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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Association of Dietary Intake of Flavonols With Changes in Global Cognition and Several Cognitive Abilities

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Equal Author Contribution:

Figure Count:

2

Table Count:

3

Search Terms:

[25] All Cognitive Disorders/Dementia, [36] Cognitive aging, [54] Cohort studies, Flavonoids, Nutrition

Disclosures:

The authors report no relevant disclosures.

ABSTRACT

Background and Objective: Previous research has examined the association between cognition and flavonoids: bioactives found in foods, known to possess anti-inflammatory and antioxidant properties. We extend this research by investigating associations of dietary intakes of total flavonols and constituents (kaempferol, quercetin, myricetin, isorhamnetin) on the change in cognitive performance in global cognition, episodic memory, semantic memory, visuospatial ability, perceptual speed, and working memory

Methods: The study was conducted using 961 participants (60-100 years) of the Rush Memory and Aging Project, a prospective cohort of community-dwelling Chicagoans who were followed for an average of 6.9 years. Diet was assessed using a validated semi-quantitative food frequency questionnaire. Cognitive performance was assessed annually with a battery of 19 standardized tests. Flavonol intake was analyzed as a continuous variable using linear mixed effects models. Cognitive domain scores were regressed on baseline calorie-adjusted flavonol variables.

Results: Higher dietary intake of total flavonols and flavonol constituents were associated with a slower rate of decline in global cognition and multiple cognitive domains. In continuous models adjusted for age, sex, education, APOE-ε4, late life cognitive activity, physical activity, and smoking, total flavonol intake was associated with slower decline in global cognition β estimate=0.004 (95% CI=0.001, 0.006), episodic memory β=0.004 (95% CI: 0.002, 0.006), semantic memory β=0.003 (95% CI: 0.001, 0.007), perceptual speed β=0.003 (95% CI: 0.001, 0.004), and working memory β=0.003 (95% CI: 0.001, 0.005) and marginally associated with visuospatial ability β=0.001 (95% CI: -0.001, 0.003). Analyses of individual flavonol constituents demonstrated that intakes of kaempferol and quercetin were associated with slower global cognitive decline [β=0.01 (95% CI: 0.006, 0.02) and β=0.004 (95% CI: 0.0005, 0.007)], respectively. Myricetin and isorhamnetin were not associated with global cognition.

Conclusion: Results suggest dietary intakes of total flavonols and several flavonol constituents may be associated with slower decline in global cognition and multiple cognitive abilities with older age.

INTRODUCTION

Flavonoids are a large class of bioactive polyphenolic compounds found in plants, with a substantial amount found in fruits and vegetables, in particular. Many flavonoids are known to have antioxidant and anti-inflammatory properties. These inherent facets are recognized as having the capability to prevent or diminish cellular damage throughout the body, including the brain.[1-3] Mechanistically, this is accomplished given their biochemical structure which provides the capability to prevent oxidative stress from reactive oxygen species and free radicals and decrease harmful neuroinflammation. [4-6]

In previous studies, high total intake of flavonoids and some subclasses has been associated with a slower rate of age-related global cognitive decline as well as Alzheimer's dementia.[1,7-10] However, there has been limited investigation of flavonoid subclasses—and even further, individual constituents that make up those subclasses—and brain health[1,11]. For example, much of the data on individual flavonoids originates from animal studies. Specifically, studies in mice have demonstrated that the constituents of the flavonoid subclass, flavonols—kaempferol, quercetin, myricetin and isorhamnetin— are particularly important for learning and memory.[12-14] Nevertheless, exploration of the relationship between the flavonol constituents and cognition in humans is limited. Therefore, in this study we explored associations of total and individual flavonols, including kaempferol, quercetin, myricetin, and isorhamnetin, with cognitive decline in a community cohort of older persons. We also investigated the role of total and individual flavonols on specific cognitive domains including episodic memory, semantic memory, visuospatial ability, perceptual speed, and working memory.

METHODS

Study Population

The study was completed in the Rush Memory and Aging Project (MAP), a 1997-present cohort study comprised of Chicago residents of retirement communities and senior public housing with no known dementia at baseline. The participants undergo yearly, in person, clinical evaluations with detailed risk factor assessments and cognitive testing. Beginning in 2004, dietary data was collected using a validated self-administered food frequency questionnaire. Starting August, 2018; 2,022 participants without known dementia at baseline were enrolled in the Memory and Aging Project[15]. Of those, 92 died or withdrew from the study before dietary data collection began in 2004. We further excluded those who were enrolled after 2004 but died or withdrew from the study prior to any FFQ assessment (n=361), refused to fill out the FFQ (n=7), or completed the FFQ but the derivation of dietary data was in process (n=494), leaving 1068 participants with complete nutrient data. Of the 1068 participants, 98 did not have a minimum of two clinical assessments to evaluate change in cognitive function, thus leaving 970 participants. We further excluded 9 individuals, from the analytical dataset, who had missing data on model covariates. This provided 961 participants for which we conducted analyses of dietary flavonol intake with cognitive change (Figure 1.)

