Journal of Alzheimer's Disease 29 (2012) 773–782
DOI 10.3233/JAD-2012-111799
IOS Press

Polyphenol-Rich Foods in the Mediterranean Diet are Associated with Better Cognitive Function in Elderly Subjects at High Cardiovascular Risk

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Handling Associate Editor: Vincenza Frisardi

Accepted 3 January 2012

Abstract. Brain oxidative processes play a major role in age-related cognitive decline, thus consumption of antioxidant-rich foods might help preserve cognition. Our aim was to assess whether consumption of antioxidant-rich foods in the Mediterranean diet relates to cognitive function in the elderly. In asymptomatic subjects at high cardiovascular risk ($n = 447$; 52% women; age 55–80 y) enrolled in the PREDIMED study, a primary prevention dietary-intervention trial, we assessed food intake and cardiovascular risk profile, determined apolipoprotein E genotype, and used neuropsychological tests to evaluate cognitive function. We also measured urinary polyphenols as an objective biomarker of intake. Associations between energy-adjusted food consumption, urinary polyphenols, and cognitive scores were assessed by multiple linear regression models adjusted for potential confounders. Consumption of some foods was independently related to better cognitive function. The specific associations [regression coefficients (95% confidence intervals)] were: total olive oil with immediate verbal memory [0.755 (0.151–1.358)]; virgin olive oil and coffee with delayed verbal memory [0.163 (0.010–0.316) and 0.294 (0.055–0.534), respectively]; walnuts with working memory [1.191 (0.061–2.322)]; and wine with Mini-Mental State Examination scores [0.252 (0.006–0.496)]. Urinary polyphenols were associated with better scores in immediate verbal memory [1.208 (0.236–2.180)]. Increased consumption of

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ISSN 1387-2877/12/$27.50

antioxidant-rich foods in general and of polyphenols in particular is associated with better cognitive performance in elderly subjects at high cardiovascular risk. The results reinforce the notion that Mediterranean diet components might counteract age-related cognitive decline.

Keywords: Aging, coffee, cognition, Mediterranean diet, nutrition, polyphenols, olive oil, walnuts, wine

INTRODUCTION

Increased lifespan in developed countries has resulted in a greatly raised frequency of diseases related to aging, such as cardiovascular and neurodegenerative disorders, including Alzheimer's disease (AD), the most common type of dementia [1]. AD is characterized by cognitive deterioration with a progressive impairment of activities of daily living. Cognitive changes, however, are not particular to severe neurodegenerative diseases like AD, as the aging process naturally entails normal age-associated cognitive decline. The cognitive functions that are most frequently affected with aging are memory, especially codification, recall, and working memory, and executive functions that imply information processing speed, divided attention, and planning [2].

Factors recognized to aid in maintaining cognitive performance include years of schooling, professional achievement, social engagement, and physical activity [3]. Such factors are encompassed in the concept of cognitive reserve, described as the brain's capacity to compensate for neuropathological damage in brain aging, making clinical symptoms unobtrusive or even imperceptible [4]. An appealing link hypothesized in recent years is the association between lifestyle habits, particularly food patterns, and cognitive reserve [3, 5]. Epidemiological studies suggest that foods such as fruits, vegetables, fish, and wine and nutrients such as polyunsaturated fatty acids, E and B-vitamins, and antioxidants might protect from age-related cognitive decline, mild cognitive impairment (MCI) and AD [6–10]

Nutritional epidemiology has evolved beyond nutrients and foods, with increasing recognition of the importance of dietary patterns, in which synergy exists among food constituents, with additive effects on health [11, 12]. One such pattern is the traditional Mediterranean diet, a reputed model of healthy eating that is characterized by a high consumption of foods and nutrients presumed to be healthy for the brain, such as vegetables, fruits, fish, unsaturated fatty acids, and diverse antioxidants, with moderate intake of alcoholic beverages, mostly wine [13]. Both prospective and clinical studies report that greater adherence to a Mediterranean-type diet is associated with a reduced incidence of coronary heart disease (CHD) [13–15]. Consistently, epidemiological studies point to a reduction in the incidence of and mortality from cardiovascular diseases [13, 15, 16] and cancer, which results in increased longevity [16]. Importantly, as recently reviewed [17], increasing compliance with Mediterranean-type diets has also been associated with slower cognitive decline [18], a reduction in the incidence of MCI [19], neurodegenerative disorders such as Parkinson's disease [20] and AD [21, 22], and mortality attributable to AD [23, 24].

