

Dietary flavonoid intake at midlife and healthy aging in women^{1–3}

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ABSTRACT

Background: Dietary flavonoids have been related to lower risks of various chronic diseases, but it is unclear whether flavonoid intake in midlife helps to maintain good health and wellbeing in aging.

Objective: We examined the relation of flavonoid intake in midlife with the prevalence of healthy aging.

Design: We included 13,818 women from the Nurses' Health Study with dietary data and no major chronic diseases in 1984–1986 when they were aged in their late 50s (median age: 59 y); all women provided information on multiple aspects of aging an average of 15 y later. Intakes of 6 major flavonoid subclasses in midlife were ascertained on the basis of averaged intakes of flavonoid-rich foods from 2 food-frequency questionnaires (1984–1986). We defined healthy compared with usual aging as of age 70 y; healthy aging was based on survival to ≥ 70 y with maintenance of 4 health domains (no major chronic diseases or major impairments in cognitive or physical function or mental health).

Results: Of women who survived until ≥ 70 y of age, 1517 women (11.0%) met our criteria for healthy aging. Compared with women in the lowest quintile of intake, women in the highest quintile of intake of several flavonoid subclasses at midlife had greater odds of healthy aging. After multivariable adjustment, ORs were as follows: flavones, 1.32 (95% CI: 1.10, 1.58); flavanone, 1.28 (95% CI: 1.08, 1.53); anthocyanin, 1.25 (95% CI: 1.04, 1.50); and flavonol, 1.18 (95% CI: 0.98, 1.42) (all P -trend ≤ 0.02). Consistently, greater intakes of major sources of these flavonoids (i.e., oranges, berries, onions, and apples) were associated with increased odds of healthy aging. We showed no association with flavan-3-ol monomers (P -trend = 0.80) or polymers (P -trend = 0.63).

Conclusion: Higher intake of flavonoids at midlife, specifically flavones, flavanones, anthocyanins, and flavonols, is associated with greater likelihood of health and wellbeing in individuals surviving to older ages. *Am J Clin Nutr* 2014;100:1489–97.

Keywords cohort studies, flavonoid, healthy aging, risk factors in epidemiology, public health

INTRODUCTION

Finding strategies to maintain health and wellbeing in aging populations represents a major challenge (1). Because the development of many chronic diseases and conditions associated with aging involve oxidative pathways, approaches to reducing oxidative stress, e.g., via greater consumption of dietary antioxidants (2), could be important to promoting healthy aging. Specifically, greater intakes of various subclasses of flavonoids, which are bioactive phenolic compounds provided by plant foods, have benefits on endothelial function and blood pressure (3–5), and these effects might be attributed to their antioxidant role and anti-inflammatory properties (6). More-recent experimental studies have also established that some dietary polyphenols may

modulate memory and learning by increasing concentrations of brain-derived neurotrophic factor in the hippocampus (7) and lower anxiety, depression, and age-related cognitive deficits (8, 9).

In epidemiologic studies, flavonoids and flavonoid-containing foods have been associated with lower risks of fatal or nonfatal cardiovascular disease (10–13), hypertension (4, 14), stroke (15–17), cancer (18), diabetes (19, 20) and neurodegenerative diseases (21–23). Hence, overall, there is a strong biological and epidemiologic rationale for a role of flavonoids in healthy aging, despite the limited research in this area.

Therefore, we investigated the relation of the intake of major subclasses of flavonoids at midlife (because midlife factors may be critical to preventing chronic conditions of aging which generally evolve over decades) to healthy aging in women from the Nurses' Health Study. As in previous publications (24–26), we defined healthy aging as surviving to older ages free of major chronic diseases and maintaining good cognitive, physical, and mental health.

SUBJECTS AND METHODS

Nurses' Health Study

The Nurses' Health Study began in 1976 when 121,700 female registered nurses aged 30–55 y, who were residing in 11 US states, completed a mailed questionnaire about their medical history, health, and lifestyle. Follow-up questionnaires are sent every 2 y; follow-up of the cohort remains $>90\%$ complete with 99% follow-up for mortality. In 1980, participants completed a 61-item semiquantitative food-frequency questionnaire (FFQ)⁴

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⁴ Abbreviations used: FFQ, food-frequency questionnaire; MHI, Mental Health Index; SF-36, Medical Outcomes Study Short-Form-36.

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(27). In 1984, the FFQ was expanded to 116 items, and similar FFQs were sent in 1986 and every 4 y thereafter. In 1992, 1996, and 2000, the Medical Outcomes Study Short-Form-36 (SF-36) was administered, which is a 36 item-questionnaire that evaluates 8 health concepts including mental health and physical functioning (28). From 1995 to 2001, a cognitive study was initiated in 21,202 participants who were ≥ 70 y old at that time and free of stroke. The study was approved by the Institutional Review Board of Brigham and Women's hospital (Boston, MA).

