y	49.8 (7.9)	50.8 (8.2)	51.1 (8.1)	51.8 (8.3)	51.7 (8.2)
Total energy intake, mean (SD), kcal/d	1,968 (525)	2,018 (524)	2,025 (515)	2,000 (513)	1,956 (499)
Total flavonoids, mean (SD), mg/d	147 (34)	224 (18)	291 (21)	381 (35)	681 (251)
Flavonols, mean (SD), mg/d	11.7 (4.8)	14.8 (5.1)	17.3 (5.2)	20.4 (5.8)	29.7 (9.6)
Flavones, mean (SD), mg/d	1.7 (1.0)	2.5 (1.0)	2.9 (1.3)	3.2 (1.4)	3.2 (1.7)
Flavanones, mean (SD), mg/d	32.0 (21.6)	48.6 (26.6)	57.6 (31.4)	64.7 (37.4)	63.8 (42.1)
Flavan-3-ols, mean (SD), mg/d	14.9 (6.9)	22.8 (8.0)	31.5 (10.3)	46.5 (15.3)	112.8 (61.9)
Total anthocyanins, mean (SD), mg/d	7.2 (4.8)	11.7 (6.8)	15.4 (8.9)	19.1 (13.2)	21.6 (20.8)
Polymeric flavonoids, mean (SD), mg/d	81 (27)	126 (30)	170 (38)	239 (60)	506 (296)
Proanthocyanidins, mean (SD), mg/d	79 (25)	115 (29)	144 (38)	171 (55)	213 (84)
Alcohol, mean (SD), g/d	12.5 (14.7)	11.9 (13.3)	11.5 (12.4)	10.5 (11.8)	10.1 (11.9)
BMI, mean (SD), kg/m^2	26.3 (3.5)	26.0 (3.3)	25.8 (3.2)	25.7 (3.1)	25.8 (3.2)
Physical activity, mean (SD), MET-h/wk	23.6 (18.5)	28.0 (20.6)	30.3 (21.4)	30.7 (22.3)	30.0 (22.0)
Smoking pack-years, n (%)					
Never smoked	2,325 (41.8)	2,753 (49.4)	2,857 (51.3)	2,910 (52.3)	2,856 (51.3)
≤24 pack-y	1,592 (28.6)	1,536 (27.6)	1,650 (29.6)	1,642 (29.5)	1,620 (29.1)
25–44 pack-y	831 (14.9)	670 (12.0)	553 (9.9)	555 (10.0)	557 (10.0)
≥45 pack-y	501 (9.0)	307 (5.5)	206 (3.7)	186 (3.3)	234 (4.2)
Missing	318 (5.7)	304 (5.5)	302 (5.4)	276 (5.0)	301 (5.4)
Depression, n (%)	362 (6.5)	312 (5.6)	329 (5.9)	251 (4.5)	306 (5.5)
Profession, n (%)					
Dentist	2,928 (52.6)	3,083 (55.4)	3,276 (58.8)	3,344 (60.0)	3,334 (59.9)
Pharmacist	544 (9.8)	503 (9.0)	444 (8.0)	417 (7.5)	431 (7.7)
Optometrist	421 (7.6)	396 (7.1)	382 (6.9)	357 (6.4)	333 (6.0)
Osteopath	237 (4.3)	216 (3.9)	216 (3.9)	259 (4.7)	206 (3.7)
Podiatrist	165 (3.0)	139 (2.5)	133 (2.4)	132 (2.4)	123 (2.2)
Veterinarian	1,272 (22.8)	1,233 (22.1)	1,117 (20.1)	1,060 (19.0)	1,141 (20.5)
Dietary intake, mean (SD), servings/d					
Sweets/desserts	1.4 (1.0)	1.6 (1.1)	1.8 (1.1)	1.8 (1.1)	1.7 (1.1)
Whole grain	0.6 (0.4)	0.6 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
Refined grain	0.4 (0.3)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
Sugar-sweetened beverages	2.0 (1.2)	1.9 (1.1)	1.9 (1.0)	1.8 (1.0)	1.7 (1.0)
Total carotenoids, μg/d	15,176 (6,410)	17,280 (6,420)	18,453 (6,625)	19,635 (7,224)	19,656 (8,174)

Abbreviations: BMI = body mass index; MET = metabolic equivalents.
[a] Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population. All values were averaged over the follow-up period except for age at baseline.

Table 2 ORs (95% CIs) for Associations Between Flavonoid Subclass Intakes and SCD

	Quintile of intakes						
	1	2	3	4	5	*p* for Trend	Continuous[a]
Total flavonoids							
NHS median intake, mg/d	149	217	282	377	618		
Model 1	Ref	0.89 (0.82–0.96)	0.76 (0.70–0.82)	0.79 (0.72–0.85)	0.73 (0.67–0.79)	<0.001	0.85 (0.80–0.90)
Model 2	Ref	0.94 (0.87–1.02)	0.83 (0.77–0.90)	0.88 (0.81–0.96)	0.81 (0.74–0.88)	<0.001	0.89 (0.84–0.94)
HPFS median intake, mg/d	153	224	290	377	601		
Model 1	Ref	0.96 (0.84–1.09)	0.79 (0.69–0.90)	0.78 (0.68–0.89)	0.75 (0.66–0.86)	<0.001	0.84 (0.77–0.92)
Model 2	Ref	1.02 (0.89–1.16)	0.87 (0.76–1.00)	0.90 (0.78–1.03)	0.86 (0.75–0.99)	0.02	0.91 (0.83–0.99)
Meta-analyzed results (model 2)	Ref	0.97 (0.89–1.03)	0.84 (0.79–0.91)	0.89 (0.81–0.94)	0.81 (0.76–0.89)	<0.001	0.89 (0.86–0.94)
Flavonols							
NHS median intake, mg/d	9.16	12.6	15.6	19.6	27.6		
Model 1	Ref	0.90 (0.83–0.97)	0.82 (0.75–0.89)	0.89 (0.82–0.96)	0.74 (0.68–0.80)	<0.001	0.83 (0.78–0.89)
Model 2	Ref	0.98 (0.90–1.07)	0.95 (0.87–1.03)	1.06 (0.97–1.15)	0.90 (0.83–0.98)	0.07	0.95 (0.89–1.02)
HPFS median intake, mg/d	9.78	13.6	17.0	21.2	29.8		
Model 1	Ref	0.89 (0.78–1.01)	0.81 (0.71–0.93)	0.81 (0.71–0.93)	0.74 (0.65–0.85)	<0.001	0.83 (0.75–0.91)
Model 2	Ref	0.97(0.85–1.11)	0.96 (0.83–1.10)	1.01 (0.88–1.17)	0.97 (0.84–1.12)	0.91	1.01 (0.91–1.12)
Meta-analyzed results (model 2)	Ref	0.97 (0.91–1.06)	0.94 (0.89–1.03)	1.06 (0.97–1.13)	0.91 (0.86–1.00)	0.08	0.97 (0.91–1.03)
Flavones							
NHS median intake, mg/d	0.99	1.56	2.04	2.60	3.49		
Model 1	Ref	0.77 (0.71–0.83)	0.72 (0.67–0.78)	0.57 (0.53–0.62)	0.51 (0.47–0.56)	<0.001	0.57 (0.54–0.61)
Model 2	Ref	0.80 (0.74–0.87)	0.78 (0.72–0.85)	0.63 (0.58–0.69)	0.60 (0.54–0.65)	<0.001	0.66 (0.61–0.71)
HPFS median intake, mg/d	1.16	1.88	2.51	3.18	4.40		
Model 1	Ref	0.93 (0.82–1.06)	0.78 (0.69–0.89)	0.65 (0.57–0.74)	0.54 (0.47–0.62)	<0.001	0.57 (0.51–0.63)
Model 2	Ref	0.99 (0.87–1.13)	0.88 (0.77–1.01)	0.76 (0.66–0.88)	0.68 (0.58–0.79)	<0.001	0.68 (0.61–0.77)
Meta-analyzed results (model 2)	Ref	0.86 (0.79–0.91)	0.81 (0.74–0.86)	0.68 (0.62–0.72)	0.62 (0.57–0.68)	<0.001	0.66 (0.62–0.70)
Flavanones							
NHS median intake, mg/d	12.2	25.0	37.0	51.1	74.3		
Model 1	Ref	0.89 (0.82–0.96)	0.79 (0.73–0.86)	0.67 (0.61–0.72)	0.59 (0.54–0.64)	<0.001	0.62 (0.58–0.66)
Model 2	Ref	0.92 (0.85–1.00)	0.83 (0.77–0.91)	0.71 (0.65–0.77)	0.63 (0.58–0.69)	<0.001	0.66 (0.62–0.71)
HPFS median intake, mg/d	14.9	31.9	48.1	66.2	96.5		
Model 1	Ref	0.88 (0.77–1.00)	0.81 (0.71–0.92)	0.67 (0.58–0.76)	0.55 (0.48–0.63)	<0.001	0.59 (0.53–0.66)
Model 2	Ref	0.89 (0.78–1.02)	0.87 (0.76–0.99)	0.73 (0.64–0.84)	0.65 (0.56–0.75)	<0.001	0.68 (0.60–0.76)
Meta-analyzed results (model 2)	Ref	0.91 (0.86–0.97)	0.84 (0.79–0.91)	0.72 (0.66–0.76)	0.64 (0.58–0.68)	<0.001	0.66 (0.62–0.70)
Flavan-3-ols							
NHS median intake, mg/d	12.2	20.9	32.1	52.7	109		
Model 1	Ref	0.83 (0.77–0.90)	0.86 (0.79–0.93)	0.83 (0.77–0.90)	0.82 (0.76–0.89)	0.001	0.93 (0.88–0.98)
Model 2	Ref	0.88 (0.81–0.96)	0.91 (0.84–0.99)	0.90 (0.83–0.97)	0.87 (0.80–0.94)	0.02	0.94 (0.90–0.99)