Oxidative stress and ensuing inflammation are believed to play major roles in the pathogenesis of age-related diseases, including cognitive impairment and AD. They also are ideal targets for nutritional intervention with antioxidants, for which the Mediterranean diet is particularly well suited [25]. Therefore, we evaluated in a cross-sectional study whether consumption of antioxidant-rich foods from the Mediterranean diet was associated with better cognitive performance in a cohort of elderly persons at high risk for CHD living in Spain, a Mediterranean country. In addition, since there is evidence that consumption of flavonoids, a subclass of polyphenols, positively relates to cognitive function [26], we complemented dietary data with urinary polyphenol excretion, an objective biomarker of phenol intake.

METHODS

Participants and design of the study

The study population was drawn from the cohort of the PREDIMED (PREvención con DIeta MEDiterránea) study, a clinical trial in asymptomatic persons at high cardiovascular risk testing the Mediterranean diet for outcomes on cardiovascular disease events (http://www.predimed.org; ISRCTN35739639). The design of the PREDIMED study has been described in detail elsewhere [27]. Candidates were community-dwelling men aged 55–80 years and women aged 60–80 years, without prior cardiovascular disease but having a prior diagnosis of diabetes or at least three cardiovascular risk factors,

namely smoking, hypertension, dyslipidemia, overweight (body mass index [BMI] $\geq$25 kg/m^2), and family history of premature cardiovascular disease ($\leq$55 years in men and $\leq$60 years in women). Other exclusion criteria were any severe chronic illness, alcohol or drug abuse, or BMI $\geq$40 kg/m^2. Participants fulfilling inclusion criteria and not meeting exclusion criteria provided informed consent to a protocol approved by the local review board and underwent various tests, including venipuncture to obtain fasting blood and collection of a spot urine sample.

Anthropometric and blood pressure measurements were performed by standard methods, as previously described [27]. Smoking status was categorized into never, current or past smoking according to self-reports. Physical activity was assessed with the validated Spanish version of the Minnesota questionnaire and expressed in minutes at a given metabolic equivalent (MET-min) per day [28]. Dietary data related to self-selected food intake during the previous year were collected during a face-to-face interview with a single trained dietitian using a validated 137-item food-frequency questionnaire (FFQ) [29] and converted to daily intakes. Energy and nutrient intake were calculated from Spanish food composition tables. The apolipoprotein E (APOE) genotype was determined by using the method of Hixson and Vernier [30]. High-sensitivity C-reactive protein (CRP) was measured using an immunoturbidimetric technique. Total polyphenols in spot urine samples were determined with the Folin-Ciocalteu assay after solid phase extraction, together with the creatinine concentration, as described [31]. Total polyphenol excretion was expressed as mg of gallic acid equivalents (GAE)/g of creatinine. Urinary total polyphenol excretion expressed by 24-h volume is a better biomarker of polyphenol dietary intake than expressed by urinary creatinine normalization. However, when total volume in 24-h is not available, creatinine-corrected urinary total polyphenol excretion may also be a suitable biomarker of total polyphenols in a free-living population [32].

From October 2004 to December 2009, 578 consecutive persons entering the PREDIMED study in the recruiting centre located at Hospital Clínic (Barcelona, Catalonia, Spain) were asked to submit to neuropsychological testing to assess cognitive function. During the screening visit, participants were asked about education years and information about exclusion criteria specific for this substudy was sought, namely depression, as assessed by the Hamilton Depression Rating Scale (participants with a score >13 were excluded) [33], severe cognitive impairment, defined by a score <25 in the Mini-Mental State Examination (MMSE) [34], illiteracy, or difficulty in expression or comprehension of Spanish language.