Ascertainment of flavonoid intake

We used 1984 and 1986 FFQs to ascertain intake of flavonoid-rich foods at midlife (except onion intake, which was determined by using the 1990 FFQ, which was the first questionnaire to include a specific question on onions). We computed midlife intakes of flavonoid subclasses by averaging intakes from 1984 and 1986 dietary assessments (or 1990 when relevant).

On the FFQs, participants were asked how often, on average, they consumed a standard portion size of each food. The reliability and validity of the FFQ has been described elsewhere in detail (29).

Intakes of flavonoid-rich foods were converted into different flavonoid subclasses by multiplying the consumption of each food by its flavonoid content. In this study, we focused on the following 6 main subclasses commonly consumed in the US diet: flavonols (quercetin, kaempferol, myricetin, and isohamnetin), flavones (luteolin and apigenin), flavanones (eriodictyol, hesperetin, and naringenin), flavan-3-ol monomers (catechins and epicatechins), flavan-3-ol polymers (including proanthocyanidins, theflavins, and thearubigins), and anthocyanins (cyanidin, delphinidin, malvidin, pelargonin, petunidin, and peonidin). Flavonoid contents of foods were obtained from a specific database constructed previously by using, as a primary source, the updated and expanded USDA flavonoid contents of foods and proanthocyanidin databases (30, 31). Moreover, for foods in the FFQ for which there were no values available in the USDA database, we searched a European database (EuroFIR eBASIS; <http://www.eurofir.org>) and other sources to ensure all available high-quality data on flavonoid values were included in the database. Thus, we were able to quantify a broad range of flavonoid subclass intakes more robustly than in previous flavonoid-based analyses (32).

Ascertainment of covariates

Sociodemographic, lifestyle, and health-related covariates (e.g., age, nurse's education, husband's education, marital status, father's and mother's occupations when the nurse was 16 y old, family histories of diabetes, cancer, and myocardial infarction, physical activity, smoking, multivitamin and aspirin use, BMI (in kg/m^2), history of high blood pressure, and history of hypercholesterolemia) were obtained from biennial questionnaires. Because the covariates of husband's education and father's and mother's occupations did not influence primary relations of diet to healthy aging in multivariable models, these covariates were not controlled for in the results presented in this article. Median annual household income and home value were estimated from the census tract of each participant's residence geocoded to the

2000 US Census. We averaged energy intakes across 1984 and 1986 questionnaires to represent the mean exposure at baseline. In addition, the overall diet quality was evaluated by using the Alternate Healthy Eating Index-2010, which reflects Dietary Guidelines for Americans and incorporates recent knowledge on nutrients and chronic disease risk (33); we averaged scores between 1984 and 1986 FFQs to represent the midlife diet quality. Physical activity and histories of smoking, hypercholesterolemia, and hypertension were ascertained in 1986. All other covariates were determined at the time of first dietary assessment (i.e., in 1984), when these data were available. Thus, we had information on demographic, lifestyle, health, socioeconomic, and dietary variables to carefully control for potential confounding.

Ascertainment of healthy aging

We separated healthy aging from usual aging on the basis of 4 health domains as of 2000 when the simultaneous assessment of mental, physical, and cognitive function was completed for participants aged ≥ 70 y. Of subjects who survived to age ≥ 70 y as of 2000, we considered individuals to be healthy agers if they were free of 11 major chronic diseases with no impairment in cognitive function, no physical disabilities, and intact mental health (24–26); all remaining women were considered usual agers.

Assessment of chronic diseases

The prevalence of the 11 chronic diseases of interest as of 2000 (i.e., cancer other than nonmelanoma skin cancer, type 2 diabetes, myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis) was determined from biennial questionnaires. In this cohort of nurses, we have shown a high validity of self-reported information on health (34–37).

Assessment of cognitive function

Cognitive testing was performed by trained interviewers by using validated telephone interviews in all women aged ≥ 70 y as of 2000 who were free of stroke. For these analyses, we focused on scores from the Telephone Interview of Cognitive Status to evaluate global cognitive performance in our participants. The Telephone Interview of Cognitive Status (38) (range: 0–41 points) is a telephone adaptation of the Mini-Mental State Examination (39). To construct the healthy aging outcome, we considered a score > 31 as the absence of cognitive impairment according to standard criteria (40).

Assessment of physical function and mental health

We identified the impairment of physical function as the presence of any of the following limitations: 1) limited at least a little on moderate activities as assessed by the SF-36 (such as moving a table, bowling, or pushing a vacuum cleaner, climbing one flight of stairs, walking > 1 mile or walking several blocks, and bathing or dressing); or 2) limited a lot on more-difficult items (such as running, lifting heavy objects, lifting or carrying groceries, climbing several flights of stairs; bending, kneeling, or stooping).

In addition, on the basis of answers to the SF-36 Mental Health Index (MHI) (41), we constructed a mental health score (range: 0–100 points) (24). Good mental health was defined as an MHI score >84 (the median value in the analytic cohort).