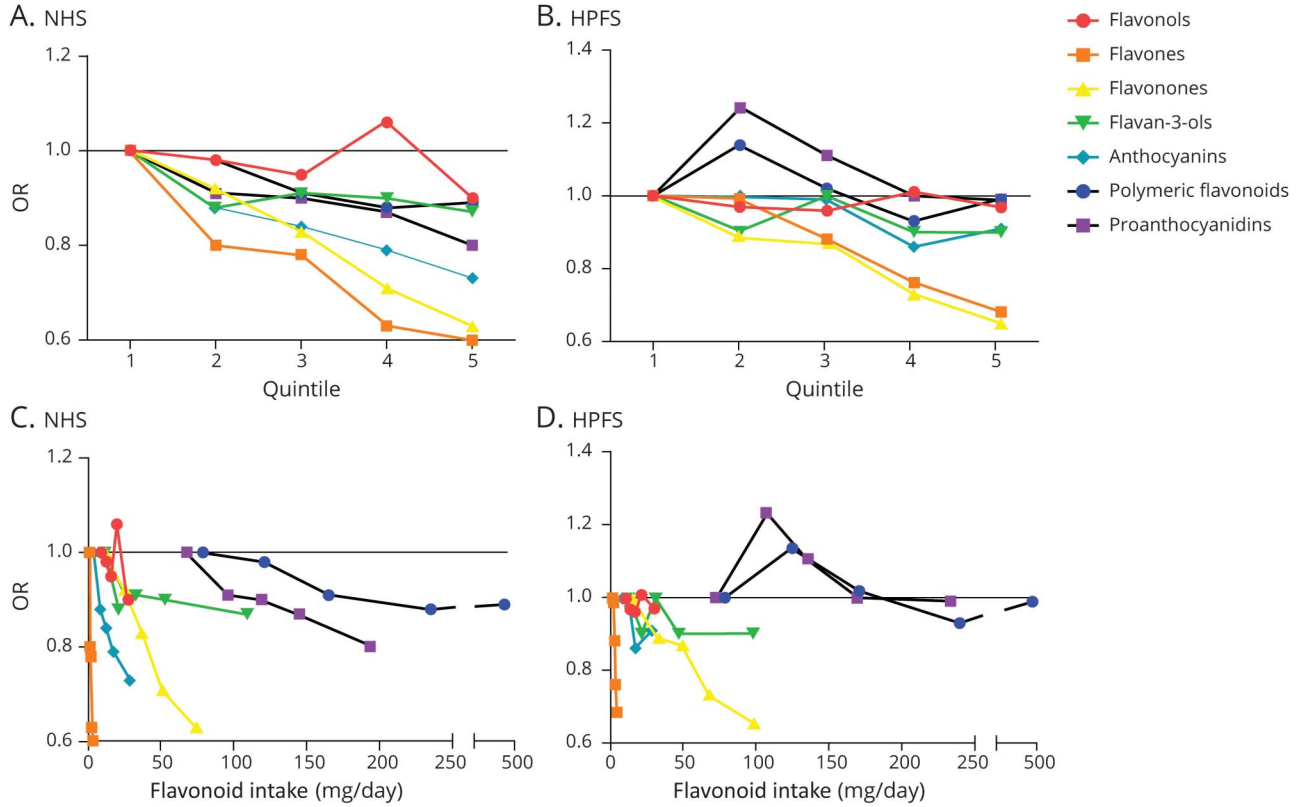
Continued

Table 2 ORs (95% CIs) for Associations Between Flavonoid Subclass Intakes and SCD *(continued)*

	Quintile of intakes						
	1	2	3	4	5	*p* for Trend	Continuous[a]
HPFS median intake, mg/d	12.8	21.1	30.5	46.7	96.4		
Model 1	Ref	0.85 (0.75–0.97)	0.90 (0.79–1.03)	0.82 (0.72–0.93)	0.83 (0.73–0.94)	0.03	0.94 (0.87–1.01)
Model 2	Ref	0.90 (0.79–1.03)	1.00 (0.88–1.14)	0.90 (0.79–1.03)	0.90 (0.79–1.02)	0.17	0.96 (0.89–1.04)
Meta-analyzed results (model 2)	Ref	0.89 (0.84–0.94)	0.94 (0.89–1.00)	0.89 (0.84–0.97)	0.89 (0.81–0.94)	0.006	0.94 (0.91–1.00)
Anthocyanins							
NHS median intake, mg/d	4.53	8.40	12.4	17.6	28.9		
Model 1	Ref	0.85 (0.79–0.92)	0.78 (0.72–0.84)	0.71 (0.65–0.77)	0.62 (0.57–0.68)	<0.001	0.72 (0.68–0.77)
Model 2	Ref	0.88 (0.82–0.96)	0.84 (0.77–0.91)	0.79 (0.72–0.86)	0.73 (0.66–0.79)	<0.001	0.81 (0.76–0.86)
HPFS median intake, mg/d	4.00	7.81	11.9	17.0	28.5		
Model 1	Ref	0.98 (0.86–1.11)	0.92 (0.81–1.05)	0.78 (0.68–0.89)	0.78 (0.68–0.89)	<0.001	0.85 (0.78–0.92)
Model 2	Ref	1.00 (0.88–1.14)	0.99 (0.87–1.13)	0.86 (0.75–0.99)	0.91 (0.79–1.05)	0.07	0.93 (0.86–1.01)
Meta-analyzed results (model 2)	Ref	0.91 (0.86–0.97)	0.89 (0.81–0.94)	0.81 (0.74–0.86)	0.76 (0.72–0.84)	<0.001	0.86 (0.81–0.89)
Polymeric flavonoids							
NHS median intake, mg/d	78.6	121	165	235	436		
Model 1	Ref	0.94 (0.86–1.02)	0.84 (0.78–0.92)	0.81 (0.75–0.88)	0.83 (0.76–0.90)	<0.001	0.94 (0.90–0.98)
Model 2	Ref	0.98 (0.91–1.07)	0.91 (0.84–0.99)	0.88 (0.81–0.96)	0.89 (0.82–0.97)	0.004	0.96 (0.91–1.01)
HPFS median intake, mg/d	77.3	122	167	235	424		
Model 1	Ref	1.11 (0.97–1.26)	0.95 (0.83–1.08)	0.85 (0.75–0.98)	0.90 (0.79–1.03)	0.009	0.94 (0.88–1.01)
Model 2	Ref	1.14 (1.00–1.30)	1.02 (0.89–1.16)	0.93 (0.81–1.07)	0.99 (0.86–1.13)	0.20	0.97 (0.91–1.04)
Meta-analyzed results (model 2)	Ref	1.03 (0.94–1.09)	0.94 (0.89–1.00)	0.89 (0.84–0.97)	0.91 (0.86–0.97)	0.003	0.97 (0.91–1.00)
Proanthocyanidins							
NHS median intake, mg/d	67.9	96.0	119	145	193		
Model 1	Ref	0.87 (0.80–0.94)	0.84 (0.78–0.91)	0.78 (0.72–0.85)	0.70 (0.65–0.77)	<0.001	0.78 (0.73–0.83)
Model 2	Ref	0.91 (0.84–0.98)	0.90 (0.83–0.97)	0.87 (0.80–0.94)	0.80 (0.74–0.88)	<0.001	0.87 (0.81–0.93)
HPFS median intake, mg/d	71.6	105	133	166	229		
Model 1	Ref	1.18 (1.04–1.35)	1.04 (0.91–1.19)	0.92 (0.80–1.05)	0.85 (0.74–0.97)	<0.001	0.84 (0.76–0.93)
Model 2	Ref	1.24 (1.09–1.41)	1.11 (0.97–1.28)	1.00 (0.88–1.15)	0.99 (0.86–1.15)	0.13	0.95 (0.86–1.05)
Meta-analyzed results (model 2)	Ref	1.00 (0.91–1.06)	0.94 (0.89–1.03)	0.91 (0.84–0.97)	0.86 (0.79–0.91)	<0.001	0.89 (0.84–0.94)