Cognitive assessment

An experienced neuropsychologist who was blinded to the subjects' diet and cardiovascular risk factors conducted the cognitive examination. The instruments used were the MMSE to assess global cognitive function [34]; the Rey auditory verbal learning test (RAVLT) to rate immediate (sum of words recalled on the five learning trials) and delayed episodic verbal memory [35]; the verbal paired associates test, a subtest of Wechsler Memory Scale (WMS) [36], to evaluate episodic memory performance; the semantic verbal fluency test [37]; the digit span test of the Wechsler Adult Intelligence Scale (WAIS) [38] to assess immediate memory (direct digits) and working memory (reverse order digits); and the Color Trail Test (part I and II) [39] to measure executive function, including attention, visual-motor speed, and cognitive flexibility.

Statistical analyses

We fitted multiple linear regression models to assess independent associations of demographic, clinical, and dietary variables and urinary polyphenol excretion with neuropsychological test scores. In the first model, with cognitive test scores as dependent variables, we introduced the energy-adjusted intakes of various food groups (cereals, vegetables, fruits, legumes, nuts, meat and meat products, seafood, olive oil, alcohol, and coffee) as independent variables. In the second model we adjusted for age, gender, education years, BMI, current smoking, physical activity, APOE genotype, diabetes, hypertension and hyperlipidemia, and the food groups that were significantly associated with test scores in the first model as potential confounders. Because in addition to questions on intake of total alcohol, olive oil, and nuts, the FFQ used in the study contains specific questions on intake of wine, virgin olive oil (VOO), and walnuts, we constructed additional models where alcohol, olive oil, and nut consumption were replaced by wine and other alcoholic beverages, VOO and common olive oil, and walnuts and other nuts, respectively. In a further model, we entered as independent variable urinary polyphenol excretion alone, to avoid collinearity with other antioxidant-rich food groups, with adjustment for the same variables plus total energy intake. Finally, the logarithmical transformed values

of urinary polyphenol excretion and serum CRP were entered in a partial correlation adjusted by gender, age and BMI. p values <0.05 were considered significant. SPSS software, version 16.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

RESULTS

Characteristics of participants

Figure 1 shows the flow of participants. By study design, there was a high prevalence of cardiovascular risk factors in the 447 participants available for analysis (Table 1).

As shown in Table 2, the self-selected participant's dietary habits reasonably conformed to the traditional Mediterranean food pattern in several aspects, as they recorded high intakes of cereals, vegetables, fruits, fish, and olive oil and moderate intakes of legumes, nuts, and wine. They deviated from the traditional Mediterranean diet, however, because of high intakes of meat and dairy products. The extreme ranges underscore the high between-subject variability of energy and food intake and urinary polyphenol excretion.

Cognitive performance

Various clinical, demographic and dietary variables were independently associated with the outcomes of neuropsychological tests by multiple linear regression analyses after adjustment for various confounders. The fully adjusted associations are shown in Table 3. Older age, diabetes, and hypertension were associated with lower MMSE scores, while higher education years and higher wine intake were associated with better performance. In the immediate recall of RAVLT, older age and cereal intake were associated with lower scores. Conversely, higher education years, the female gender, and higher intake of total olive oil were associated with immediate verbal memory. Intake of coffee and

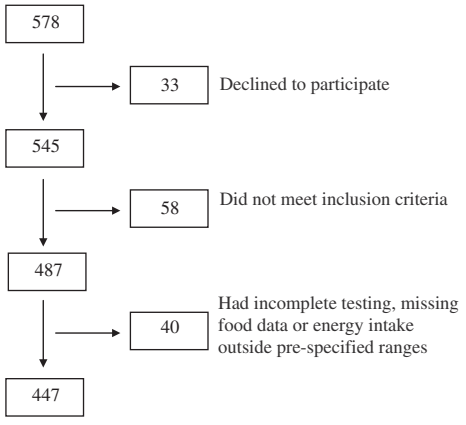

Fig. 1. Flow chart of participants.

