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ABSTRACT

Cognitive decline occurs with age and may be slowed by dietary measures, including increased intake of dietary phytochemicals. However, evidence from large and long-term studies of flavonol intake is limited. Dietary intakes of flavonols were assessed from a large biracial study of 10,041 subjects, aged 45–64, by analysis of a food frequency ques tionnaire administered at visit 1 of triennial visits. Cognitive function was assessed at visits 2 and 4 with the following three cognitive performance tests: the delayed word recall test, the revised Wechsler Adult Intelligence Scale digit symbol subtest, and the word fluency test of the Multilingual Aphasia Examination. The change in each score over 6 years was calculated, and a combined standardized change score was calculated. Generalized linear models controlled for age, ethnicity, gender, education level, energy intake, current smoking, physical activity, body mass index, diabetes, and vitamin C intake. Total flavonols across quintiles of intake were positively associated with preserved combined cognitive function ($P < .001$). This pattern with preserved combined cognitive function was consistent for the three major individual flavonols in the diet, myricetin, kaempferol, and quercetin (each $P < .001$). The positive association with total flavonols was strongest for the digit symbol subtest ($P < .001$). In this cohort, flavonol intake was correlated with protected cognitive function over time

Martin Root, Erin Ravine, and Anne Harper(2015) Flavonol Intake and Cognitive Decline in Middle-Aged Adults. *JOURNAL OF MEDICINAL FOOD [DOI 10.1089]* copy available @ (http://online.liebertpub.com/doi/pdfplus/10.1089/jmf.2015.0010)

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ABSTRACT Cognitive decline occurs with age and may be slowed by dietary measures, including increased intake of dietary phytochemicals. However, evidence from large and long-term studies of flavonol intake is limited. Dietary intakes of flavonols were assessed from a large biracial study of 10,041 subjects, aged 45 – 64, by analysis of a food frequency ques tionnaire administered at visit 1 of triennial visits. Cognitive function was assessed at visits 2 and 4 with the following three cognitive performance tests: the delayed word recall test, the revised Wechsler Adult Intelligence Scale digit symbol subtest, and the word fluency test of the Multilingual Aphasia Examination. The change in each score over 6 years was calculated, and a combined standardized change score was calculated. Generalized linear models controlled for age, ethnicity, gender, education level, energy intake, current smoking, physical activity, body mass index, diabetes, and vitamin C intake. Total flavonols across quintiles of intake were positively associated with preserved combined cognitive function ($P < .001$). This pattern with preserved combined cognitive function was consistent for the three major individual flavonols in the diet, myricetin, kaempferol, and quercetin (each $P < .001$). The positive association with total flavonols was strongest for the digit symbol subtest ($P < .001$). In this cohort, flavonol intake was correlated with protected cognitive function over time.

INTRODUCTION

Cognitive decline is highly associated with the aging process and is a common health concern among older adults. Although its rate and degree of severity vary among individuals, its presence is seen in decreased neurocognitive performance, increased neurodegenerative diseases, physical disabilities, a loss of independence, and a decreased quality of life.[1,2]

There are many risk factors for cognitive decline. In addition to the nonmodifiable risk factors of age and genetic predisposition, factors such as hypertension, smoking, and diabetes have been associated with increased rates of cognitive decline.[3,4] Higher education level, literacy level, and physical activity have been shown to be associated with a slower rate of cognitive decline.[5,6] These factors may be linked through the interrelationship between vascular function and neuroinflammation.[7,8]

Certain dietary risk factors have been linked to cognitive function. Ortega *et al.* showed that among the elderly, better cognitive scores were associated with greater intakes of total food, carbohydrate, fiber, folate, vitamin C, b-carotene, iron, and zinc and with lower intakes of saturated fatty acids.[9] Similarly, Scarmeas *et al.* found that high adherence to the Mediterranean diet, a diet high in olive oil, legumes, unrefined cereals, fruits, vegetables, and fish, led to a 28% lower risk of developing mild cognitive impairment and a 48% lower risk for developing Alzheimer's disease compared to subjects with low adherence.[10]