Population for analysis

Of 19,415 nurses who participated in the cognitive function substudy, we excluded 2671 women with a history of the 11 chronic diseases previously listed as of 1986 and 2596 women with no dietary data in 1984 and 1986. We further excluded 43 nurses who did not complete the SF-36 and 287 women who skipped >2 items on the MHI or >5 items on the physical function scale, which left 13,818 participants available for analyses.

Statistical analyses

We assessed flavonoid intake when women were aged in their late 50s and very early 60s (median age: 59 y; upper and lower quartiles: 57 and 61 y, respectively) for several reasons. First, most chronic diseases and health conditions develop over many years, and thus, midlife risk factors are likely a key determinant of health in older ages. Second, imposing a long lag period between the ascertainment of flavonoid intakes and determination of healthy aging (average follow-up: 15.2 y) minimizes the possibility of reverse causation (i.e., an effect of disease or its treatment on dietary choices).

With the use of logistic regression, we estimated the odds of healthy aging compared with usual aging according to quintiles of mean intake of each flavonoid subclass across 1984–1986. Very few data were missing; for nurses' education and physical activity, data were missing for >4% of the sample (4.6% and 7.9%, respectively), thus, specific missing categories were created. We examined linear trends across quintiles of flavonoid intake by using a continuous variable in which participants in a given category were assigned the median value. All *P* values were 2 sided. Data were analyzed with the SAS software package version 9.1 (SAS Institute).

We conducted a series of secondary analyses. First, to identify whether associations with dietary flavonoids might be attributable to specific healthy aging domains, we modeled separately relations between flavonoids and each of the 4 healthy aging components. We also secondarily examined top dietary sources of flavonoid subclasses in relation to healthy aging (i.e., citrus fruit, onions, apples, tea, and berries, which accounted for >80% of the between-person variation in total flavonoid consumption in this cohort). In another set of secondary analyses, we examined the robustness of our definition of healthy aging; because there is no standard definition, we investigated alternative classifications. Specifically, we tried by using a more stringent definition for mental health limitations such that impairment in mental health was defined as an MHI score ≤ 60 [a standard cutoff for major depression in older populations (42)].

RESULTS

Of 13,818 participants in our study, 12,403 subjects (89.8%) had no cognitive impairment, 9565 subjects (69.2%) had none of the 11 chronic diseases in our definition of healthy aging, 5947 subjects (43.0%) had no mental health limitations, and 3750

subjects (27.1%) had no impairment of physical function. Overall, 1517 subjects (11.0%) were considered healthy agers, whereas the remaining 12,301 participants (89.0%) were considered usual agers (Table 1).

Of usual agers, multiple health domains were generally impaired. For example, 31.5% of usual agers had both chronic diseases and limitations in cognitive, physical, or mental health; 65.4% of usual agers had limitations in cognitive, physical, or mental health only, whereas 3.1% of usual agers had one or more chronic diseases only (data not shown in tables). After standardization for age, compared with usual agers, healthy agers had a lower prevalence of obesity and smoking, exercised more, and reported higher alcohol intake at midlife. Healthy agers also had a lower prevalence of hypertension and hypercholesterolemia than usual agers (Table 1).

When we considered flavonoid intake at midlife, healthy agers had higher baseline intakes of all subclasses of flavonoids (e.g., age-standardized average flavonol and anthocyanin intakes were 20.1 and 14.3 mg/d, respectively) compared with those of usual agers (19.1 and 12.2 mg/d, respectively) (Table 2). The overall diet, as reflected by the Alternate Healthy Eating Index-2010 score, was also of higher quality in healthy agers.

Flavonoid intake at midlife and odds of healthy aging

In age-adjusted analyses of flavonoid intake at midlife and healthy aging, greater intakes of most flavonoid subclasses (e.g., flavonols, flavones, flavanones, flavan-3-ol polymers, and anthocyanins), as well as total flavonoids, were related to better odds of healthy aging (all *P*-trend across quintiles < 0.05; Table 3). For example, the odds of healthy compared with usual aging was 1.47 (95% CI: 1.22, 1.76) for women in the upper compared with lower quintiles of total flavonoid intake. We showed no significant association with flavan-3-ol monomers (*P*-trend = 0.33).

In multivariable analyses, greater intakes of the majority of flavonoid classes (flavonols, flavones, flavanones, and anthocyanins) were related to better odds of healthy aging, with trends of increasingly better odds of healthy aging with increasing quintile of intake (all *P*-trend ≤ 0.02 ; Table 3). However, associations for specific quintile comparisons were generally significant in only the highest compared with lowest quintiles of intake. For example, compared with women in the lowest quintile of intake, women in the highest quintiles of flavone (32%; 95% CI: 10%, 58%), flavanone (28%; 95% CI: 8%, 53%), anthocyanin (25%; 95% CI: 4%, 50%), and flavonol (18%; 95% CI: -2%, 42%) intakes at midlife had greater odds of healthy aging after multivariable adjustment.