Table 1
Socio-demographic and anthropometric characteristics, physical activity, cardiovascular risk factors and APOE genotype of the study population ($n = 447$)

Variables	Mean or median	Range
Age (years)	66.9	(54.7–80.2)
Women, *n* (%)	233 (52.1)	
Education (years)	7.18	(0–14)
Body mass index (kg/m^2)	28.5	(18.8–36.8)
Leisure-time physical activity (Kcal/d)	235*	(0–1382)
Home physical activity (Kcal/d)	179*	(0–1755)
Energy expenditure in physical activity (MET-min/d)	492*	(0–2028)
Family history of early-onset CVD, *n* (%)	133 (29.8)	
Smoking, *n* (%)	72 (16.1)	
Diabetes, *n* (%)	250 (55.9)	
Antidiabetic medication, *n* (%)	180 (72.0)	
Hyperlipidemia, *n* (%)	322 (72.0)	
Lipid-lowering agents, *n* (%)	218 (67.7)	
Hypertension, *n* (%)	336 (75.2)	
Antihypertensive medication, *n* (%)	296 (88.1)	
APOE 4 genotype, *n* (%)†	79 (17.8)	
Serum C-reactive protein (mg/l)	0.48	(0.01–9.95)
Total polyphenol excretion (mg GAE/g Cr)‡	136	(31–773)

*Median. †Sum of E4/3 and E4/4 genotypes (E2/4 excluded). ‡GAE/g Cr, gallic acid equivalents (GAE)/g of creatinine. Abbreviations: MET-min, minutes at a given metabolic equivalent level (units of energy expenditure in physical activity, 1 MET-min roughly equivalent to 1 Kcal); CVD, cardiovascular disease; APOE, apolipoprotein E.

Table 2
Daily intake of energy and food groups of the study population ($n = 447$)

Variables	Mean or median	Range
Total energy (Kcal/d)	2362	(1066–3898)
Cereals/grains (g/d)	252	(0–704)
Vegetables (g/d)	406	(0–1480)
Legumes (g/d)	19	(0–103)
Fruits (g/d)	470	(0–1190)
Total nuts (g/d)	5.13	(0–60)
Walnuts (g/d)	1.10	(0–30)
Meat and meat products (g/d)	89	(2–229)
Fish and seafood (g/d)	114	(7–427)
Dairy products (g/d)	359	(0–1367)
Total olive oil (ml/d)	38	(0–75)
Virgin olive oil (ml/d)	4*	(0–70)
Total alcohol (g/d)	4*	(0–92)
Wine (ml/d)	21*	(0–702)
Coffee (ml/d)	21*	(0–350)

*Median.

Table 3
Independent associations of cognitive test scores with food intake by multiple linear regression

Neuropsychological test	Independent variables	Regression coefficient (95% confidence interval)	β*	*p*
MMSE	Wine per 200 ml/d	0.252 (0.006 to 0.496)	0.096	0.044
	Age per 10 years	−0.405 (−0.624 to −0.186)	−0.170	<0.001
	Education per 5 years	0.529 (0.324 to 0.734)	0.238	<0.001
	Diabetes	−0.289 (−0.553 to −0.025)	−0.104	0.032
	Hypertension	−0.419 (−0.717 to −0.121)	−0.132	0.006
RAVLT (immediate recall)	Total olive oil per 10 g/d	0.755 (0.151 to 1.358)	0.109	0.014
	Cereals per 40 g/d	−0.431 (−0.823 to −0.038)	−0.098	0.032
	Age per 10 years	−5.079 (−6.454 to −3.704)	−0.329	<0.001
	Gender (women)	2.549 (0.932 to 4.165)	0.142	0.002
	Education per 5 years	3.304 (2.045 to 4.562)	0.231	<0.001
RAVLT (delayed recall)	Virgin olive oil per 10 g/d	0.163 (0.010 to 0.316)	0.094	0.037
	Coffee (50 ml/d)	0.294 (0.055 to 0.534)	0.106	0.016
	Cereals per 40 g/d	−0.235 (−0.379 to −0.091)	−0.149	0.001
	Meat per 100 g/d	−0.845 (−1.556 to −0.135)	−0.109	0.020
	Age per 10 years	−1.606 (−2.108 to −1.105)	−0.288	<0.001
	Gender (women)	1.443 (0.814 to 2.072)	0.223	<0.001
	Education per 5 years	0.838 (0.372 to 1.304)	0.162	<0.001
	Hypertension	−0.735 (−1.411 to −0.059)	−0.098	0.033
Digit span (reverse)	Walnuts per 30 g/d	1.191 (0.061 to 2.322)	0.149	0.039
	Education per 5 years	0.365 (0.126 to 0.603)	0.220	0.003
	Energy expenditure in physical activity per 100 MET-min/d	−0.103 (−0.155 to −0.051)	−0.286	<0.001

