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MEDITERRANEAN DIET AND COGNITIVE FUNCTION: THE SUN PROJECT

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Abstract: *Objective:* Our aim was to evaluate the association between adherence to the Mediterranean Diet (MedDiet) and cognitive function in 823 participants (62 ± 6 years at baseline) from a Spanish prospective cohort (SUN project). *Method:* A validated 136-item food frequency questionnaire was used to assess the adherence to the MedDiet at baseline. The 10-point (0 to 9) MedDiet Score was used to categorize adherence to MedDiet. Cognitive function was assessed twice at follow-up with a mean follow-up time between exposure and outcome assessment of 6 and 8y using the Telephone Interview of Cognitive Status-modified (TICS-m, range 0 to 54 points). ANCOVA models were used to assess the association between adherence to the MedDiet and cognitive decline. *Results:* In the multivariable-adjusted analysis of 2-year changes, a higher cognitive decline was observed among participants with low or moderate baseline adherence to the MedDiet than among those with better adherence (adjusted difference = -0.56 points in TICS-m, 95% CI = -0.99 to -0.13). *Conclusion:* A higher adherence to the MedDiet might be associated with better cognitive function. However, observed differences were of small magnitude and further studies are needed to confirm this finding.

Key words: Mediterranean diet, olive oil, monounsaturated fatty acids, cognitive function.

Introduction

Due to the increasing life expectancy, the incidence and prevalence of cognitive decline leading to dementia and other age-related diseases has increased (1). Treatments for cognitive decline have limited effectiveness and prevention through modifiable lifestyle factors, such as diet could be an approach to help to reduce or slow the age-related propensity to cognitive impairment (2). In this context, the Mediterranean diet (MedDiet) has been associated with a reduced risk of chronic disease such as cardiovascular disease (CVD) (3-5). Cognitive decline and dementia have a strong vascular component; hence, the MedDiet has been proposed to have a protective effect (6).

The term "Mediterranean diet" refers to a food pattern that provides a characteristic profile of nutrient intake with a high MUFA:SFA (monounsaturated fatty acids: saturated fatty acids) ratio due to a high intake of olive oil; together with high intakes of fibre, vitamins, folate, natural antioxidants, and a low intake of animal protein (5, 7-9). The most used score to define this food pattern is the 10-point MedDiet Score proposed by Trichopoulou et al. (5), that ranges from 0 to (minimum adherence) to 9 points (maximum adherence).

The association between MedDiet and cognitive function or cognitive decline has been assessed with inconsistent results (10-24). Adherence to the MedDiet was not related to dementia but only with less cognitive decline in a French cohort (12). Other studies did not report any association between MedDiet adherence and cognitive function (14, 17, 24). In contrast, two U.S. cohorts, with low baseline overall adherence to the MedDiet observed that higher adherence to the MedDiet was associated with lower risk of Alzheimer disease (21), mild cognitive impairment (20), and slower cognitive decline (22). In addition, two recent reports of a subset of participants in the PREDIMED-NAVARRA trial found better cognitive function after 6.5 years of intervention with a MedDiet than in the control group (15). However, both in the French cohort and in the PREDIMED-NAVARRA study no information on baseline cognitive function was available (14-16).

Therefore, evidence on this issue is conflicting. The aim of this work was to prospectively assess the association between MedDiet adherence and cognitive function, as well as cognitive decline in a two years period, in the SUN (Seguimiento Universidad de Navarra) Study.

Subjects and Methods

Study sample

The design and methods of the SUN Project have been reported elsewhere (25). The SUN Project is a dynamic cohort composed of Spanish university graduates. It was started in 1999, patterned after the models of the Nurses' Health Study and the Health Professionals Follow-up Study, from the Harvard School of Public Health (26). Baseline assessment and follow-up information is gathered through postal or web-based questionnaires collected biennially.

In May 2008, a new sub-study within the SUN Project frame was started. This sub-study was designed to evaluate the nutritional and environmental factors involved in the