These dietary factors may be acting through oxidative stress and neuroinflammation, resulting in cognitive decline and neurodegenerative diseases.[2,11] Consumption of antioxidants may help to protect against oxidative stress in the brain, slowing cognitive decline.[12,13] Vitamins E, C, and b-carotene have been studied for their relation to cognitive function with mixed results. A cross-sectional study by Peacock *et al.* used the Atherosclerosis Risk in Communities (ARIC) study to examine antioxidant intake, supplement use, and cognitive function. They found that the intake of carotenoids and vitamins C and E had no effect on cognitive performance.[14] However, Perrig *et al.* found a significant positive association between the plasma levels of these antioxidants and the cognitive performance tests and concluded that the serum levels of these antioxidants were significant predictors of memory performance. These results were not associated with supplemental intake because of the small (6%) number of their population that mentioned supplement use.[15] Since these levels of plasma antioxidants may have represented an intake of fruits and vegetables, it is plausible that memory performance in these populations was related to the intake of fruits and vegetables in general. The fruits and vegetables also contain flavonols and other polyphenols.

Flavonols have antioxidant properties; these are plant-based polyphenolic compounds that can be found in foods and beverages such as blueberries, tea, wine, and fruit juices. Passing through the blood – brain barrier, flavonols and their metabolites can have positive effects on cell-to-cell communication, vascular function, and neuroinflammation, through the inhibition of specific enzymes and the activation of specific signaling pathways in the brain. These mechanisms have been proposed to increase neuronal integrity, ultimately deterring brain aging and cognitive decline.[16]

Research has been conducted on the effects of flavonoid consumption on neurocognitive performance, cognitive decline, and prevention of neurodegenerative diseases. Previous animal studies found that flavonoid consumption was associated with increased neurocognitive performance and decreased incidences of age-related cognitive decline.[16,17] In addition, the PAQUID study found high intakes of flavonoids to be associated with slowed incidences of cognitive decline over a 10-year period in a population of 1640 older adults ($P = .046$).[18]

Our research will further investigate these findings in a biracial longitudinal study of over 10,000 middle-aged adults. Our hypothesis is that high intake of dietary flavonols in middle-aged adults is associated with decreased rates of cognitive decline over time.

MATERIALS AND METHODS

Participants

This article was prepared using ARIC Research Materials obtained from the National Heart Lung Blood Institute (NHLBI) Biologic Specimen and the Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ARIC research groups or the NHLBI. The Institutional Review Board of Appalachian State University approved the acquisition and use of this dataset. Details of the methodology of the ARIC study are described elsewhere.[19]

The ARIC study is a prospective epidemiological study that explores the causes and outcomes of atherosclerosis in four communities located in the United States. These are Washington County, Maryland, Forsyth County, North Carolina, the city of Jackson, Mississippi, and selected northwestern suburbs of Minneapolis, Minnesota. The study protocol was approved by institutional review boards at each clinical site.

Study participants underwent extensive examinations, including measurements of cardiovascular conditions, various risk factors, a dietary questionnaire, and cognitive function tests. Baseline examinations occurred from 1987 to 1989 at visit 1, and reexaminations took place from 1990 to 1992 for visit 2, 1993 to 1995 for visit 3, and 1996 to 1998 for visit 4. Specific ARIC data that are of particular interest to this study include dietary intake and certain covariates from visit 1 and data on cognitive function from visits 2 to 4. A food frequency questionnaire (FFQ) was not administered at visit 2.

Dietary intake

Dietary assessment was conducted by trained interviewers with use of a 66-item FFQ during visit 1. Nutrient analysis of the FFQ was completed with use of Willett's nutritional database. The analysis provided information on 90 different nutrients, including the nutrients of interest for this study, which were the major flavonols myricetin, kaempferol, and quercetin.[20,21] Flavonol intakes were calculated by multiplying the individual flavonol content of each food item by the frequency of its daily consumption and summing over all items.

Cognition

Measures of cognitive function were assessed with the use of three cognitive performance tests: the delayed word recall test, the revised Wechsler Adult Intelligence Scale (WAIS-R) digit symbol subtest, and the word fluency test of the Multilingual Aphasia Examination.[22] The tests were administered by trained interviewers in a standardized order in a quiet room. Interviewer performance was monitored by tape recording, reviewing a sample of the testing sessions, and by confirming that there were no systematic differences in mean scores obtained by the different interviewers who gave the tests.[23]

The delayed word recall test is a test of verbal learning and recent memory that requires the participant to recall 10 common nouns following a 5-min interval during which another psychometric test is given. After the 5 min and to standardize the elaborative processing of the words to be recalled, individuals are asked to compose sentences incorporating the nouns as they were presented. A point is given for each word recalled, with a maximum of 10 points. This test has been shown to have a high 6-month test – retest reliability in a study, including 26 normal elderly persons ($R = 0.75$).[24]