Cognitive test scores are the dependent variables. The independent variables listed are those showing $p < 0.05$ after regression analyses. *β: Standardized regression coefficient. Abbreviations: MMSE, Mini Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; MET-min, minutes at a given metabolic equivalent level. Variables allowed into the models were gender, age, education, body mass index, smoking, APOE ε4 allele, energy expenditure in physical activity, diabetes, hypertension, and hyperlipidemia.

VOO, higher education years, and the female gender were associated with better performance in the delayed recall of RAVLT, while older age, hypertension, and intake of cereals and meat were associated with lower scores. Total olive oil intake was also independently associated with the delayed recall of RAVLT (regression coefficient 0.36, $p = 0.001$), but only data on VOO is shown in Table 3 because of the novelty of the finding. The consumption of walnuts was also associated with better working memory, as assessed by the reverse digit span test of the WAIS battery.

Total urinary polyphenol excretion was significantly and independently associated with the immediate recall score of RAVLT and nearly significantly with the delayed recall of RAVLT (Table 4), but not with the other neuropsychological test. Female gender and higher education years (directly) and age and diabetes (inversely) also related independently to RALVT scores. Figure 2 shows that there was a dose-relationship between urinary polyphenols and enhancement of the RAVLT score. Moreover, after adjusting by gender, age, and BMI, we found a significant albeit weak inverse correlation between the logarithmically transformed values of total urinary polyphenol excretion and CRP ($r = -0.102$, $p = 0.044$).

DISCUSSION

In this cross-sectional evaluation of dietary habits and cognitive function in older persons at high cardiovascular risk living in a Mediterranean country, higher intakes of both total olive oil and the virgin variety of olive oil, coffee, walnuts, and wine were associated with better memory function and global cognition. The magnitude of these associations was variable and they were present in some but not in all tests of cognitive function, but were independent of known cognition-related confounders and consumption of other food groups. The findings on VOO and walnuts, two foods with high antioxidant capacity [40, 41], are novel. Another novel finding is the independent association of total urinary polyphenol excretion, an objective biomarker of polyphenol-rich food intake, with human memory function. Taken together, these results suggest that antioxidants in the usual diet might counteract age-related cognitive decline [6].

Table 4
Independent associations of cognitive test scores with urinary polyphenols excretion by multiple linear regression analysis

Neuropsychological test	Independent variables	Regression coefficient (95% confidence interval)	β*	*p*
RAVLT (immediate recall)	Polyphenol excretion per 100 mg GAE/g Cr	1.208 (0.236 to 2.180)	0.112	0.015
	Age per 10 years	−5.547 (−6.987 to −4.106)	−0.351	<0.001
	Gender (women)	2.436 (0.637 to 4.234)	0.133	0.008
	Education per 5 years	3.734 (2.423 to 5.045)	0.258	<0.001
	Diabetes	−1.719 (−3.419 to −0.018)	−0.094	0.048
RAVLT (delayed recall)	Polyphenol excretion per 100 mg GAE/g Cr	0.357 (−0.004 to 0.719)	0.092	0.053
	Age per 10 years	−1.673 (−2.209 to −1.137)	−0.295	<0.001
	Gender (women)	1.343 (0.673 to 2.012)	0.205	<0.001
	Education per 5 years	1.037 (0.549 to 1.525)	0.200	<0.001
	Diabetes	−0.621 (−1.254 to 0.112)	−0.095	0.054

Cognitive test scores are the dependent variables. The independent variables listed are those showing *P* values close to <0.05 after regression analyses. *β: Standardized regression coefficient. Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; GAE/g Cr, gallic acid equivalents/g of creatinine. Variables allowed in the models were gender, age, education, body mass index, energy intake (Kcal/day), smoking, APOE ε4 allele, energy expenditure in physical activity, diabetes, hypertension, and hyperlipidemia.