In secondary analyses of each component of healthy aging, flavones and flavanones were significantly associated with 2 of 4 domains in our definition of healthy aging (i.e., absence mental health limitations and impairment of physical function; all *P*-trend < 0.005; Table 4), although associations were generally weaker than for overall healthy aging. For example, compared with women in the lowest quintile, women in the highest quintiles of flavone and flavanone intakes had 32% (95% CI: 18%, 47%) and 24% (95% CI: 11%, 38%), respectively, better odds of no mental health limitations and 23% (95% CI: 8%, 40%) and 15% (95% CI: 1%, 31%), respectively, better odds of no physical function limitations. Flavonol and anthocyanin

TABLE 1
Age-standardized baseline characteristics (in 1984–1986) of healthy agers and usual agers in the Nurses' Health Study¹

	Healthy agers (<i>n</i> = 1517)	Usual agers (<i>n</i> = 12,301)
Age at baseline, ² y	58.6 ± 2.5 ³	59.1 ± 2.5
Education, %		
Associate's degree	73	78
Bachelor's degree	18	15
Graduate degree	9	6
Husband's education, %		
High school degree or less	47	52
College degree	29	28
Graduate school	24	20
Marital status, %		
Married	93	93
Widowed	5	5
Separated/divorced	2	3
BMI, %		
<22 kg/m ²	34	22
22–24.9 kg/m ²	38	33
25–29.9 kg/m ²	24	32
≥30 kg/m ²	3	13
Smoking, %		
Never	54	47
Former	35	36
Current	11	17
Physical activity, metabolic equivalent task-hours/wk	19.3 ± 22.2	14.1 ± 19.8
Energy intake, kcal/d	1701 ± 489	1736 ± 484
Alcohol intake, g/d	7.2 ± 10.6	6.7 ± 10.5
Regular aspirin use, %		
<1 tablet/wk	37	31
1–2 tablets/wk	38	32
>2 tablets/wk	25	37
Multivitamin use, %	57	61
History of high blood pressure, %	21	32
History of hypercholesterolemia, %	12	17
Family history of diabetes, %	26	29
Family history of cancer, %	16	18
Family history of myocardial infarction, %	16	18

¹Values were standardized to the age distribution of the study population. Percentages are of nonmissing values.

²Value was not age standardized.

³Mean ± SD (all such values).

intakes at midlife were marginally associated with an absence of mental health limitations and of impairment of physical function, respectively. For example, compared with the lowest quintile, women in the highest quintile of flavonol intake had

9% (95% CI: –2%, 23%) better odds of no limitation in mental health, and women with highest anthocyanin intake had 14% (95% CI: 0%, 30%) better odds of no physical function limitations. Greater flavonoid intake in midlife was not significantly

TABLE 2
Mean (±SD) age-standardized baseline flavonoid intake and overall diet (in 1984–1986) of healthy agers and usual agers in the Nurses' Health Study¹

Intake	Healthy agers (<i>n</i> = 1517)	Usual agers (<i>n</i> = 12,301)
Flavonols, ² mg/d	20.1 ± 12.8	19.1 ± 12.6
Flavones, mg/d	2.4 ± 1.3	2.2 ± 1.2
Flavanones, mg/d	52.2 ± 36.9	47.0 ± 33.3
Flavan-3-ol monomers, mg/d	54.0 ± 64.6	51.9 ± 62.2
Flavan-3-ol polymers, mg/d	233 ± 219	219 ± 211
Anthocyanins, mg/d	14.3 ± 16.9	12.2 ± 12.1
Total flavonoids, ² mg/d	376 ± 298	352 ± 282
Alternative Healthy Eating Index-2010 score	53.0 ± 10.4	50.6 ± 10.1

¹All values are average of intakes from 1984 and 1986 dietary assessments, except for flavonols, of which intakes were ascertained in 1990.

²Values are given for the subgroup of women with flavonols ascertained in 1990 (i.e., 11,040 usual agers and 1401 healthy agers).

TABLE 3
ORs (95% CIs) of healthy aging, according to quintiles of flavonoid intakes at midlife¹