The WAIS-R digit symbol subtest is a paper and pencil task requiring timed translation of numbers 1 – 9 to symbols using a key. The test measures psychomotor performance and is relatively unaffected by intellectual ability, memory, or learning for most adults.[25] It is scored as the number of numbers translated to symbols correctly within 90 sec, with a maximum score of 93. Short-term test – retest reliability has been found to be high in middle-aged individuals ($R = 0.82$).[25]

The word fluency test requires participants to generate as many words as possible in 60 sec, beginning with a letter from the alphabet. Three trials using the letters F, A, and S were conducted, and word fluency was scored as the total number of words generated over the three trials. The test is sensitive to linguistic impairment[26] and early mental decline in older persons.[27] The immediate test – retest correlation coefficient based on an alternate test form has been found to be high ($R = 0.82$).[28]

For the present study, the three test scores were standardized by taking the difference of the test scores at visit 2 from visit 4 and dividing by the standard deviation of the difference. A summed score of change in cognitive function

was created by summing the three standardized scores for each subject.

Other measurements

Education level, ethnicity, and presence of diabetes and hypertension were assessed by standardized interviews during baseline examinations. Education levels were categorized into the following three groups: £11 years of education, 12 – 16 years of education, and ‡17 years of education. Presence of diabetes was defined as serum fasting glucose ‡126 mg/dL, self-reported physician diagnosis of diabetes, or use of oral hypoglycemic agents. Hypertension was defined as systolic blood pressure ‡140 mmHg, diastolic blood pressure ‡90 mmHg, or in a person taking antihypertensive medication. Black ethnicity was self-reported and defined as black or nonblack. Current smoking was self-reported. Prevalent coronary heart disease was identified by a complex algorithm involving electrocardiogram results and self-reported heart conditions. Body mass index (BMI) was calculated as kg/m^2. Total calories and vitamin C intake were assessed from the FFQ. Physical activity was assessed as the sum of work-related, leisure, and sports activity scores.

Statistical analysis

A total of 15,750 individuals between the ages of 45 and 64 years at baseline were available for this analysis. A large number of subjects were lost to the analysis if cognitive function scores were unavailable, principally from the fourth visit (4755). Subjects were lost to the analysis for missing data from the FFQ (216), physical activity (39), diabetes diagnoses (73), smoking status (9), and educational status (15). Also, excluded were those whose change scores in cognitive function were greater than or less than five standard deviations from zero (33). These were removed for a concern over reverse causality and an abundance of concern about excessive influence in the models.

With use of the statistical software SPSS version 20.0, generalized linear models of change in cognitive function versus flavonol intake were performed. Controlling factors included age, ethnicity, gender, educational level, energy intake, current smoking, physical activity, BMI, diabetes di agnosis, and vitamin C intake. The key outcomes in Tables 3 and 4 were expressed as relative changes in the standardized cognitive change scores compared to group 5, the highest intake group of flavonols. A model adjusting for only gender and age was prepared, but showed little difference from the unadjusted model; therefore, the results were not presented.

RESULTS

A total of 10,041 subjects were included in the analysis after exclusions. As seen in Table 1, there were significant trends in subject characteristics across quintiles of total flavonol intake. As flavonol intake increased, the percentage of black ethnicity and smokers decreased and the percentage of males, level of education, total calories, age, and physical activity increased.

Cognitive function scores were consistently lower for women compared to men after controlling for important confounders (Table 2). Women's scores decreased more rapidly than men's for words recalled and word fluency,

Table 1. Characteristics of ARIC Cohort by Quintiles of Total Flavonol Intake

	Quintiles of dietary intake of total flavonols					
Variable	*1*	*2*	*3*	*4*	*5*	
N	*2008*	*2006*	*2004*	*2008*	*2015*	*P-value for trend**
Total flavonols mean intake, mg/day	2.8	6.2	9.7	15.1	34.7	
Percentages						
Black ethnicity	26.0	19.0	18.6	16.8	12.5	<.001
Male gender	50.0	47.9	42.7	42.8	40.5	<.001
Current smokers	28.4	20.6	18.7	19.5	19.5	<.001
Diabetes	8.5	8.9	9.5	8.1	9.0	.065
Education >16 years	35.1	38.8	41.7	41.9	39.4	<.001
Means						
Age, visit 1	53.5	54.0	54.2	54.2	54.0	<.001
BMI, kg/m^2	27.5	27.3	27.3	27.6	27.6	.018
Total energy intake, kJ/day	345	375	396	397	434	<.001
Physical Activity sum of activity codes	6.90	7.11	7.19	7.22	7.13	<.001
Vitamin C intake, mg/day	78	109	133	134	155	<.001
	Quintiles of dietary intake of flavonols (mean intake, mg/day)					
Myrictin	0.05	0.27	0.52	1.03	2.69	
Kaempferol	0.2	0.8	2.1	4.1	11.6	
Quercetin	1.9	4.2	6.7	9.7	20.9	