Standard protocol approvals, registrations, and patient consents

The institutional review board of Rush University Medical Center approved the study and all participants gave written, informed consent.

Data availability

The anonymized data, used for the study, are available through the Rush Alzheimer's Disease Center (RADC). Qualified investigators can find information regarding the formal requirements for access to data on the RADC research resource-sharing hub (radc.rush.edu).

Cognitive Assessment

The annual structured clinical evaluations include a battery of 19 cognitive tests administered by trained and certified technicians. Composite scores of global cognition (all 19 tests) and five cognitive domains were calculated using the average of standardized scores[16] of the individual tests, including for episodic memory (7 tests, including: word list, word list recall, word list recognition, East Boston immediate recall, East Boston delayed recall, logical memory immediate recall, and logical memory delayed recall.), semantic memory (3 tests, including; Boston naming-15 items, category fluency, and reading test-10 items) , visuospatial ability (2 tests , including; line orientation and progressive matrices-16 items), perceptual speed (4 tests, including; simple digits modality test, number comparison, Stroop color naming, and Stroop word reading.), and working memory (3 tests, including; digits forward, digits backward, digits ordering). The composite measure of each aforementioned domain was formed by converting raw scores on each cognitive test, making up the domain, to z scores, using the mean and standard deviation of the cohort, and then averaging the z scores to yield the composite.

Dietary Assessment

Diet was assessed using a modified version of the Harvard food frequency questionnaire (FFQ) that was validated for use in an older Chicago population [17]. For these analyses, baseline FFQ was used

to establish the dietary intake of flavonols. The MAP FFQ ascertains usual frequency of intake of 144 food items consumed over the previous 12 months. Total calorie intake and nutrient levels for each of the food items were based on natural proportion sizes, (e.g. 1 egg), or according to age and sex specified serving sizes reported in national diet surveys. The various flavonol contents of foods are based on the Nutrition Coordinating Center Flavonoid and Proanthocyanidin Provisional Table from the University of Minnesota[18], which draws heavily on the USDA Database for the Flavonoid Content of Selected Foods, Release 3.3 (March 2018,) and The USDA Database for the Proanthocyanidin Content of Selected Foods, Release 2.1 (March 2018), with additional data from other study publications.[19]
 Using the aforementioned database, we derived the flavonoid content for each food item within our FFQ as milligrams per 100g. We then multiplied this by the serving size, grams per serving, to obtain the flavonoid amounts (milligrams per serving) for each food item. The flavonoid contents were multiplied by the frequency of intake (servings per day) and summed across all food items to obtain total daily intake of each flavonoid.

$$flavonoid\ content\ (mg/100g)\ x\ serving\ size\ (g/serving) = flavonoid\ content\ (mg/serving)$$

$$flavnoid\ content\ (mg/serving)\ x\ intake\ f\ (serving/day); \sum food\ items = participants\ total$$
$$flavonoid\ intake\ in\ (mg/day)$$

The top food item contributors to the individual flavonoids (subgroup flavonols) presented in this current study, shown as the mean(SD) of flavonol intake (in milligrams/day), were: kale 0.07(0.15), beans 0.19(0.22), tea 0.22(0.34), spinach 0.12(0.15), and broccoli 0.20(0.18) for kaempferol; tomatoes 0.10(0.09), kale 0.07(0.15), apples 0.29(0.29), and tea 0.22(0.34) for quercetin; tea 0.21(0.34), wine 0.18(0.41), kale 0.06(0.15), oranges 0.22(0.29), and tomatoes 0.28(0.28) for myricetin, and pears 0.10(0.17), olive oil 0.15(0.24), wine 0.18(0.41), and tomato sauce 0.06(0.06) for isorhamnetin.

Nutrients and polyphenols were calorie-adjusted using the regression residual method, a method of

analyses by which the dietary intakes of nutrients, and/or bioactives are evaluated in relation to total dietary calories.[17] For analyses, the first completed valid FFQ established the baseline for each participant. Total flavonol intake was moderately stable (Spearman's r=0.60; p<0.0001), between the first and last acquired FFQ which were on average, 3 years apart with an intra-class correlation between r= 0.37 and r= 0.60.