Abbreviations: CI = confidence interval; HPFS = Health Professionals Follow-Up Study; NHS = Nurses' Health Study; OR = odds ratio; Ref = referent; SCD = subjective cognitive decline.
Multivariate model 1: NHS: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years), total calorie intake, Census tract income, education (registered nursing degrees, bachelor degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), race (White, Black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, >24 pack-years), depression, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, intakes of alcohol, postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984 to 2006, multivitamin use (yes/no), parity (nulliparous, 1–2, >2). HPFS: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years), total calorie intake, smoking history (never, ≤24 pack-years, 25–44 pack-years, ≥45 pack-years), cancer (yes/no), depression, family history of dementia, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, multivitamin use (yes/no), intake of alcohol, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986 to 2002. Multivariate model 2: in addition to the variables adjusted in multivariate model 1, further adjusted for dietary intakes of total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid.
[a] Comparing 90th to 10th percentile of intake.

Figure 1 Associations and Dose-Response Relationships Between Flavonoid Subclasses and SCD



(A and B) Multivariate odds ratios (ORs) for flavonoid subclasses by quintiles in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). (C and D) Multivariate-adjusted dose-response relationship between flavonoid subclasses and OR of 3-unit increments in subjective cognitive decline (SCD) in the NHS and HPFS.

with missing values. Linear trends were tested by assigning median values within each quintile and modeling these variables continuously. We performed sensitivity analyses by additionally adjusting for total fat and protein intakes and by adjusting for individual carotenoids (α-carotene, β-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin) instead of total carotenoids.

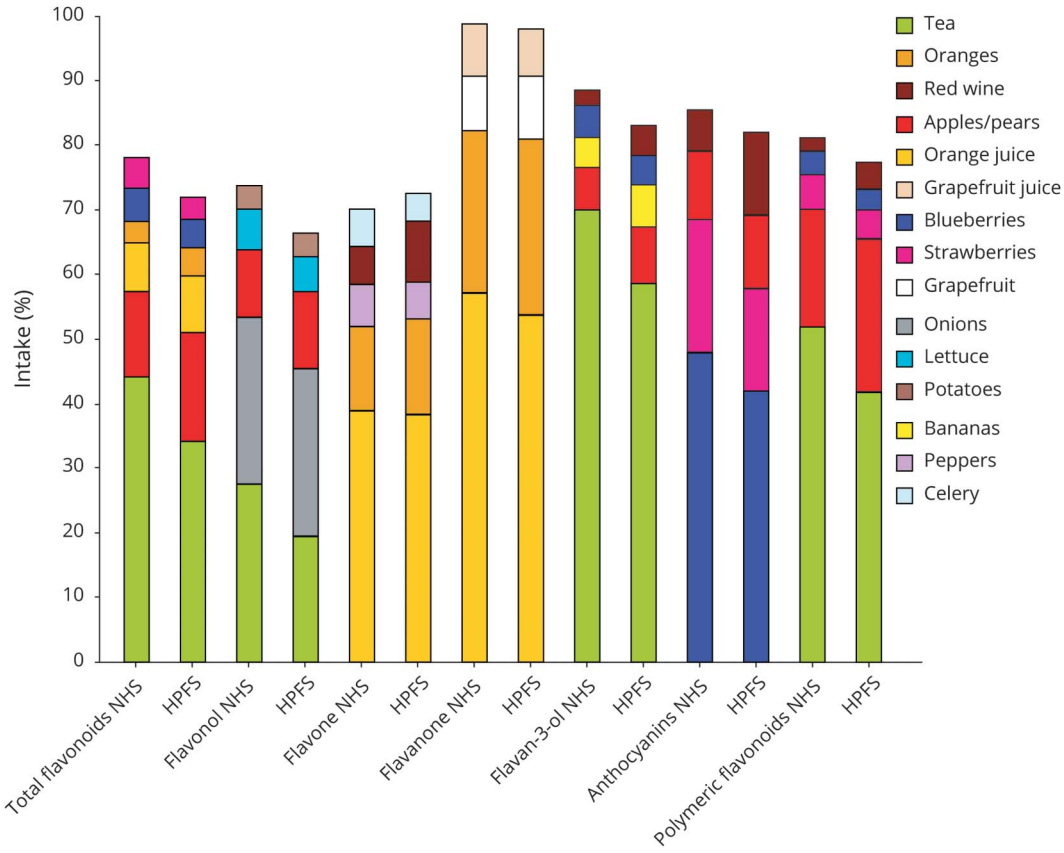
In the food-based analyses, age, total energy intake, and the above-mentioned nondietary factors were adjusted. To investigate whether the associations were independent of other major food groups, we also adjusted for sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. Flavonoid-containing foods were treated as continuous variables, and ORs for every 3 servings per week were estimated. Spearman correlations were calculated to evaluate correlations between total and each flavonoid subclass, total and individual carotenoids, vitamin C, vitamin E, and folate within foods. The amounts of these nutrients within foods were calculated according to USDA data.

We further investigated whether the associations between flavonoids and SCD differed by baseline age (<50, ≥50 years), smoking status (never smokers, past smokers, and current smokers), presence of depression (yes/no), CVD (yes/no), and *APOE* ε4 allele carrier status (yes/no) in a subgroup of participants who had their *APOE* ε4 measured or imputed from a genome-wide association analysis.

We evaluated temporal relationships between flavonoid intakes and SCD. The associations between dietary intake at each individual year with SCD were estimated. In addition, both recent (the average intake from 2002 to 2006 in the NHS and average intake from 1998 to 2002 for the HPFS) and remote (the average intake from 1984 to 1990 in the NHS and average intake from 1986 to 1990 for the HPFS) intakes were mutually included in the same model to examine whether these associations were independent of each other. In these analyses, covariates closest in time to the dietary assessments were used.