*Controlled for age, ethnicity, gender, education level, energy intake, and current smoking where appropriate.
ARIC, Atherosclerosis Risk in Communities; BMI, body mass index.

Table 2. Measures of Cognitive Function and Changes in Cognitive Function Over 6 Years Comparing Men and Women in the ARIC Cohort

Cognitive measure	*Men*	*Women*	P *for difference**
Visit 2			
Words recalled	6.97−1.42	6.42−1.46	<.001
Digit symbols	48.2−13.7	43.9−12.5	<.001
Words listed	34.7−12.0	33.5−12.3	<.001
Visit 4			
Words recalled	6.86−1.54	6.22−1.57	<.001
Digit symbols	45.5−13.6	41.4−12.4	<.001
Words listed	34.4−12.1	32.6−12.7	<.001
Changes			
Words recalled	-0.12−1.55	-0.20−1.54	.033
Digit symbols	-2.65−6.89	-2.51−6.30	.017
Word fluency	-0.25−7.78	-0.89−7.83	<.001
Global total change score	-0.47−1.75	-0.58−1.70	.043

*Controlled for age, ethnicity, education level, energy intake, and current smoking.

while men's scores in digit symbols decreased more rapidly than for women. The overall standardized change score was slightly lower for women than men.

Standardized total cognitive change scores were lower (more rapid decline in cognitive function) in lower quintiles of total flavonol intake when controlling for a number of important covariates (Table 3). The results were consistent for the three major individual flavonols.

Across quintiles of total flavonols, the individual cognitive function change scores gave variable results with changes in digit symbols being most significantly correlated with flavonol intake as seen in Table 4.

DISCUSSION

In this population of middle-aged adults, preserved cognitive function was significantly associated with increased flavonol intake. In particular, standardized total cognitive decline did not decline as fast with increased intake of total flavonols and the individual intakes of myricetin, kaempferol, and quercetin. Our findings support evidence that greater intake of flavonol-containing foods may reduce cognitive decline in the middle aged and supports the relationship of specific phytochemicals with cognition.[29] Previous studies have been limited by their short length of follow-up, small sample sizes, elderly populations, and minimal adjustments for confounding factors. In the present study, we compared a standardized change score over 6 years with initial dietary flavonol intake in a large, biracial middle-aged population. Although causation cannot be attributed, it is interesting to note that the adjusted difference in global cognitive change between the first and fifth quintile for total flavonols (-0.211) represents about 2.4 years of the preserved change in standardized cognitive function seen in the cohort over 6 years (-0.52).

The trajectory of cognitive function was measured by a combined change score for the delayed word recall test, the WAIS-R digit symbol subtest, and the word fluency test of the Multilingual Aphasia Examination. Advantages of using a combined score of change in cognitive function are comprehensiveness and stability, since many overlapping areas of brain function contribute to these cognitive abilities and their change over time. Similar combined scores have been calculated and used in other studies for analysis of cognitive function.[30,31] The change in the test score for the digit symbol was positively associated with increased total flavonol intake (*P*-values < .001). Change in word fluency was only marginally associated with flavonol intake (*P* = .27 for the unadjusted model and not significantly correlated for the adjusted models). Changes in word recall were not associated with flavonol intake.