Model Covariates

Non-dietary covariates were obtained from measurements and structured interview questions at the participants' baseline clinical evaluation. Education (years) is self-reported years of regular schooling. APOE- genotyping was performed using high throughput sequencing as previously described [20]. Age (in years) at the analytical baseline visit was computed from self-reported birth date and the date of the baseline cognitive assessment and is utilized in these analyses as a continuous variable. Age is an established risk factor for cognitive decline. Physical activity (hours per week) was computed from self-reported minutes spent within the previous two weeks on five activities: walking for exercise, yard work, calisthenics, biking, and water exercise [21]. Participation in cognitively stimulating activities was computed as the average frequency rating, based on a 5-point scale, of different activities (e.g. reading, playing games, writing letters, visiting the library) [22]. Utilizing the FFQ responses calorie measures are calculated by Harvard University. The total energy of each food item, Calories, are based on age-specific portion sizes from national dietary surveys or natural portion sizes. Smoking status was self-reported at baseline utilizing two questions, "Do you smoke cigarettes now?" and "Did you ever smoke cigarettes?" The responses to these questions determined smoking history, defined as "never smokers", versus "former smokers", versus "current smokers."[23] Body Mass Index (weight in kg/height in m^2) was computed from measured weight and height and modeled as two indicator variables,

BMI≤20 and BMI ≥30, with the referent group 20< BMI <30. The number of depressive symptoms was evaluated by a modified 10-item version of the Center for Epidemiological Studies-Depression scale [24]. Myocardial infarction history was based on self-reported medical diagnosis or use of cardiac glycosides (e.g. lanoxin, digitoxin). Diabetes history was determined by self-reported medical diagnosis or current use of diabetic medications. Clinical diagnosis of stroke was based on clinician review of self-reported history and neurological examination.[25] Hypertension history was determined by self-reported medical diagnosis, measured blood pressure (average of 2 measurements ≥160 mmHg systolic or ≥90 mmHg diastolic) or current use of hypertensive medications[15]. Dietary intakes of nutrients that have been associated with cognition, vitamin E[26], saturated fat[27], folate[28], lutein[29], and omega-3 fatty acids[30,31] are measured via the aforementioned food frequency questionnaire. The individual nutrient measures were calculated from the FFQ responses by determining the nutrient content (grams per serving) for each food item and multiplying by the frequency of intake. In the same fashion as was done with flavonoids, the intake was summed across all food items to obtain total daily intake of each nutrient, in milligrams per day.

Statistical Analyses

To investigate the association between dietary intakes of total flavonols and flavonol constituents to global cognition and five cognitive domains, we used linear mixed models in SAS© 9.4. Basic-adjusted models included covariates with the most established scientific evidence for association with cognitive decline[32], including age, sex, education, participation in cognitively stimulating activities, physical activity, smoking and APOE-ε4 status. In an effort to investigate and address potential confounding due to disease processes with established associations to cognitive decline, further models included additional covariates (e.g., depressive symptoms and BMI and individual

cardiovascular diseases) to the basic-adjusted model. We analyzed flavonol intake as a continuous

variable. All model estimates are presented as Beta coefficients and 95% confidence intervals. Effect

modification was investigated between flavonol associations and various covariates by including the

products of the flavonol variables and potential effect modifiers (e.g., age, sex, education, APOε-4

status) in the basic-adjusted model, with a significance level at p ≤ 0.05. Statistically significant

interactions were further investigated by stratifying on the effect modifier and re-analyzing the basic-

adjusted models.

RESULTS

The study sample population, of 961 individuals, was followed for an average of 6.9 years (± 3.6), had a

mean age at baseline of 81.4 years (SD=7.2) with an age range of 58-100 years of age. The analytical

sample had an average educational level of 15.0 years (± 2.9), and was primarily female (75%) and non-

Latino White (98%), with 22% having at least one APOE-ε4 allele, and 42% reporting a history of

smoking. Participants with the highest levels of flavonol intake were on average younger, more

educated, consumed fewer calories and were more physically and cognitively active than those with

the lowest flavonol intakes. (Table 1) Dietary intake of the individual flavonols had low to moderate

correlations with each other (Spearman r range 0.11 to 0.49; all p≤0.05). Mean intake of total flavonols

was 9.6 (SD=3.6) mg/day, Kaempferol 1.89 (1.49) mg/day, Quercetin 7.05 (2.42) mg/day, Myricetin

0.58 (0.50) mg/day, and Isorhamnetin 0.10 (.012) mg/day.