Analyses were done separately for the NHS and HPFS. An inverse variance-weighted, fixed-effect meta-analysis was then used to combine the results across cohorts. We interpreted our findings using the conservative Bonferroni correction because our analyses included multiple comparisons. All analyses were performed with SAS software,

Figure 2 Major Food Sources of Flavonoids By Subclass[a]



[a]Average for 1984 to 2006 in the Nurses' Health Study (NHS) and 1986 to 2002 in the Health Professionals Follow-Up Study (HPFS).

version 9.2 (SAS Institute Inc, Cary, NC) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Figures were generated by Prism, version 8.0.0.

Data Availability

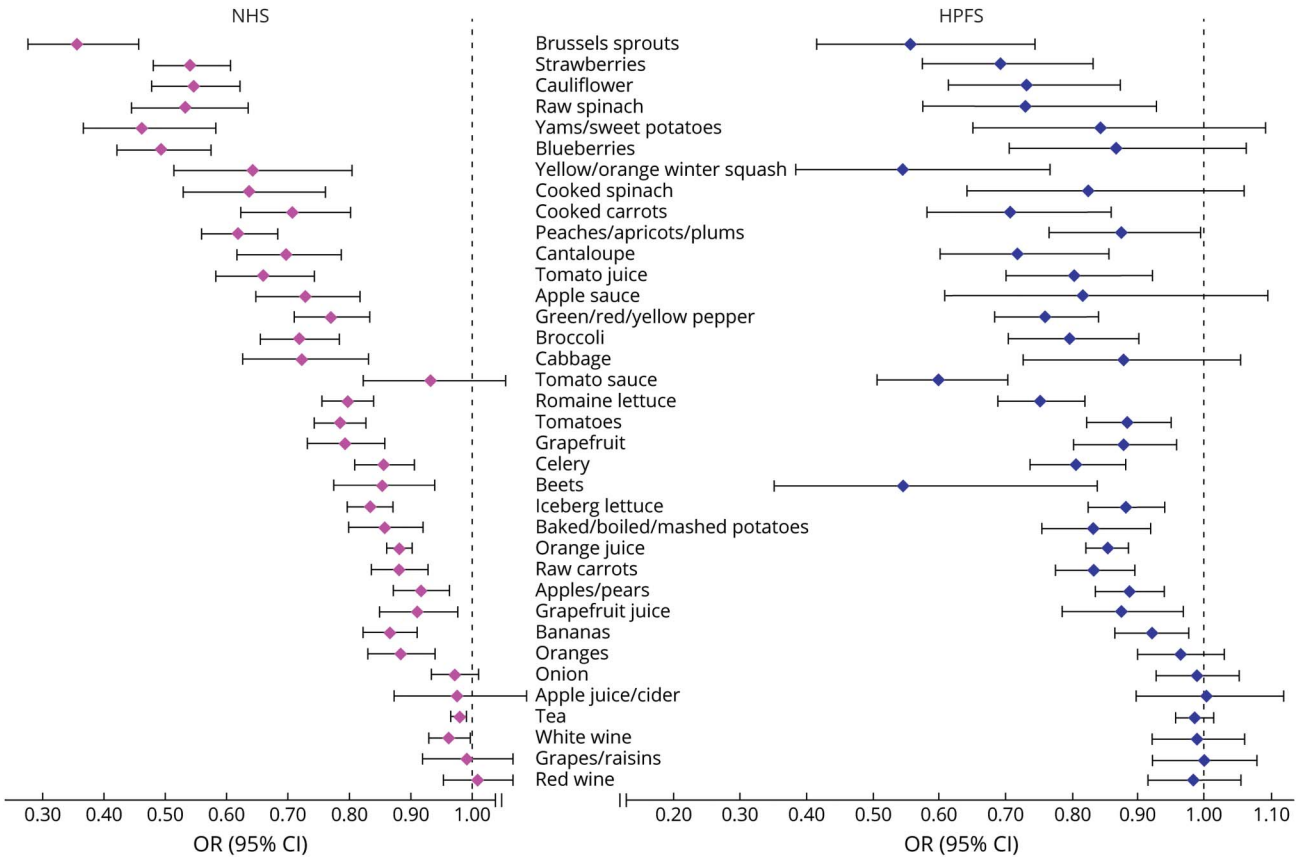
Any data not published within the article will be shared at the request of other qualified investigators for purposes of replicating procedures and results. Our NHS and HPFS websites[32,33] include guidelines for external users and links to all questionnaires.

Results

The mean age of participants at the initial SCD assessment was 76.3 years for the NHS and 73 years for the HPFS. Characteristics of study participants were generally similar across quintiles of total flavonoid intake except that participants with higher intake were more likely to be nonsmokers and had higher carotenoid intake (table 1). The mean intake of total flavonoids was 345 mg/d in both men and women. Among flavonoid subclasses, intake of polymeric flavonoids was the highest and intake of flavones was the lowest (table 2). The frequencies of SCD at each assessment and the percentage of positive answers in each question are shown in efigure 2 and etable 1 available from Dryad (doi.org/10.5061/dryad.p5hqbzkpj).

Significant inverse associations between total flavonoids and all the flavonoid subclasses with SCD were observed after controlling for age, total energy intake, and major nondietary factors in both the NHS and HPFS (table 2). After further adjustment for total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid, associations remained significant for total flavonoids and all subclasses in the NHS; in contrast, in the HPFS, associations were significant only for total flavonoids, flavones, and flavanones after full adjustment. In the pooled results, when the highest and lowest quintiles of intakes were compared, the strongest associations among flavonoid subclasses were observed for flavones and flavanones (figure 1). Inverse linear trends across quintiles were observed (p trend <0.001). In the multivariate model, we observed significant positive associations between age, smoking history, family history of dementia, depression, and total energy intake and SCD in both the NHS and HPFS; significant inverse associations were observed for physical activity and intakes of carotenoids and vitamin C in both cohorts; and higher education and higher income in the NHS also had inverse association with SCD. In stepwise regression, flavanones were selected as

Figure 3 ORs[a] (95% CIs) for Associations Between Food Sources of Flavonoids and 3-Unit Increments in SCD