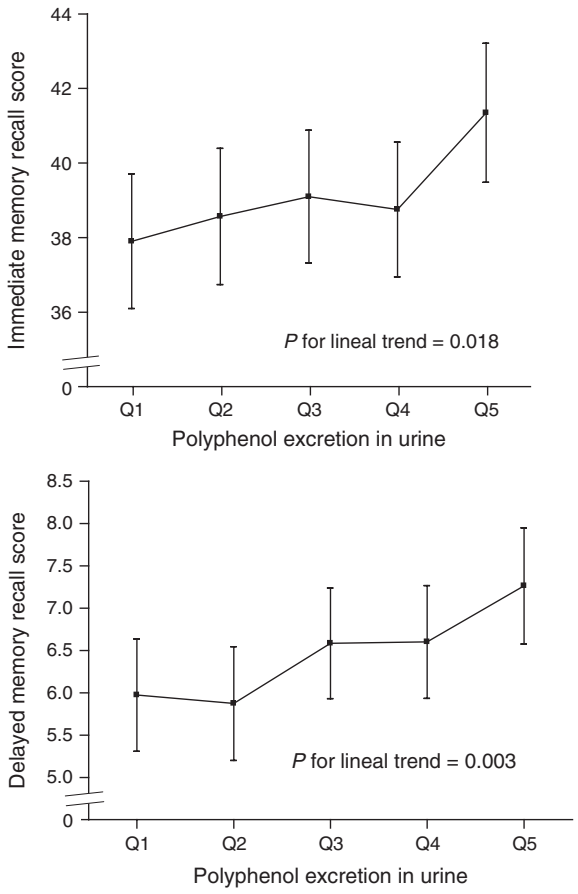

Fig. 2. RAVLT scores across quintiles of urinary polyphenol excretion.

Olive oil is a major component of the traditional Mediterranean diet. It contains abundant monounsaturated fatty acids (MUFA), mostly oleic acid, and, depending on the degree of refinement, variable proportions of bioactive micronutrients, such as phytosterols, vitamin E, and phenolic compounds [40]. Because of a lower cost, common olive oil (a mixture of refined oil with a small proportion of VOO) is widely used in Spain in the kitchen and at the table, while VOO, which is obtained by cold pressing of the ripe fruit and is much richer in minor but bioactive components, has a more restricted consumption, as shown in our study group (Table 2). Greater consumption of VOO in the Mediterranean diet has been associated with various health benefits [40]. Few epidemiological studies have related consumption of MUFA with cognitive function. MUFA is contained in other foods, for example beef, besides olive oil. This heterogeneity in the dietary sources of MUFA might explain why some results are inconsistent [42–46]. Recently, in line with our results, a weak association of total olive oil intake with a reduced risk of cognitive impairment was reported in a large French cohort [47].

We found that increasing consumption of walnuts, but not of other nuts, was associated with better working memory scores. Interestingly, walnuts are among the foods with highest antioxidant capacity, by far surpassing other nuts [48]. They are also the whole food richest in α-linolenic acid, the vegetable n-3 fatty acid [41]. Consistent evidence from prospective studies suggests that frequent nut intake relates to lower CHD rates [49]. This may be due in part to the beneficial effects of nuts on blood lipids [50] and other disease biomarkers, including oxidation, inflammation, and endothelial dysfunction [41]. Furthermore, higher intake of nuts has been related with better cognitive function and lesser cognitive decline in a prospective study [51]. Our findings, together with those of a recent experimental study showing that walnut supplementation improves both motor and cognitive function in

aged rats [52], point to the need for further studies on nuts and cognition.

There is consistent epidemiological evidence that moderate consumption of alcohol relates inversely to risk of CHD and total mortality [53]. Among alcoholic beverages, wine possibly provides additional cardiovascular benefits because it counteracts oxidative stress through its high polyphenolic content [54]. In our study participants who consumed alcohol were mostly moderate wine drinkers, and the daily dose of wine related to a better overall cognitive function in them. These findings concur with the results of other studies showing an association of moderate alcohol consumption with better cognitive performance and a reduced risk of neurodegenerative diseases [55, 56].