Higher dietary intakes of total flavonols and flavonol constituents were associated with a slower

rate of decline in global cognition and several cognitive domains (Table 2). In the basic-adjusted

continuous model, higher intake of total dietary flavonols was associated with slower rate of decline in

global cognition, episodic memory, semantic memory, perceptual speed, and working memory. (Table

2) Total flavonol intake through diet was not associated with change in visuospatial ability. (Table 2)

This is re-demonstrated when comparing quintile 5 vs quintile 1; dietary intake of total flavonols was associated with global cognition β= 0.04 (95% CI: 0.02, 0.06) (Figure 2), episodic memory β= 0.05 (95% CI: 0.03, 0.08), semantic memory β= 0.04 (95% CI: 0.01, 0.06), perceptual speed β= 0.02 (95% CI: 0.0003, 0.04), and working memory β= 0.03 (95% CI: 0.002, 0.05).

In analyses of individual flavonol constituents as continuous variables, higher kaempferol intake was associated with slower decline in the global cognitive score and all five cognitive domains. (Table 2) Quercetin intake was associated with slower decline in global cognition, episodic memory and semantic memory and suggestive for both perceptual speed and working memory. (Table 2) Isorhamnetin was associated with a slower rate of episodic memory and suggestive for visuospatial memory. Myricetin was not associated with change in any cognitive abilities but was suggestive for working memory. (Table 2). The highest quintile vs lowest quintile intake of the flavonol constituents Kaempferol β= 0.04 (95% CI: 0.02, 0.07), Quercetin β= 0.02 (95% CI: 0.0002, 0.05), and Myricetin β= 0.03 (95% CI: 0.003, 0.05) were associated with a decrease in the rate of global cognitive decline (Figure 2). Q5 versus Q1 intake of Isorhamnetin was not associated with global cognition (Figure 2).

We investigated possible confounding due to cardiovascular conditions on the observed protective relations of flavonol intake to cognitive decline by adding these covariates (myocardial infarction, stroke, diabetes, and hypertension) to the basic-adjusted model. However, there were no material changes in the effect estimates or the findings (Table 3).

In further analyses, we re-analyzed the data with the addition of BMI and depressive symptoms to the basic-adjusted model, covariates that have the potential to be both confounders and/or clinical manifestations of neurodegenerative conditions. The effect estimates and findings for flavonols were virtually unchanged with these adjustments (Table 3).

We also explored possible confounding by other dietary components by adding to the basic model, dietary intakes of vitamin E, saturated fat, folate, lutein, and omega-3 fatty acids. After adjustment for these dietary components, neither quercetin nor myricetin was associated with global cognitive score (p-trend = 0.09) (Table 3).

We considered the possibility that the observed protective relations may be due to latent effects of neurodegenerative conditions on dietary behaviors. The analytic sample excluded those with dementia at baseline, however we conducted sensitivity analyses, in an effort to account for reverse causation and further excluded 217 participants with mild cognitive impairment at their baseline of enrollment. We then re-analyzed the basic models with the continuous variable for total intake of dietary flavonols. The results were similar for intakes of total flavonols (and individual constituents) β= 0.04, 95% (CI:0.02, 0.07) for global cognition; β=0.05 (95% CI:0.02, 0.08) for episodic memory; β=0.04, (95% CI:0.01, 0.07) for semantic memory; β=0.02, 95% CI:0.000, 0.05 for visuospatial ability; β=0.03, (95% CI:0.008, 0.05) for perceptual speed; and β=0.04, (95% CI:0.01, 0.06) for working memory.

There was no effect modification in the observed associations by age (≤80, >80), sex, education (≤12 years, >12 years), or APOE-ε4 status.

DISCUSSION

In this prospective community-based cohort study of older people, we found evidence that higher dietary intake of total flavonols and several individual flavonol constituents are associated with slower rates of decline in global cognition and in multiple cognitive domains. The observed associations were independent of cardiovascular conditions and lifestyle factors. Further after adjusting for dietary intake

of vitamin E, saturated fat, folate, lutein, and omega-3 fatty acids, flavonol associations with episodic memory, semantic memory and visuospatial ability were unchanged.