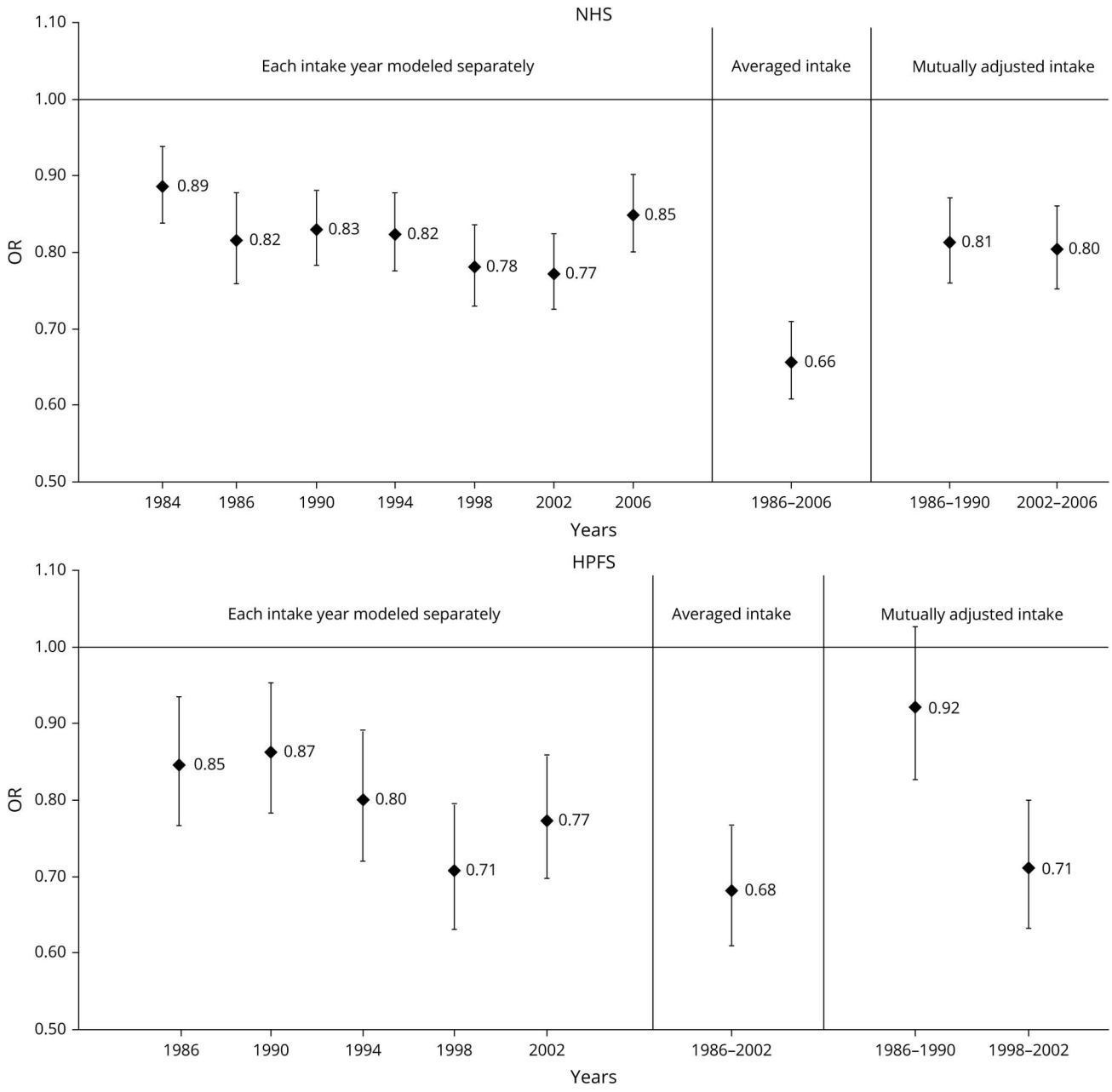


Multivariate model: Nurses' Health Study (NHS): adjusted for age, total energy intake, Census tract income, education (registered nursing degrees, bachelor degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), race (White, Black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, >24 pack-years), depression, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, intakes of alcohol, postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for subjective cognitive decline (SCD) measurement at 2012 or 2014, number of dietary assessments during 1984 to 2006, multivitamin use (yes/no), and parity (nulliparous, 1–2, >2). Health Professionals Follow-Up Study (HPFS): adjusted for age, total energy intake, smoking history (never, ≤24 pack-years, 25–44 pack-years, ≥45 pack-years), cancer (yes/no), depression, family history of dementia, elevated physical activity level (metabolic equivalent-hours per week, quintiles), and body mass index, multivitamin use (yes/no), intake of alcohol, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986 to 2002. Both cohorts also adjusted for dietary intakes of sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. The foods were ranked starting with the lowest odds ratios (ORs) based on the meta-results of the 2 cohorts. [a]ORs for every 3 servings/wk as continuous variables. CI = confidence interval.

independent predictors of subsequent SCD in both the NHS and HPFS; flavones, anthocyanins, flavonols, and total flavonoids were also selected in the NHS. The dose-response relationship was steepest for flavones, followed by anthocyanins (figure 1). Results remained similar when total fat and protein intakes were adjusted for. In the sensitivity analysis adjusted for individual carotenoids (α-carotene, β-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin) instead of total carotenoids, the associations were only modestly attenuated: for total flavonoids, OR = 0.89 (95% CI 0.81, 0.94); for flavones, OR = 0.74 95% CI (0.66, 0.81); and for flavanones, OR = 0.74 (95% CI 0.66, 0.84). For subgroup analyses, results were similar across strata of smoking status, depression status, CVD status, and *APOE* ε4 allele carrier status; the inverse associations for flavones and flavanones were even stronger in younger participants (baseline age <50 years) (NHS 0.57 [95% CI 0.49, 0.65], HPFS 0.67 [95% CI 0.51, 0.87] for flavones; NHS 0.60 [95% CI 0.52, 0.68], HPFS 0.60 [95% CI 0.47, 0.78] for flavanones).

Top food contributors to flavones in our cohorts during the follow-up period were orange juice, oranges, peppers, celery, and red wine. Orange juice, oranges, grapefruits, and grapefruit juice were the main food sources of flavanones; blueberries, strawberries, apples, and red wine were major contributors to anthocyanins (figure 2). Many flavonoid-containing foods were significantly associated with lower odds of SCD (figure 3). In stepwise regression, blueberries, strawberries, apples, orange juice, grapefruit juice, bananas, onions, tea, peaches, cauliflower, brussels sprouts, lettuce, and potatoes were selected as independent predictors of subsequent SCD status. Generally, flavonoid content did not correlate well with the contents of carotenoids, vitamins C

Figure 4 Temporal Relationships Between Flavone Intake and OR[a] of 3-Unit Increments in SCD