	Flavonoid intake					<i>P</i> -trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Flavonols, mg/d	7.7 (6.2–8.8) ²	11.6 (10.7–12.5)	15.4 (14.4–16.7)	21.7 (19.7–24.1)	35.9 (31.2–43.2)	—
Healthy ager, <i>n</i>	243	272	267	308	311	—
Age adjusted	Reference	1.13 (0.95, 1.36)	1.11 (0.93, 1.34)	1.32 (1.10, 1.57)	1.35 (1.13, 1.61)	<0.001
Multivariable adjusted ³	Reference	1.01 (0.84, 1.22)	0.95 (0.78, 1.15)	1.13 (0.94, 1.36)	1.18 (0.98, 1.42)	0.02
Flavones, mg/d	0.9 (0.6–1.0)	1.5 (1.4–1.7)	2.1 (2.0–2.3)	2.7 (2.5–2.9)	3.7 (3.4–4.4)	—
Healthy ager, <i>n</i>	242	287	300	325	363	—
Age adjusted	Reference	1.22 (1.02, 1.46)	1.30 (1.09, 1.55)	1.41 (1.18, 1.68)	1.61 (1.36, 1.91)	<0.001
Multivariable adjusted ³	Reference	1.11 (0.92, 1.33)	1.15 (0.95, 1.38)	1.19 (0.99, 1.44)	1.32 (1.10, 1.58)	0.002
Flavanones, mg/d	9.0 (5.0–13.4)	26.8 (22.5–31.0)	43.1 (39.2–46.9)	60.0 (55.4–64.9)	89.8 (78.3–108.2)	—
Healthy ager, <i>n</i>	260	276	310	298	373	—
Age adjusted	Reference	1.07 (0.90, 1.28)	1.22 (1.03, 1.46)	1.18 (0.99, 1.41)	1.53 (1.29, 1.81)	<0.001
Multivariable adjusted ³	Reference	1.00 (0.83, 1.20)	1.11 (0.93, 1.33)	1.05 (0.87, 1.26)	1.28 (1.08, 1.53)	0.003
Flavan-3-ol monomers, mg/d	9.2 (6.9–11.3)	16.6 (14.7–18.7)	27.7 (24.0–32.8)	54.5 (46.0–64.3)	128.2 (96.6–178.0)	—
Healthy ager, <i>n</i>	255	326	319	305	312	—
Age adjusted	Reference	1.32 (1.11, 1.57)	1.30 (1.09, 1.55)	1.23 (1.03, 1.47)	1.26 (1.06, 1.50)	0.33
Multivariable adjusted ³	Reference	1.11 (0.92, 1.33)	1.07 (0.89, 1.28)	1.03 (0.86, 1.24)	1.04 (0.87, 1.25)	0.80
Flavan-3-ol polymers, mg/d	55 (41–67)	100 (89–112)	152 (138–169)	238 (211–271)	478 (377–641)	—
Healthy ager, <i>n</i>	251	307	319	315	325	—
Age adjusted	Reference	1.27 (1.06, 1.51)	1.32 (1.11, 1.57)	1.30 (1.09, 1.55)	1.35 (1.13, 1.60)	0.02
Multivariable adjusted ³	Reference	1.11 (0.92, 1.33)	1.11 (0.92, 1.33)	1.05 (0.88, 1.27)	1.10 (0.92, 1.32)	0.63
Anthocyanins, mg/d	2.8 (1.8–3.6)	5.6 (4.9–6.4)	9.4 (8.3–10.6)	14.5 (13.1–16.0)	24.2 (20.4–32.1)	—
Healthy ager, <i>n</i>	242	262	289	342	382	—
Age adjusted	Reference	1.10 (0.91, 1.32)	1.23 (1.02, 1.47)	1.47 (1.24, 1.75)	1.69 (1.43, 2.01)	<0.001
Multivariable adjusted ³	Reference	0.97 (0.80, 1.18)	1.04 (0.86, 1.26)	1.18 (0.98, 1.42)	1.25 (1.04, 1.50)	0.002
Total flavonoids, mg/d	124 (99–144)	194 (178–211)	269 (248–291)	383 (348–428)	705 (568–918)	—
Healthy ager, <i>n</i>	221	281	291	299	309	—
Age adjusted	Reference	1.32 (1.09, 1.59)	1.38 (1.15, 1.66)	1.42 (1.18, 1.71)	1.47 (1.22, 1.76)	0.001
Multivariable adjusted ³	Reference	1.14 (0.94, 1.38)	1.12 (0.92, 1.35)	1.12 (0.92, 1.36)	1.18 (0.97, 1.42)	0.22

¹ORs >1 denote greater odds of healthy aging. These analyses included 1517 healthy agers compared with 12,301 usual agers for all flavonoid subclasses except flavonols and total flavonoids, for which analyses included 1401 healthy agers and 11,036 usual agers (e.g., women with flavonols ascertained in 1990).

²Median; IQR in parentheses (all such values).

³Logistic regression models were adjusted for age (y); education (associate's degree, bachelor's degree, graduate degree); marriage status (married, widowed, or separated/divorced); median income (quintiles); median house value (quintiles); family histories of diabetes, cancer, and myocardial infarction (yes or no); physical activity (quintiles of metabolic equivalent task-hours); energy intake (quintiles of kcal); smoking (never smoker, past smoker of 1–14, 15–24, or ≥25 cigarettes/d, or current smoker of 1–14, 15–24, or ≥25 cigarettes/d); multivitamin use (yes or no); aspirin use (<1, 1–2, or >2 tablets/wk); BMI (in kg/m²; <22, 23–24, 25–29, or ≥30); history of high blood pressure (yes or no); history of hypercholesterolemia (yes or no); and Alternative Healthy Eating Index-2010 score (quintiles).

related to odds of no chronic diseases or cognitive impairment (all *P*-trend ≥ 0.17; Table 4). In secondary analyses that examined a more stringent definition of mental health limitations (i.e., with impaired mental health defined as an MHI score ≤60), results were generally similar (data not shown in tables), which suggested that findings were robust to variations in this cutoff.