This study extends the limited number of investigations into the association of dietary flavonols to objectively measure cognitive decline. A previous study by our group reported that kaempferol, a flavonol that is abundant in green leafy vegetables, was associated with a reduced rate of global cognitive decline [11]. A limited number of cohort studies have reported an inverse association between flavonoid intake and subjective and objective cognition[1,7,11,33], the latter of which relied on participants self-reported cognitive abilities (i.e. subjective cognitive decline), while our investigation assessed cognitive function using a 19 cognitive test battery (objective cognitive decline) by a trained study staff member. In addition, we conducted annual assessments of these standardized cognitive battery tests to study potential change in cognition and the various cognitive domains. Further, our study also investigates the association between the individual constituents found within the subclass of flavonols as well as individual cognitive domains. Additionally, two studies have reported a positive association between total flavonol intake and cognition in middle-aged samples. [34,35] As such, in the current study, we focused on flavonols, a subclass of flavonoids, as their biochemical structures suggest particularly effective antioxidant capabilities compared with other flavonoid subclasses.[2,3] Although the mechanisms are not fully understood, the inherent properties flavonols contain, antioxidant and anti-inflammatory may have the ability to diminish or even prevent cellular damage systemically, extending to the brain[1-3]. By having anti-inflammatory features flavonols can decrease the amplitude or duration of neuroinflammation. Additionally, containing antioxidant characteristics allow dietary flavonol's to potentially prevent or reduce oxidative stress from reactive oxygen species and free radicals[4-6]. To our understanding, no previous study has investigated individual flavonol constituents and their

associations with objective global cognition nor the association of total flavonols and constituents to specific objective cognitive domains.

Several animal models demonstrate protective roles for individual flavonol constituents on cognition. Quercetin supplementation improved memory and learning in triple transgenic Alzheimer's Disease mice ,[13] whereas in other mouse models, kaempferol and myricetin treatments improved learning and memory and reduced oxidative stress.[12] In mice with $A\beta_{25-35}$ injected Alzheimer's disease, oral quercetin supplementation improved cognitive function and memory.[36] In transgenic mice with an induced Alzheimer's disease-like pathology, three months of treatment with a myricetin derivative, dihydromyricetin improved cognition as measured by object familiarization and subsequent novel object recognition. [37]

A number of strengths provide support for the findings of this study. The prospective design provides temporality, albeit, causality cannot be established due to the nature of observational studies. However, the long follow-up time (up to 14 years) lends confidence to the results of change over time. Further, tests of cognitive abilities were administered annually using a battery of 19 cognitive tests, thus providing a robust measure of cognitive function. The dietary intake data were based on a comprehensive food frequency questionnaire that was validated among older Chicago community-dwelling residents[17] and found to be unbiased by age, sex, educational level and cognitive impairment. Additionally, lifestyle and other factors that are associated with ones' cognitive status were assessed annually. These factors were adjusted to help minimize residual confounding, considering higher dietary intake of flavonols may be a proxy for a healthy lifestyle. Even still, some residual confounding may persist. The current study also has limitations. Self-reports of dietary intake are prone to recall bias. Further, based on their age, MAP participants are at risk of mild cognitive impairment or subclinical disease. This could lead to unreliable reports of consumption on the FFQ or

changes in dietary habits, which may not have been captured, when using the baseline FFQ to establish a participant's dietary intake of flavonols. Both aspects could bias the results leading to an over or under-estimation of reported associations. An additional limitation, reverse causality, remains due to the length of the prodromal phase revolving around the cognitive decline of Alzheimer's disease and related dementias. However, the findings did not change in sensitivity analyses that reanalyzed the data after eliminating an additional 217 participants with mild cognitive impairment, beyond those with dementia, who were excluded in the baseline analysis. Another limitation rests in the ever-evolving science for estimating flavonol intake in foods. The derived estimates may be imprecise given that the flavonoid contents of food are inherently variable[38]. Flavonoid content is dependent upon several conditions, for example, sun exposure, soil quality geographic location, and time of harvest to name a few. Also, given two predominant flavonoid databases--the NDSR provisional flavonoid tables (based on USDA databases) and the Phenol-Explorer (a European-based polyphenol database)--objective food analyses via PCR and potential imputation of flavonoid content data--further concentration variability may be observed. Even then, the error, in nature, should be more random and bias toward the null. Although we had a mean follow-up time of 6.9 years (± 3.6), some participants may not have consumed the specific flavonoids for an adequate amount of time to demonstrate benefit. Finally, the study has limited generalizability as it is based on a sample that is largely non-Latino White (98%), highly educated, and from the Midwest.

The current study's findings suggest that dietary intake of total flavonols and several constituents may slow the rate of decline in global cognition and in several cognitive domains including episodic memory, semantic memory, visuospatial ability, perceptual speed, and working memory. There is great value in investigating additional cohorts and groups, to aid in future validation. Further

studies are required to confirm the observed associations in other populations and help elucidate and

understand the underlying biologic mechanisms involved.