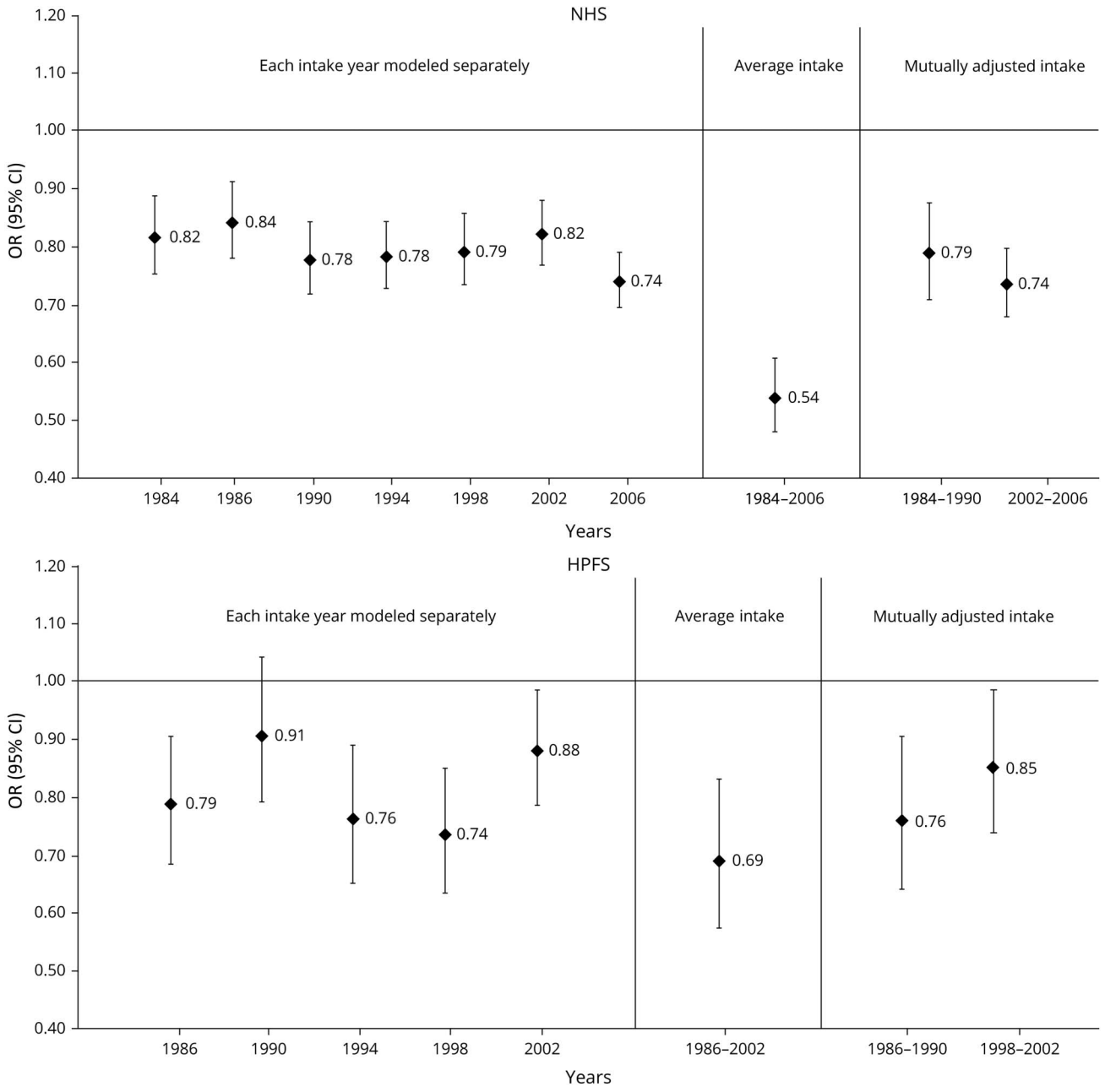


Multivariate model: Nurses' Health Study (NHS): adjusted for age, total energy intake, Census tract income, education (registered nursing degrees, bachelor degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), race (White, Black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, >24 pack-years), depression, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, family history of dementia, vitamin C, vitamin D, and vitamin E supplementation use (yes/no), intakes of alcohol, postmenopausal status and hormone replacement therapy use, missing indicator for subjective cognitive decline (SCD) measurement at 2012 or 2014, number of dietary assessments during 1984 to 2006, multivitamin use (yes/no), parity (nulliparous, 1–2, >2), and intakes of total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid. Health Professionals Follow-Up Study (HPFS): adjusted for age, total energy intake, smoking history (never, ≤24 pack-years, 25–44 pack-years, ≥45 pack-years), cancer (yes/no), depression, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, multivitamin use (yes/no), intake of alcohol, family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), percentage of energy intake from dietary total protein (quintiles), missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1986–2002, and intakes of total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid. OR = odds ratio. [a]Comparing 90th to 10th percentile of flavone intake.

and E, and folate within the foods we examined (efigure 3 available from Dryad [doi.org/10.5061/dryad.p5hqbzkpj]).

In the analyses of the temporal relationships, the flavonoid subclass and commonly consumed flavonoid-containing food with the strongest associations are presented (i.e., flavones and strawberries). Higher intake of flavones was significantly associated with lower odds of SCD at all of the time points during follow-up (7 times in the NHS and 5 times in the HPFS) (figure 4). The average of all

Figure 5 Temporal Relationships Between Strawberry Intake and OR[a] of 3-Unit Increments in SCD



Multivariate model: Nurses' Health Study (NHS): adjusted for age, total energy intake, Census tract income, education (registered nursing degrees, bachelor degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), race (White, Black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, >24 pack-years), depression, physical activity level (metabolic equivalent-hours per week, quintiles), body mass index, family history of dementia, vitamin C, vitamin D, and vitamin E supplementation use (yes/no), intakes of alcohol, postmenopausal status and hormone replacement therapy use, missing indicator for subjective cognitive decline (SCD) measurement at 2012 or 2014, number of dietary assessments during 1984 to 2006, multivitamin use (yes/no), parity (nulliparous, 1–2, >2), and intakes of sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. Health Professionals Follow-Up Study (HPFS): adjusted for age, total energy intake, smoking history (never, ≤24 pack-years, 25–44 pack-years, ≥45 pack-years), cancer (yes/no), depression, physical activity level (metabolic equivalent-hour per week, quintiles), and body mass index, multivitamin use (yes/no), intake of alcohol, family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), percentage of energy intake from dietary total protein (quintiles), missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1986 to 2002, and intakes of sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. OR = odds ratio. [a]OR for every 3 servings/wk as continuous variables.

dietary assessments had the strongest associations in both cohorts. When we included both recent and remote intakes in the model, both intakes were significantly associated with lower odds of SCD in the NHS. The findings were similar for flavanones. For intakes of strawberries (figure 5), the associations with SCD were significant for almost all the individual years, and both recent and remote intakes were significant when mutually adjusted for in the model.

These results were similar for orange juice and brussels sprouts.

Discussion

Combining the results from these 2 large prospective cohort studies of US men and women, we found that higher intakes of flavonoids were associated with better later-life subjective cognitive function. The strongest associations were observed for flavones, flavanones, and anthocyanins. The associations remained statistically significant even after adjustment for carotenoids, vitamin C, vitamin D, vitamin E, protein, and fatty acid intakes.

Although several epidemiologic studies have been conducted on the relationships between flavonoids and cognitive function, results have been inconclusive. In the Rotterdam study, Honolulu-Asia Aging Study, and Zutphen study, no associations between dietary flavonoids and Alzheimer disease (AD) or cognitive decline were seen.[13-16] However, in the PAQUID (Personnes Agées Quid) study, dietary flavonoids were associated with a lower risk of cognitive decline[17] and did not differ by smoking status.[18] Among participants in our NHS who completed repeated telephone-administered cognitive tests,[19] greater consumption of berries, anthocyanidins, and total flavonoids was associated with less cognitive decline; similar results were shown in the Rush Memory and Aging Project,[34] with an additional finding of an inverse association between flavonol (kaempferol and isorhamnetin) intake and AD.[35] Flavonol and anthocyanin intakes were also found to be associated with reduced risk of AD and related dementia in the Framingham Offspring Cohort.[36] In contrast, in the Doetinchem Cohort Study, greater intake of flavonoids was associated with a larger decline in cognitive flexibility during a 5-year follow-up.[20] In the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study, flavonols, proanthocyanidins, and catechins were adversely associated with executive functioning, whereas many polyphenol classes were beneficially associated with language and verbal memory.[37] These inconsistencies may be partly due to the different ages of enrolled participants, different food sources of flavonoids, or chance because some of these studies were modest in size. Studies with older participants have generally appeared to find more favorable effects of antioxidants or flavonoids,[17,34] while middle-aged individuals appeared less likely to benefit from such dietary intakes.[20] Different follow-up durations may also influence the detection of significant associations; reverse causation (changes in cognitive function may influence diets) is possible in studies with relatively short duration. In addition, substantial differences in the flavonoid intake amounts recorded in various studies were noted. While the flavonoid intakes in the current study (mean 345 mg/d) were similar to those of the SU.VI.MAX study[37] and amounts previously reported,[19] they were considerably higher compared to the Rotterdam study (mean 28.5 mg/d),[14] the PAQUID study (mean 14.4 mg/d),[17,18] and the Honolulu-Asia Aging Study (mean 4.1 mg/d).[15] These differences may stem from the different flavonoid-containing foods included in the questionnaire, the use of different reference databases, different definitions of total flavonoids, and variation in major sources of flavonoids in different study populations. We note that our study was far larger and had much longer follow-up than most previous studies; in addition, most other studies had only a single assessment of diet.