Intake of dietary sources of flavonoids at midlife and odds of healthy aging

We further examined major dietary sources of flavones, flavanones, anthocyanins, and flavonols (i.e., the flavonoid subclasses significantly associated with healthy aging in the main analysis). Citrus fruit were main food sources of flavones and flavanones in our cohort (23), and when we examined the relation of citrus intake (fresh fruit and juices) at midlife to healthy aging, we showed that higher intake of oranges was related to modestly better odds of healthy aging after multivariable adjustment [OR: 1.30 (95% CI: 1.01, 1.67) for ≥5 servings/wk compared with <1 serving/mo; *P*-trend = 0.01; Table 5]. Intake of grapefruit [less-important contributors of flavonols and flavones than

oranges were in the cohort (23)] at midlife was not associated with odds of healthy aging (*P*-trend = 0.27). Likewise, onions, which were the main source of flavonols, were related to modestly better odds of healthy aging [OR (95% CI: 1.10, 1.64) for ≥5 servings onions/wk compared with <1 serving onions/mo = 1.34; *P*-trend = 0.003]. There was a trend of increasingly better odds of healthy aging with increasing intake of apples, which are another source of flavonols (*P*-trend = 0.008), although the increased odds of healthy aging in women with ≥5 servings/wk compared with <1 serving/mo was quite modest and did not reach significance (OR: 1.14; 95% CI: 0.89, 1.46). Moreover, tea, which is a source of flavonols (and the main source of flavan-3-ol and polymers) was not related to healthy aging (*P*-trend = 0.89). Finally, berries (strawberries and blueberries) were the top contributors of anthocyanins, and higher berry intake at midlife was significantly related to better odds of healthy aging (*P*-trend = 0.04). For example, compared with women with <1 serving berries/wk, women with ≥2 servings berries/wk had a 24% (95% CI: 0%, 54%) greater odds of healthy aging in multivariate models.

TABLE 4
ORs (95% CIs) of each component of healthy aging according to quintiles of flavonoid intakes at midlife¹

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend
Flavonols						
Healthy aging component:						
No chronic disease	Reference	1.05 (0.93, 1.19)	1.12 (0.99, 1.27)	1.11 (0.98, 1.26)	1.00 (0.89, 1.13)	0.75
No cognitive impairment (TICS score ≥ 31)	Reference	0.85 (0.70, 1.02)	0.90 (0.74, 1.09)	0.88 (0.72, 1.06)	0.92 (0.76, 1.11)	0.82
No impairment of physical function	Reference	1.03 (0.90, 1.18)	0.95 (0.83, 1.09)	1.19 (1.04, 1.36)	1.07 (0.94, 1.23)	0.10
No limitation of mental health (MHI score < 84)	Reference	1.00 (0.90, 1.13)	0.97 (0.87, 1.09)	1.06 (0.95, 1.19)	1.09 (0.98, 1.23)	0.04
Flavones						
No chronic disease	Reference	1.02 (0.90, 1.14)	1.06 (0.94, 1.19)	1.02 (0.91, 1.15)	1.09 (0.97, 1.23)	0.17
No cognitive impairment (TICS score ≥ 31)	Reference	1.00 (0.84, 1.20)	1.04 (0.87, 1.24)	1.15 (0.96, 1.38)	1.00 (0.84, 1.20)	0.63
No impairment of physical function	Reference	1.09 (0.95, 1.24)	1.12 (0.98, 1.27)	1.09 (0.96, 1.25)	1.23 (1.08, 1.40)	0.004
No limitation of mental health (MHI score < 84)	Reference	1.08 (0.96, 1.20)	1.18 (1.05, 1.31)	1.21 (1.08, 1.35)	1.32 (1.18, 1.47)	< 0.001
Flavanones						
No chronic disease	Reference	1.07 (0.96, 1.21)	1.14 (1.01, 1.28)	1.07 (0.95, 1.21)	1.10 (0.97, 1.24)	0.20
No cognitive impairment (TICS score ≥ 31)	Reference	1.24 (1.04, 1.48)	1.14 (0.96, 1.36)	1.28 (1.07, 1.53)	1.06 (0.90, 1.26)	0.61
No impairment of physical function	Reference	0.89 (0.78, 1.01)	1.03 (0.91, 1.17)	0.97 (0.86, 1.11)	1.15 (1.01, 1.31)	0.005
No limitation of mental health (MHI score < 84)	Reference	1.09 (0.98, 1.22)	1.15 (1.03, 1.28)	1.15 (1.03, 1.28)	1.24 (1.11, 1.38)	< 0.001
Anthocyanins						
No chronic disease	Reference	0.99 (0.88, 1.11)	0.93 (0.83, 1.05)	1.06 (0.94, 1.20)	1.02 (0.90, 1.16)	0.36
No cognitive impairment (TICS score ≥ 31)	Reference	1.02 (0.85, 1.21)	1.12 (0.93, 1.34)	1.07 (0.89, 1.28)	1.04 (0.86, 1.25)	0.74
No impairment of physical function	Reference	0.96 (0.84, 1.09)	0.96 (0.84, 1.09)	1.01 (0.89, 1.15)	1.14 (1.00, 1.30)	0.009
No limitation of mental health (MHI score < 84)	Reference	1.03 (0.92, 1.14)	1.08 (0.96, 1.20)	1.08 (0.97, 1.21)	1.09 (0.97, 1.23)	0.12