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Table 1. Baseline Characteristics by quintile of 961 MAP participants

Characteristic	Total Flavonol Intake Quintile (mean; ±SD)				
	Q1	Q2	Q3	Q4	Q5
n	191	192	193	191	194
Total flavonol intake (mg/day) 9.61 (3.64)	5.26 (1.07)	7.45 (0.5)	9.11 (0.5)	11.02 (0.68)	15.18 (2.67)
Kaempferol 1.89 (1.49)	0.75 (0.48)	1.19 (0.64)	1.63 (0.75)	2.14 (1.01)	3.71 (1.91)
Quercetin 7.05 (2.42)	4.16 (0.95)	5.8 (0.82)	6.86 (0.94)	8.08 (1.17)	10.33 (1.86)
Myricetin 0.58 (0.50)	0.28 (0.21)	0.38 (0.31)	0.51 (0.38)	0.7 (0.43)	1.01 (0.68)
Isorhamnetin 0.10 (0.12)	0.07 (0.1)	0.08 (0.1)	0.1 (0.1)	0.1 (0.1)	0.17 (0.19)
Age (years)	82.1±7.3	81.0±7.4	81.8±6.8	82.0±7.0	80.0±7.2
Education (yrs.)	14.2±2.8	14.7±3.1	14.9±2.8	15.4±2.7	15.6±3.1
Physical Activity (hours/wk.)	2.3±3.3	3.2±3.3	3.3±3.5	3.8±3.9	4.1±3.7
Late life cog activity (no. /wk.)	3.0±0.7	3.2±0.7	3.2±0.7	3.3±0.6	3.4±0.6
Total calories (kcal/day)	1708±687	1777±545	1821±542	1767±500	1646±405
Sex n (% female)	150 (79)	141 (73)	148 (77)	138 (72)	138 (71)
APOE-ε4 n (%)	44 (23)	38 (20)	44 (23)	42 (22)	44 (23)
Smoking n (%)	85 (45)	86 (45)	71 (37)	77 (40)	81 (42)
Depressive Symptoms	1.3±1.7	1.2±1.8	1.1±1.5	0.82±1.3	0.97±1.5
Body Mass Index	27.7±5.2	27.4±5.2	26.7±4.7	27.3±5.4	26.8±4.8
Cardiovascular conditions					
Diabetes n (%)	27 (14)	39 (20)	29 (15)	17 (9)	19 (10)
Hypertension n (%)	135 (71)	130 (68)	140 (73)	133 (70)	115 (61)
Myocardial Infarction n (%)	36 (19)	23 (12)	35 (18)	30 (16)	34 (18)
Stroke n (%)	24 (14)	23 (13)	22 (12)	18 (10)	20 (11)

217 (22.5%) individuals had mild cognitive impairment at baseline

Data are mean ± SD or number (%) as appropriate.

Table 2. Estimated continuous effects[a] (β, 95% CI) of calorie-adjusted intakes of total flavonols and individual constituents, on change in global cognition and five cognitive domains for 961 participants of the Memory and Aging Project in adjusted linear mixed models[b]

Flavonols (basic adjustment)

β (95% confidence interval)

	Mean Intake (std Dev) (mg/day)	Global Cognition	Episodic Memory	Semantic Memory	Visuospatial Ability	Perceptual Speed	Working Memory
Total flavonols	9.6 (3.6)	0.004	0.004	0.003	0.001	0.003	0.003
		(0.001, 0.006)	(0.002, 0.006)	(0.001, 0.007)	(-0.0005, 0.003)	(0.001, 0.004)	(0.0007, 0.005)
Kaempferol	1.9 (1.5)	0.01	0.01	0.01	0.005	.01	0.01
		(0.006, 0.02)	(0.004, 0.02)	(0.005, 0.02)	(0.001, 0.01)	(0.003, 0.01)	(0.003, 0.01)
Quercetin	7.1 (2.4)	0.004	0.005	0.004	0.001	0.003	0.002
		(0.0005, 0.007)	(0.002, 0.01)	(0.0002, 0.007)	(-0.002, 0.004)	(-0.0001, 0.005)	(-0.0005, 0.005)
Myricetin	0.6 (0.5)	0.008	0.007	0.01	0.001	0.006	0.01
		(-0.006, 0.023)	(-0.01, 0.02)	(-0.007, 0.02)	(-0.01, 0.02)	(-0.07, 0.02)	(-0.002, 0.03)
Isorhamnetin	0.1 (0.12)	0.04	0.1	0.04	0.05	0.03	0.04
		(-0.017, 0.11)	(0.005, 0.15)	(-0.02, 0.11)	(-0.01, 0.11)	(-0.03, 0.1)	(-0.02, 0.1)

[a] β estimates are based on flavonol variables modeled as a continuous variable

[b] Models adjusted for age, sex, education, APOE-ε4, caloric intake, participation in late life cognitive activities, physical activity, and smoking

Table 3. Estimated continuous effects (β, 95% CI) of calorie-adjusted intake of total flavonols on change in global cognition for 961 participants of the Memory and Aging Project over an average of 6.4 years in four distinct models.