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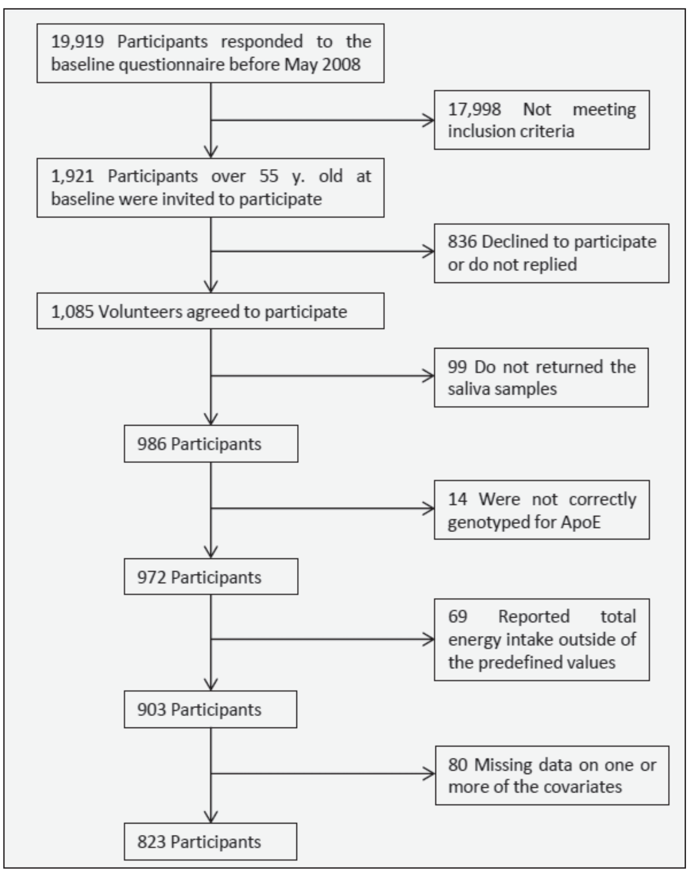
development of cognitive impairment. With this aim, we invited 1,921 participants of SUN Project over 55 years at the time of the baseline assessment to be included in this substudy. By including participants over 55 years we tried to increase the efficiency of our design because the majority of the potentially important cases of cognitive decline would be expected to occur in participants older than 55 years. After our invitation, 1,085 volunteers agreed to participate and 972 volunteers were correctly genotyped for *ApoE*. This gene variant has been proposed as the main genetic factor for cognitive impairment (27-29). Sixty nine subjects reported their total energy intake outside of predefined values (<800 kcal/d for men, <500 kcal/d for women and > 4000 kcal/d for men, > 3500 kcal/d for women) and were excluded. Subjects with missing data on one or more of the covariates were excluded (n=80) leaving a total of 823 participants available for analyses (Figure 1).

Figure 1

Flow chart of the participants in the cognitive impairment-SUN study



Dietary assessment and MedDiet

Dietary intake at baseline was assessed using a mailed and self-reported semiquantitative food-frequency questionnaire (136 food items) validated in Spain (30) and more recently re-evaluated (31, 32).

The MedDiet Score proposed by Trichopoulou et al. (5) was used to classify participants according adherence to the MedDiet at baseline. This score is the most widely used and evaluates the main components of the MedDiet. This assigns 0 or 1 points according to the daily intake of each of these 9 components: 1) high ratio MUFA:SFA; high intake of 2) fruit and nuts; 3) vegetables; 4) cereals; 5) legumes; 6) fish; low intake of 7) meat and meat products; 8) milk and dairy products; and 9) moderate alcohol consumption. Sex-specific medians of the sample are used as cut-off points. For alcohol, 1 point was given only for moderate amounts of intake (5-25 g/d for women or 10-50 g/d for men). For the 6 components in accordance with the MedDiet, participants received 1 point if the intake was beyond the sample median. For the 2 components not in line with the MedDiet (meat or meat products and dairy products) participants scored 1 point if the intake was below the median. The total score, which ranges from 0 to 9, was categorized into 3 groups (0-3 points low adherence, 4-6 moderate, and 7-9 high).

Cognitive assessment

The cognitive function was evaluated with the Telephone Interview of Cognitive Status-modified (TICS-m) for the first time in 2008-2009 and for a second time two years later. A member of the trained team of dieticians especially prepared for this task was responsible for conducting the telephone interviews. The TICS-m in Spanish is a translation of the TICS-m in English (33) and it is a modified version of the TICS, which includes additionally delayed verbal recall, however it has not been still formally validated in Spanish. The TICS-m score ranges from 0 point to 54 points and contains the following items; 1) full name (2 points); 2) date (5 points); 3) address (5 points); 4) counting backward (2 points); 5) 10-word list learning exercise (10 points); 6) serial sevens backward (5 points); 7) responsive naming (4 points); 8) repetition (2 points); 9) semantic memory (current Spanish President and King, 2 points); 10) finger tapping (5 points); 11) word opposites (2 points) and, 12) delayed recall of the 10-word list in task 5 (10 points). The TICS-m includes five domains: immediate memory; delayed recall; orientation; attention/calculation; and language.

Statistical analysis

We used t-tests and chi-squared tests for the comparison of baseline characteristics between included and excluded participants (Table 1). ANOVA models were performed for the comparison of mean values of variables across baseline categories of the MedDiet (Table 2).