¹ORs > 1 denote greater odds of the healthy aging component. For flavones, flavanones, and anthocyanins (all ascertained in 1984–1986), analyses included comparison of 9565 women with no chronic disease and 4253 women with at least one chronic disease; 12,403 women with an absence of cognitive impairment and 1415 women with presence of cognitive impairment; 3750 women with unimpaired physical function and 10,068 women with impaired physical function; and 5947 women with no limitation and 7871 women with a limitation of mental health. For flavonols (ascertained in 1990), analyses included comparison of 8634 women with no chronic disease and 3807 women with at least one chronic disease; 11,195 women with an absence of cognitive impairment and 1246 women with a presence of cognitive impairment; 3418 women with unimpaired physical function and 9023 women with impaired physical function; and 5403 women with no limitation and 7038 women with a limitation of mental health. Logistic regression models were adjusted for age (y); education (associate's degree, bachelor's degree, graduate degree); marriage status (married, widowed, or separated/divorced); median income (quintiles); median house value (quintiles); family histories of diabetes, cancer, and myocardial infarction (yes or no); physical activity (quintiles of metabolic equivalent task-hours); energy intake (quintiles of kcal); smoking (never smoker, past smoker of 1–14, 15–24, or ≥ 25 cigarettes/d, or current smoker of 1–14, 15–24, or ≥ 25 cigarettes/d); multivitamin use (yes or no); aspirin use (< 1 , 1–2, or > 2 tablets/wk); BMI (in kg/m^2 ; < 22 , 23–24, 25–29, or ≥ 30); history of high blood pressure (yes or no); history of hypercholesterolemia (yes or no); and Alternative Healthy Eating Index-2010 score (quintiles). MHI, Mental Health Index; TICS, Telephone Interview for Cognitive Status.

DISCUSSION

In this large prospective study, higher intake of several flavonoid subclasses (i.e., flavones, flavanones, anthocyanins, and flavonols) was associated with better odds of healthy aging. Relations were supported by consistent associations with the main food sources of these flavonoids (i.e., oranges, berries, onions, apples). Together, our findings suggest that flavonoids may be important to promoting broad health and wellbeing in aging.

Our study had important strengths, including the large sample size, high follow-up, and a comprehensive, multidomain evaluation of healthy aging with validated instruments. Moreover, we evaluated dietary habits by using repeated, validated FFQs in midlife, which is likely the most-relevant period of exposure for preventing chronic conditions of aging that develop over many years. We also used an updated flavonoid database containing a large number of foods that are relevant in an American population for the assessment of 6 flavonoid subclasses. We minimized possible bias because of reverse causation (i.e., that poor health leads to poor diet rather than the reverse) by excluding participants with chronic diseases at baseline and imposing a long lag between the dietary assessment and healthy aging. Potential limitations of our study should also be considered. Our sample

included female, mostly white health care professionals with generally high levels of education. This inclusion was useful to decrease extraneous variability and enhance the validity of health information, but results may not be generalizable to populations with different demographic features. Moreover, there might also have been measurement error in the assessment of dietary exposure, especially for total flavonoid intakes that combined subclasses derived from different FFQs (i.e., 1984–1986 and 1990). However, such measurement error was not likely to have affected differently cases and controls and, thus, would most likely have led to underestimations of the magnitude of the associations between flavonoids and healthy aging. Because we examined several flavonoid subclasses and flavonoid-rich foods, multiple tests were conducted (e.g., the main analysis on flavonoid subclasses was based on 7 different statistical tests), and there was some possibility that multiple comparisons may have been an issue. Furthermore, in studies of older populations, there is risk of survival bias. However, death rates before age 70 y were quite low in our cohort; in addition, by imposing similar requirements for survival on both healthy and usual agers, our methods limited opportunities for such bias. Finally, in an observational study, there is always concern for confounding. We adjusted for many potential confounders, including lifestyle,

TABLE 5

ORs (95% CIs) of healthy aging according to categories of intake of major food sources of flavones, flavanones, anthocyanins, and flavonols at midlife¹