β (95% confidence interval)

MODEL	Global Cognition	Episodic Memory	Semantic Memory	Visuospatial Ability	Perceptual Speed	Working Memory
Basic	0.004	0.004	0.003	0.001	0.003	0.003
	(0.001, 0.006)	(0.002, 0.006)	(0.001, 0.007)	(-0.0005, 0.003)	(0.001, 0.004)	(0.001, 0.005)
Basic + CVD	0.004	0.005	0.004	0.002	0.003	0.003
	(0.002, 0.006)	(0.002, 0.007)	(0.001, 0.006)	(-0.0001, 0.004)	(0.001, 0.005)	(0.001, 0.005)
Basic + BMI and depression	0.003	0.004	0.003	0.002	0.002	0.003
	(0.001, 0.006)	(0.002, 0.006)	(0.001, 0.006)	(-0.0004, 0.004)	(0.001, 0.004)	(0.001, 0.005)
Basic + other nutrients	0.002	0.004	0.003	0.0004	0.002	0.002
	(-0.001, 0.005)	(0.001, 0.007)	(0.0001, 0.006)	(-0.002, 0.003)	(-0.0004, 0.005)	(-0.0006, 0.005)

[a] Basic adjustment -- age, sex, education, APOE-ε4, caloric intake, participation in late life cognitive activity, physical activity, and smoking

[b] CVD – Myocardial infarction, Stroke, Diabetes, Hypertension

[c] Other Nutrients – saturated fat, omega-3 fatty acids, Vitamin E, folate, and lutein