Previous studies investigating the relationship between cognition and plant compounds, including antioxidants, B vitamins, vitamin D, fatty acids, and other phytochemicals,

Table 3. Standardized Cognitive Change Score Over 6 Years in Quintiles of Intake of Flavonols in the ARIC Cohort

	Quintiles of flavonol intake					P *for trend*
	1	*2*	*3*	*4*	*5*	
Total flavonols	-0.173*	-0.184*	-0.220*	-0.032	0	<.001
	-0.211*	-0.191*	-0.214*	-0.028	0	<.001
Myricetin	-0.244*	-0.232*	-0.121*	0.009	0	<.001
	-0.266*	-0.238*	-0.118*	-0.004	0	<.001
Kaempferol	-0.240*	-0.187*	-0.323*	-0.084	0	<.001
	-0.246*	-0.172*	-0.304*	-0.068	0	<.001
Quercetin	-0.104	-0.210*	-0.150*	-0.055	0	.001
	-0.145*	-0.225*	-0.151*	-0.049	0	.001

Analysis was performed using generalized linear models. The first row in each group was an unadjusted model. The second row was adjusted for age, ethnicity, gender, education level, energy intake, current smoking, physical activities, BMI, diabetes, and vitamin C intake. Asterisks (*) indicate a significant difference with quintile 5 at $P < .05$.

Table 4. Changes in Cognitive Functions Over 6 Years in Quintiles of Total Flavonol Intake in the ARIC Cohort

	Quintiles of total flavonol intake					P *for*
Cognitive function	*1*	*2*	*3*	*4*	*5*	*trend**
Total cognitive function	-0.173*	-0.184*	-0.220*	-0.032	0	<.001
	-0.211*	-0.191*	-0.214*	-0.028	0	<.001
Words recalled	-0.008	-0.009	-0.029	0.015	0	.569
	-0.012	0.009	-0.027	0.018	0	.582
Digit symbol	-0.107*	-0.088*	-0.121*	-0.031	0	<.001
	-0.167*	-0.115*	-0.133*	-0.040	0	<.001
Word fluency	-0.058	-0.087*	-0.070*	-0.017	0	.027
	-0.033	-0.067*	-0.054	-0.006	0	.137

Analysis was performed using generalized linear models. The first row in each group was an unadjusted model. The second rows were adjusted for age, ethnicity, gender, education level, energy intake, current smoking, physical activities, BMI, diabetes, and vitamin C intake. Asterisks (*) indicate a significant difference with quintile 5 at $P < .05$.

have yielded mixed results.[32,33] Generally, a trend is seen toward the benefits of plant consumption in a wellbalanced diet. The present results support previous research related to fruit and vegetable compounds and cognition, although specific to flavonols in a large diverse population. In the ARIC, cohort flavonols were most commonly consumed in fruits and vegetables, particularly apples and broccoli. Tea was an especially rich source.

Women experienced slightly greater overall cognitive decline over the 6-year study ($P = .043$), despite their greater total flavonol intake. This gender difference was driven largely by the differences in delayed word fluency test de cline, while the cognitive decline correlation with flavonol intake was driven largely by the change in digit symbols. Despite these gender differences, both genders had more preserved overall cognitive function with higher total fla vonol intake.

Foods, particularly fruits and vegetables, contain a num ber of compounds with putative salutary effects, including acting as an antioxidant. The flavonols in question in this study have measurable antioxidant activity.[16,18] However, previous work with the ARIC cohort showed that dietary antioxidants did not protect against cognitive decline.[14] However, other work has shown that flavonoids have a wide range of other possible neuroprotective effects. These pri marily work by reducing neuroinflammation and associated cytokine release. In addition, neural signaling pathways have been shown to be activated together with neurogenesis and improved blood flow through inducible nitric oxide synthase activation.[16,34] Vitamin C was included as a co factor in the analysis as the major water-soluble antioxidant nutrient in these fruits and vegetables. By controlling for this antioxidant, this analysis was able to show that the corre lations seen were independent of this major antioxidant in the food sources of flavonols.

The current study was limited by having only one test for each cognitive domain. Within the tests that were taken, there is the potential for a lack of correspondence between the cognitive scores and the latent cognitive abilities they were meant to measure.[35] Some of these limitations are corrected for by the combined, standardized, and total cognitive decline score. The dietary assessment also pre ceded the first cognitive measure by 3 years. Although the statistical model adjusts for a number of variables, it cannot control for all possible known and unknown confounding variables that may contribute to changes in cognition. Fi nally, this is a strictly observational study and cause and effect cannot be implied from this analysis.

Our data support existing research on the consumption of fruits and vegetables, and also possibly tea, and cognitive decline. An overall increased consumption of flavonols was significantly correlated with slower cognitive decline in this large, diverse middle-aged population.

AUTHOR DISCLOSURE STATEMENT

This research received no specific grant from any funding agency, commercial sectors, or not-for-profit sectors.

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