Despite the aforementioned mixed results from epidemiologic studies, several animal and in vitro studies, as well as some human interventional studies, have provided insights into the possible mechanisms of flavonoids on cognitive function. The antioxidant properties of flavonoids are one of the many reasons cited for a potential neuroprotective effect.[38] The findings of antioxidant activity were especially noted for flavanones from citrus,[39] which also inhibited β-amyloid–induced neurotoxicity[40] and improved cognitive function and brain blood flow in healthy adults.[41] Flavanones and anthocyanins can also destabilize β-amyloid fibril aggregation[42] and suppress neuroinflammation.[43] Flavones also possessed strong antioxidant and anti-inflammatory biological activities.[44] Apigenin, one of the flavones included in the current study, possessed a potent anti-inflammatory effect and prevented neuronal apoptosis.[45] Another flavone, luteolin, examined in our cohorts ameliorated spatial learning and memory impairment in the rat AD model,[46] and these beneficial effects could be due to its ability to serve as reactive oxygen species scavenger.[47] Flavonoids could also improve spatial working memory by increasing brain-derived neurotrophic factors, preventing endothelial dysfunction,[48] and facilitating synaptic strength.[49]

Our findings are consistent with the above mechanistic studies of flavones, flavanones, and anthocyanins by showing that among all the flavonoid subclasses, flavones had the strongest inverse associations with SCD (a 38% lower odds of SCD when participants in highest and lowest quintiles were compared, equivalent to being 3–4 years younger) and the steepest dose-response curve. Flavanones possessed the second strongest relationship with SCD (a 36% lower odds of SCD when participants in the highest and lowest quintiles were compared). Anthocyanins had the second steepest dose-response curve. To the best of our knowledge, the current study is the first to present dose-response relationships for various flavonoid subclasses. Furthermore, the interaction between flavonoid subclasses and age revealed that the magnitude of inverse associations for flavones and flavanones increased 5% to 6% for every 10 years younger in age for both men and women, suggesting that earlier consumption of flavones and flavanones may be related to additional benefits or that the association may be stronger with earlier-onset dementia.

We also found significant inverse associations between many flavonoid-containing foods such as orange juice, oranges, peppers, celery, grapefruits, grapefruit juice, apples/pears, blueberries, and strawberries and SCD; these foods were the

major contributors to flavones, flavanones, and anthocyanidins in our cohorts. Fisetin, another flavonoid abundant in strawberries, has been found to have senolytic, anti-inflammatory, antioxidant, and neuroprotective activities in animal studies.[50] Although it was not included in the USDA database and therefore was precluded from the current study, its possible neuroprotective effect could at least partially account for the inverse association seen in strawberries. Taken together, our findings on the food level mirrored the results on the phytochemical level and added to the existing evidence from some short-term human and animal interventional studies[41,49] that these flavonoid-containing foods may have beneficial roles in cognitive function. To investigate the possible causal agents within these foods for the inverse associations that we observed, we examined the correlations between flavonoid content and other nutrient contents and found relatively low correlations between flavonoid content and carotenoids, vitamin C, vitamin E, and folate contents of the foods we examined. We also noticed that oranges and orange juice were top food contributors to flavones, flavanones, and β-cryptoxanthin in our cohorts due to the high amount of their intakes; therefore, both flavonoids and β-cryptoxanthin may contribute to the inverse associations seen in orange and orange juice. Nonetheless, the associations between flavonoid subclasses and SCD remained robust after adjustment for other nutrients, including β-cryptoxanthin, other individual carotenoids, and vitamin C. Therefore, our findings on the food level further supported the hypothesis that flavonoids may be beneficial for SCD, although we cannot exclude the effects of other phytochemicals.

Strengths of the present study include >20 years of follow-up, allowing us to capture a range of potential critical exposure windows and to minimize potential reverse causation. The large sample size provided great statistical power. Average dietary intakes from multiple dietary assessments over time reduced errors and within-person variations and best represented long-term diet. To minimize the influence of dietary change due to altered cognitive function, we stopped updating dietary data 6 years before SCD assessments. Our data included comprehensive information on possible confounders, and adjusting for these variables minimized residual confounding. Some limitations of the current study include the following. First, data are lacking on baseline cognitive function, and our 2 SCD assessments were close in time, so estimation of rate of change was not possible. However, all cohort participants are health professionals with relatively high education levels, and high baseline cognitive function can be assumed; they are also more likely to have good insight[51] into reporting subtle cognitive changes. Second, our study does not include objective cognitive assessment, and SCD assessment may be subject to errors. However, SCD has been validated repeatedly to demonstrate strong associations with both concurrent objective cognitive function[30] and subsequent cognitive decline.[30] In addition, SCD can be more informative than objective cognitive function assessments because it could be used to detect subtle cognitive change, especially in those with higher education.[31] Third, complaints related to object naming and word finding were not assessed in the SCD questions. However, the SCD questions evaluate memory and executive functions, which has been shown to well differentiate participants who develop subsequent cognitive decline from those who do not.[52] Fourth, participants who did not complete the second SCD assessment might have more severe cognitive impairment. However, this scenario would bias our results toward the null. Furthermore, the SCD is probably mixed pathology (including AD and other dementias), and except for Parkinson disease, we cannot distinguish among other disorders that could lead to SCD. However, we conducted a stratified analysis for CVD, which is a major cause of cognitive decline, and noted that the results were similar among participants with and those without CVD. Another limitation is potential recall bias in the measurement of the exposure given that our dietary data were self-reported, and we have no data on biomarkers for flavonoid intake such as plasma levels. However, the SFFQ has been validated repeatedly,[21] and we tried to reduce the possible errors by averaging the multiple dietary assessments over the follow-up period. Another potential concern would be a potential worse recall bias among those with SCD; this was addressed by using increasing lags between assessment of flavonoid intake and assessment of SCD, and the results were robust over several decades. In addition, although we adjusted for many potential confounding factors and noted that the results remained similar after adjustment for education, income, profession, physical activity, family history of dementia, and depression, there could still be residual confounding. Psychoaffective factors such as depression can be early symptoms of cognitive loss and could be difficult to distinguish from pure cognitive decline. However, adjusting for depression may partly account for the effect of psychoaffective factors on the self-report of SCD, and we observed that the associations between flavonoids and SCD remained similar when participants with depression were excluded. The different results observed in the 2 cohorts may be related to not only a sex difference but also the difference in their professions and other socioeconomic or unmeasured factors. The larger sample size and longer follow-up period in the NHS may also contribute to the different findings in the 2 cohorts. Last, generalizability could be limited because our participants were mainly White health care professionals who required relatively high cognitive function for their occupations and may have better health awareness. However, this relatively uniformly high cognitive function may reduce residual confounding.

Our study findings suggest that higher flavonoid intakes may help maintain cognitive function. Flavones, flavanones, and anthocyanins had the strongest apparent protective associations with SCD. These findings may suggest future interventional studies in search of possible therapeutic or preventive strategies for cognitive decline, including the

possible effects of specific flavonoids on cognitive function and the effective dosage. In the meantime, consumption of flavonoid-rich foods such as berries and citrus fruits and juices may be beneficial to maintain cognitive function.

Disclosures

All authors have declared that no conflict of interest exists. Go to Neurology.org/N for full disclosures.

Study Funding

This work was supported by grants from the NIH (UM1 CA186107, UM1 CA 167552).

Publication History

Received by *Neurology* February 7, 2021. Accepted in final form June 10, 2021.

Appendix Authors

Name	Location	Contribution
Tian-Shin Yeh, MD, PhD	Harvard University, Boston, MA	Designed and conducted the analysis, interpreted the data, and wrote the manuscript
Changzheng Yuan, ScD	Zhejiang University, Hangzhou, China	Contributed to data analysis and completed the technical review of the results
Alberto Ascherio, MD, DrPH	Harvard University, Boston, MA	Contributed to the interpretation of the results, provided critical feedback, and revision of the manuscript for important intellectual content
Bernard A. Rosner, PhD	Harvard University, Boston, MA	Contributed to the interpretation of the results, provided critical feedback, and revision of the manuscript for important intellectual content
Walter C. Willett, MD, DrPH	Harvard University, Boston, MA	Designed the analysis, interpretation of the results, revision of the manuscript for important intellectual content, and supervised the project
Deborah Blacker, MD, ScD	Harvard University, Boston, MA	Contributed to the interpretation of the results, provided critical feedback, revision of the manuscript for important intellectual content, and supervised the project