Figure 1: Study population flow chart


```
┌─────────────────────────────────────┐
│ MAP participants without known       │
│ dementia (N = 2,022)                 │
└─────────────────────────────────────┘
            │
            │   ┌───────────────────────────────────────────┐
            ├──▶│ Excluded (n = 92):                        │
            │   │ • Deceased before 2004 (when the FFQ      │
            │   │   substudy started) or withdrew from      │
            │   │   the study (92)                          │
            │   └───────────────────────────────────────────┘
            ▼
┌─────────────────────────────────────┐
│ MAP participants (n = 1,930)         │
└─────────────────────────────────────┘
            │
            │   ┌───────────────────────────────────────────┐
            ├──▶│ Excluded (n = 361):                       │
            │   │ • Deceased, developed dementia, or        │
            │   │   withdrew from the study prior to any    │
            │   │   FFQ assessment (361)                    │
            │   └───────────────────────────────────────────┘
            ▼
┌─────────────────────────────────────┐
│ MAP participants (n = 1,569)         │
└─────────────────────────────────────┘
            │
            │   ┌───────────────────────────────────────────┐
            ├──▶│ Excluded (n = 501):                       │
            │   │ • FFQ completed but dietary data          │
            │   │   derivation in process (494)             │
            │   │ • Refused to fill the FFQ (7)             │
            │   └───────────────────────────────────────────┘
            ▼
┌─────────────────────────────────────┐
│ MAP participants (n = 1,068)         │
└─────────────────────────────────────┘
            │
            │   ┌───────────────────────────────────────────┐
            ├──▶│ Excluded (n = 107):                       │
            │   │ • Did not have a minimum of two           │
            │   │   clinical assessments for cognitive      │
            │   │   function (98)                           │
            │   │ • Had missing data of model covariates (9)│
            │   └───────────────────────────────────────────┘
            ▼
┌─────────────────────────────────────┐
│ MAP participants (n = 961)           │
└─────────────────────────────────────┘
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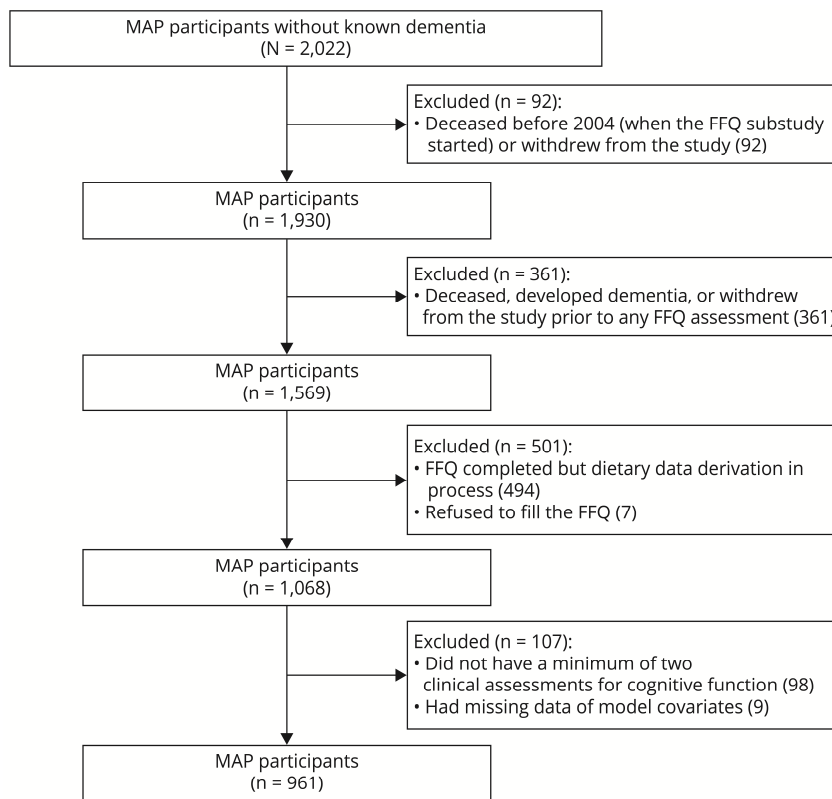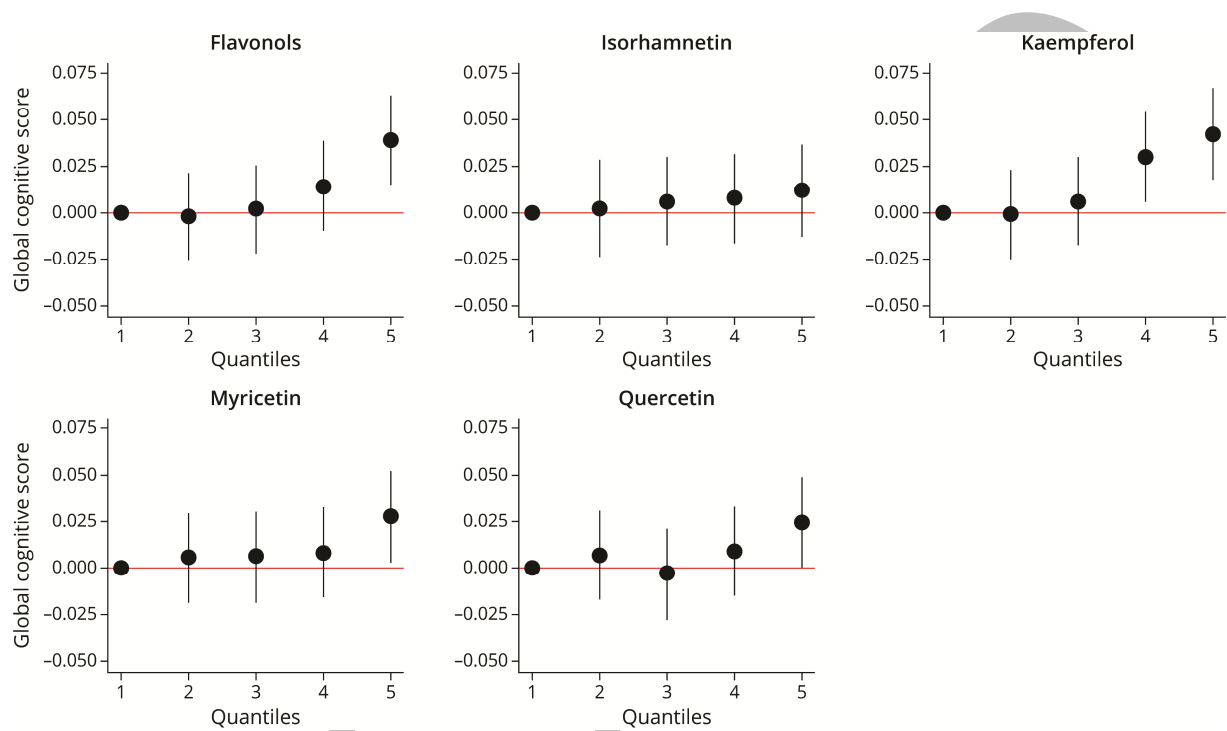
Figure 2: Estimated effects (β, 95% CI) of energy-adjusted intakes of total flavonols and flavonol constituents by quantile, on change in global cognition for 961 participants of the Memory and Aging Project in adjusted linear mixed models*

*Basic adjustment -- age, sex, education, APOE-ε4, late life cognitive activity, physical activity, and smoking

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This information is current as of November 22, 2022

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