Because coffee, a beverage with high antioxidant content, is commonly consumed in European Mediterranean countries, we assessed its association with cognitive performance. The observed direct association with verbal memory is consistent with prior evidence on the protective effect of caffeine against development of AD [57].

A common characteristic of the foods directly related to cognitive performance in our study is their richness in polyphenols, highly bioactive molecules with beneficial effects that go beyond the modulation of oxidative stress to improve brain function, at least in experimental models of aging [58]. Indeed, urinary polyphenol excretion was independently associated with memory performance with a continuous, dose-related effect. These findings, heretofore not described, support the validity of the observed associations among antioxidant-rich foods and cognition. Antioxidant-rich foods, but not total polyphenol excretion, have been related to better cognitive performance also in other clinical studies [6, 26, 59–61]. Furthermore, animals fed antioxidant foods showed improved cellular signaling and neuronal communication that translated into better cognitive and motor performance [52, 58, 63]. A chronic inflammatory state promoted by oxidative stress is an integral part of neurodegenerative diseases. The inverse correlation between urinary polyphenols and serum CRP observed in our study is an additional argument in favor of antioxidant-rich foods. Our results further support the general theory of oxidative stress as a major driving force for age-related neurodegenerative processes [53].

Other variables independently associated with cognitive function in our study, such as gender, age, education years, diabetes, hypertension, and meat intake showed relationships in the expected direction [3, 5], except for those concerning cereal intake and physical activity. That cereal intake related inversely to memory function might be due to the fact that little amounts of whole grains are consumed in Spain. Refined grains have a high glycemic index that is associated with insulin resistance, a covariate of cognitive dysfunction [5]. The inverse association between physical activity and verbal memory was unexpected and is difficult to explain. Given the cross-sectional design of our study, it might be explained by reverse causation if participants at higher vascular risk, hence more prone to develop impaired cognition, exercised more following advice of their caretakers.

Our study has limitations. First, the sample size is relatively small. Second, given the cross-sectional design of the study, we cannot exclude the possibility of reverse causation or residual confounding. Third, the neuropsychological test battery used does not include all cognitive functions, although verbal memory, one of the first areas to be affected with aging, was well assessed with RAVLT and WMS associated pairs. Finally, our cohort was at a particularly high vascular risk, thus the results may not be generalized to the average elderly population. The study also has strengths, such as the wide between-subject variability of food consumption, a comprehensive evaluation of cardiovascular risk and dietary intake and, in particular, the use of urinary polyphenols as an objective biomarker of intake that is not subject to the possibilities of bias or inaccurate reporting.

In conclusion, in the context of the Mediterranean diet, increasing consumption of antioxidant-rich foods in general and of polyphenols in particular is associated with better cognitive performance in an elderly cohort at high cardiovascular risk. The results reinforce the notion that Mediterranean diet components might counteract age-related cognitive decline [19, 21–23]. While causality cannot be inferred from results of a cross-sectional assessment such as the present one, antioxidant-rich foods are known for many beneficial properties with no harm, thus they can be recommended to the general public to promote better health, including probably better cognitive function. The prospective examination of the whole cohort of the 6-year PREDIMED trial will eventually provide firmer evidence regarding the potential of the Mediterranean diet to counteract the effects of aging on cognitive decline and reduce the incidence of neurodegenerative diseases, including AD.

ACKNOWLEDGMENTS

We thank the PREDIMED participants for their willingness and enthusiasm to collaborate in the study and Emili Corbella for providing expert assistance with statistical analyses. CIBERobn and RETIC RD06/0045 are initiatives of ISCIII, Spain. This study was supported by PI07-0954 from ISCIII and GVACOMP2010-181 from Generalitat Valenciana (Prof Corella); AGL2010-22319-C03-01/02/03 (Drs Lamuela-Raventós and Medina-Remón); FIS PI 07/0473 and AGL2007-66638-C02-01/02 (Dr Estruch); PI070240, PI070312, and PI081943 from ISCIII (Prof Martínez-González).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1126).

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