	Intake category					<i>P</i> -trend
	<1 serving/mo	1–3 servings/mo	1 serving/wk	2–4 servings/wk	≥5 servings/wk	
Oranges ²	Reference	1.29 (0.95, 1.74)	1.06 (0.81, 1.37)	1.20 (0.92, 1.55)	1.30 (1.01, 1.67)	0.01
Grapefruit ²	Reference	1.15 (0.98, 1.35)	1.14 (0.97, 1.33)	1.22 (1.02, 1.45)	1.12 (0.90, 1.40)	0.27
Onions	Reference	1.09 (0.86, 1.37)	1.17 (0.96, 1.43)	1.23 (1.00, 1.51)	1.34 (1.10, 1.64)	0.003
Apples	Reference	0.92 (0.72, 1.16)	0.87 (0.70, 1.08)	1.05 (0.83, 1.31)	1.14 (0.89, 1.46)	0.008
Tea	Reference	0.89 (0.70, 1.12)	0.86 (0.60, 1.26)	0.87 (0.69, 1.10)	0.97 (0.80, 1.18)	0.89
Berries ³	Reference ⁴	1.14 (1.02, 1.29) ⁵	1.24 (1.00, 1.54) ⁶	—	—	0.04

¹ORs >1 denote greater odds of healthy aging. These analyses included 1517 healthy agers versus 12,301 usual agers for all foods except onions, for which analyses included 1401 healthy agers and 11,036 usual agers (e.g., women with onion intake assessed in 1990). Logistic regression models were adjusted for age (y); education (associate's degree, bachelor's degree, graduate degree); marriage status (married, widowed, or separated/divorced); median income (quintiles), median house value (quintiles); family histories of diabetes, cancer, and myocardial infarction (yes or no); physical activity (quintiles of metabolic equivalent task-hours); energy intake (quintiles of kcal); smoking (never smoker, past smoker of 1–14, 15–24, or ≥25 cigarettes/d, or current smoker of 1–14, 15–24, or ≥25 cigarettes/d); multivitamin use (yes or no); aspirin use (<1, 1–2, or >2 tablets/wk); BMI (in kg/m²; <22, 23–24, 25–29, or ≥30); history of high blood pressure (yes or no); history of hypercholesterolemia (yes or no); and Alternative Healthy Eating Index-2010 score (quintiles). Foods were introduced in separate models.

²Included intakes of fresh fruit and juices.

³Strawberries and blueberries.

⁴<1 serving/wk.

⁵1 serving/wk.

⁶2 servings/wk.

socioeconomic, and health factors; however, we could not exclude the possibility of unmeasured confounding, and results should be interpreted with caution.

In previous research, a number of diseases and conditions considered in our healthy aging outcome have been individually associated with flavonoid intake. For example, the 3 most-common chronic diseases in our population were myocardial infarction and coronary artery bypass surgery (12% of usual agers), diabetes (8%), and breast cancer (6%), and consistent associations between greater flavonoid intake and lower risk of these diseases have been reported. In a pooled analyses of cohort studies that involved ~200,000 US participants, anthocyanins were related to lower risk of type 2 diabetes (19), and meta-analyses have established associations between flavonols and flavones and lower risks of coronary heart diseases (43, 44) and breast cancer (especially in postmenopausal women) (45). Associations with other types of cancers (e.g., lung, colorectal, or ovarian cancers) have been less consistent in previous studies (46–49), although these cancers contributed minimally to our healthy aging outcome (e.g., <1.5% of usual agers).

Flavonoid intake has been related to better cognitive health, although data has been more limited. In several small randomized controlled trials, flavonoid supplementation improved cognitive function (50, 51), and accordingly, greater intakes of total flavonoids and of anthocyanins (and berries, which are their main food source) were related to a lower rate of cognitive decline in 2 large populations of older persons (22, 23). Therefore, the overall, previous literature supports a role of flavonoids on a wide range of age-related diseases and brain health in aging as we showed in our large epidemiologic study.

Flavonoids may contribute to reducing chronic diseases and maintaining physical, cognitive, and mental health with aging via their potential to decrease oxidative stress and inflammation,

which are 2 general pathways underlying many age-related chronic diseases and health conditions. Indeed, aging has been associated with chronic, low-grade oxidative stress and inflammation, both in the periphery and central nervous system, which may trigger the development of chronic diseases and cognitive and behavioral changes (52–54). Antioxidant and anti-inflammatory properties of flavonoids have been shown in vitro (6), and a few observational studies have related specific flavonoids (e.g., flavones and flavanones) to lower blood concentrations of oxidative and inflammatory markers (55, 56), suggesting a potential ability to improve systemic inflammatory status in humans. Moreover, animal studies have shown that flavonoids, especially anthocyanins, improve glucose metabolism and insulin resistance by modulating the expression of glucose transporter proteins (57, 58). Also, substantial experimental data have suggested that flavonoids may decrease neuroinflammation via their potential to modulate signaling pathways controlling the activation of glial cells and those determining neuronal apoptosis and neurogenesis in the hippocampus (a key structure for memory and mood), thereby lowering age-related cognitive impairment, depression, and anxiety in rodents (8, 59).

In conclusion, our findings suggest that intake of dietary flavonoids at midlife may be related to improved odds of overall health and wellbeing in aging. Because the avoidance of the spectrum of health conditions in aging may be of more importance to individuals than avoiding any single chronic disease, these findings could help the adherence to public health recommendations regarding diet quality.

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