References

1. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *BMJ.* 2017;358:j2856.
2. Prince M, Knapp M, Guerchet M, et al. *Dementia UK: Second Edition–Overview*: Alzheimer's Society; 2014.
3. Rabin LA, Smart CM, Amariglio RE. Subjective cognitive decline in preclinical Alzheimer's disease. *Annu Rev Clin Psychol.* 2017;13:369-396.
4. Galluzzi S, Frisoni GB. Imaging, subjective complaints, and MCI: 30 years before. *J Nutr Health Aging.* 2008;12:80s-83s.
5. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7:280-292.
6. Tucker KL. Nutrient intake, nutritional status, and cognitive function with aging. *Ann NY Acad Sci.* 2016;1367:38-49.
7. Liu RH. Health-promoting components of fruits and vegetables in the diet. *Adv Nutr.* 2013;4:384s–392s.
8. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci.* 2016;5:e47.
9. Hajjar I, Hayek SS, Goldstein FC, et al. Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. *J neuroinflammation.* 2018;15:17.
10. Sonee M, Sum T, Wang C, Mukherjee SK. The soy isoflavone, genistein, protects human cortical neuronal cells from oxidative stress. *Neurotoxicology.* 2004;25:885-891.
11. Ryan J, Croft K, Mori T, et al. An examination of the effects of the antioxidant pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. *J Psychopharmacol.* 2008;22:553-562.
12. Whyte AR, Cheng N, Butler LT, Lamport DJ, Williams CM. Flavonoid-rich mixed berries maintain and improve cognitive function over a 6 h period in young healthy adults. *Nutrients.* 2019;11:2685.
13. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA.* 2002;287:3223-3229.
14. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary antioxidants and long-term risk of dementia. *Arch Neurol.* 2010;67:819-825.
15. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. *Am J Epidemiol.* 2004;159:959-967.
16. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol.* 1997;145:33-41.
17. Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. *Eur J Epidemiol.* 2000;16:357-363.
18. Letenneur L, Proust-Lima C, Le Gouge A, Dartigues JF, Barberger-Gateau P. Flavonoid intake and cognitive decline over a 10-year period. *Am J Epidemiol.* 2007;165:1364-1371.
19. Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol.* 2012;72:135-143.
20. Nooyens AC, Milder IE, van Gelder BM, Bueno-de-Mesquita HB, van Boxtel MP, Verschuren WM. Diet and cognitive decline at middle age: the role of antioxidants. *Br J Nutr.* 2015;113:1410-1417.
21. Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr.* 1998;52:588-596.
22. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet.* 1991;338:464-468.
23. Bernstein AM, Rosner BA, Willett WC. Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up. *Eur J Epidemiol.* 2011;26:877-886.
24. Cassidy A, O'Reilly EJ, Kay C, et al. Habitual intake of flavonoid subclasses and incident hypertension in adults. *Am J Clin Nutr.* 2011;93:338-347.
25. Neilson AP, O'Keefe SF, Bolling BW. High-molecular-weight proanthocyanidins in foods: overcoming analytical challenges in pursuit of novel dietary bioactive components. *Annu Rev Food Sci Technol.* 2016;7:43-64.
26. Xu Y, Li S, Chen R, et al. Antidepressant-like effect of low molecular proanthocyanidin in mice: involvement of monoaminergic system. *Pharmacol Biochem Behav.* 2010;94:447-453.
27. Yue Y, Petimar J, Willett WC, et al. Dietary flavonoids and flavonoid-rich foods: validity and reproducibility of FFQ-derived intake estimates. *Public Health Nutr.* 2020;23:3295-3303.
28. Yuan C, Fondell E, Bhushan A, et al. Long-term intake of vegetables and fruits and subjective cognitive function in US men. *Neurology.* 2019;92:e63–e75.
29. Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. *Alzheimers Dement.* 2017;13:296-311.
30. Samieri C, Proust-Lima C, Glymour MM, et al. Subjective cognitive concerns, episodic memory, and the APOE epsilon4 allele. *Alzheimers Dement.* 2014;10:752-759.e751.
31. van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MM. Subjective memory complaints, education, and risk of Alzheimer's disease.*Alzheimers Dementia.* 2007;3:92-97.
32. Nurses' Health Study. Available at: nurseshealthstudy.org.
33. Health Professionals Follow-Up Study. Accessed Jan 28, 2021. sites.sph.harvard.edu/hpfs/
34. Agarwal P, Holland TM, Wang Y, Bennett DA, Morris MC. Association of strawberries and anthocyanidin intake with Alzheimer's dementia risk. *Nutrients.* 2019;11:3060.
35. Holland TM, Agarwal P, Wang Y, et al. Dietary flavonols and risk of Alzheimer dementia. *Neurology.* 2020;94:e1749–e1756.
36. Shishtar E, Rogers GT, Blumberg JB, Au R, Jacques PF. Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort. *Am J Clin Nutr.* 2020;112:343-353.
37. Kesse-Guyot E, Fezeu L, Andreeva VA, et al. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. *J Nutr.* 2012;142:76-83.
38. Pietta PG. Flavonoids as antioxidants. *J Nat Prod.* 2000;63:1035-1042.
39. Parhiz H, Roohbakhsh A, Soltani F, Rezaee R, Iranshahi M. Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models. *Phytotherapy Res.* 2015;29:323-331.
40. Heo HJ, Kim DO, Shin SC, Kim MJ, Kim BG, Shin DH. Effect of antioxidant flavanone, naringenin, from Citrus junoson neuroprotection. *J Agric Food Chem.* 2004;52:1520-1525.

41. Alharbi MH, Lamport DJ, Dodd GF, et al. Flavonoid-rich orange juice is associated with acute improvements in cognitive function in healthy middle-aged males. *Eur J Nutr.* 2016;55:2021-2029.
42. Ma H, Johnson SL, Liu W, et al. Evaluation of polyphenol anthocyanin-enriched extracts of blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry for free radical scavenging, reactive carbonyl species trapping, anti-glycation, anti-beta-amyloid aggregation, and microglial neuroprotective effects. *Int J Mol Sci.* 2018;19:461.
43. Kim MJ, Rehman SU, Amin FU, Kim MO. Enhanced neuroprotection of anthocyanin-loaded PEG-gold nanoparticles against Abeta1-42-induced neuroinflammation and neurodegeneration via the NF-KB/JNK/GSK3beta signaling pathway. *Nanomedicine.* 2017;13:2533-2544.
44. Catarino MD, Alves-Silva JM, Pereira OR, Cardoso SM. Antioxidant capacities of flavones and benefits in oxidative-stress related diseases. *Curr Top Med Chem.* 2015; 15:105-119.
45. Balez R, Steiner N, Engel M, et al. Neuroprotective effects of apigenin against inflammation, neuronal excitability and apoptosis in an induced pluripotent stem cell model of Alzheimer's disease. *Sci Rep.* 2016;6:31450.
46. Wang H, Wang H, Cheng H, Che Z. Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. *Mol Med Rep.* 2016;13:4215-4220.
47. Yu D, Li M, Tian Y, Liu J, Shang J. Luteolin inhibits ROS-activated MAPK pathway in myocardial ischemia/reperfusion injury. *Life Sci.* 2015;122:15-25.
48. Schroeter H, Heiss C, Balzer J, et al. (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. *Proc Natl Acad Sci USA.* 2006;103:1024-1029.
49. Williams CM, El Mohsen MA, Vauzour D, et al. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. *Free Radic Biol Med.* 2008;45: 295-305.
50. Currais A, Farrokhi C, Dargusch R, et al. Fisetin reduces the impact of aging on behavior and physiology in the rapidly aging SAMP8 mouse. *J Gerontol A Biol Sci Med Sci.* 2018;73:299-307.
51. Li Y, Schoufour J, Wang DD, et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. *BMJ.* 2020;368:l6669.
52. Go RC, Duke LW, Harrell LE, et al. Development and validation of a structured telephone interview for dementia assessment (STIDA): the NIMH Genetics Initiative. *J Geriatr Psychiatry Neurol.* 1997;10:161-167.