We used ANCOVA models to compare means of changes in cognitive function (TICS-m) across categories of baseline adherence to the MedDiet (0-3 points low adherence, 4-6 moderate, and 7-9 high). Adjusted models were fitted as follow: 1) initial cognitive function was adjusted for age (continuous), sex, *ApoE* genotype (e4e4, e3e4, e2e4, e3e3, e3e2 and e2e2), follow-up time between baseline and cognitive evaluation (continuous), total energy intake (kcal/day, as continuous), body mass index (BMI, kg/m^2, as continuous), smoking status (current, former, never smoker), physical activity practice (METs-h/week, as continuous), baseline diabetes, baseline hypertension, baseline hypercholesterolemia, history of CVD, and years of university education (continuous); 2) final cognitive function was adjusted for the same confounding variables as the initial cognitive evaluation plus TICS-m score at initial evaluation (continuous) and the follow-up time between baseline and the final cognitive evaluation; 3) 2-year cognitive change from the first to the second evaluation was adjusted for the same confounding variables as the final cognitive evaluation. The covariables included in the model have been previously associated with cognitive function, most of them due to a vascular mediation. Information about the covariables (BMI, smoking status, physical activity, diabetes, hypertension, hypercholesterolemia, history of CVD, and years of university education have been gathered through the self-reported questionnaire. Several validation studies of this self-reported data have been published (34-36). Follow-up time between baseline and cognitive evaluation was calculated for each participant from the date of returning the baseline questionnaire to the date of evaluation. Cognitive change was calculated as TICS-m at final evaluation minus TICS-m at initial evaluation. Statistical test were 2-sided, with type I error set at <0.05. Values in the text are mean ± SD unless otherwise indicated.

Table 1
Comparison of the baseline characteristics of the participants included in the study with those not included [a]

	Included	Not included	p value
n	823	1098	
Male (%)	71	71	0.185
Age at baseline (y)	61.9 ± 6.0	61.9 ± 7.1	0.858
University education (y)	5.4 ± 1.9	5.2 ± 1.8	0.049
Body mass index (kg/m^2)	25.8 ± 3.1	25.9 ± 3.3	0.418
Physical activity (METs-h/week)	21.5 ± 21.0	19.3 ± 19.0	0.060
Smoking status			
Current smoker, n (%)	111 (13.5)	203 (17.0)	
Former smoker, n (%)	428 (52.0)	567 (47.4)	0.016
Energy intake (kcal/d)	2195 ± 866	2398 ± 1011	<0.001
Total fat (% of energy)	34.5 ± 7.2	34.1 ± 7.9	0.180
Proteins (% of energy)	19.1 ± 4.0	18.7 ± 4.1	0.028
Carbohydrates (% of energy)	43.2 ± 8.9	44.1 ± 9.3	0.033

a. Values are means ± SD unless otherwise stated. Continuous variables were compared using Student-t tests. Categorical variables were compared using Chi-squared tests. MET: metabolic equivalent task.

This study was approved by the Institutional Review Board of the University of Navarra.

Results

Finally, 823 participants (597 men and 223 women) were included in the analysis. In a general comparison between participants included in the study and subjects invited to participate but not included (Table 1), we observed that the included subjects might have a healthier lifestyle; they were physically more active, less likely to be current smokers and with a slightly lower BMI. The baseline mean age of participants was 61.9 ± 6.0 y. At the first cognitive evaluation age was 67.4 ± 5.7 y, and at the second evaluation it was 69.4 ± 5.8 y. Table 2 shows the characteristics of our participants according to the three levels of adherence to the MedDiet. Participants with better adherence (>6) were older, more physically active, more likely to be non-smokers, and to have a higher total energy intake. Better adherence to the MedDiet was associated with a higher intake of carbohydrates, a lower intake of fat and protein, and a high intake of MUFAs and fibre.

Individuals with low and moderate adherence to the MedDiet showed lower scores in cognitive function at the final evaluation than subjects with a higher adherence to the MedDiet (Table 3). This same pattern was also observed in the analysis of the cognitive changes between the final and the initial cognitive evaluation. A low and moderate adherence to the MedDiet were both associated with significantly higher decline in the cognitive function when considering as reference those subjects with a better baseline adherence to the MedDiet (adjusted difference = -0.56, 95% CI: -0.99 to -0.13). When we analysed the association between the MedDiet score and cognitive function, excluding the MUFA/SFA ratio from the score and adjusting the model for this variable, the inverse association between the MedDiet and cognitive impairment disappeared, suggesting that the fatty acid profile of olive oil was important to explain this association.

When we separately assessed each of the 9 components of the score, a low MUFA:SFA ratio was significantly associated with higher decline of the cognitive function (adjusted difference in change for participants below versus above the median = -0.53, 95% CI: -0.84 to -0.22, p = 0.001) in the 2-year change in cognition (Table 4).

Discussion

In this subpopulation of a Mediterranean cohort, subjects with lower adherence to the MedDiet exhibited poorer cognitive performance in the final of two evaluations of cognition performed 2-year apart. This same tendency was observed for changes in cognitive function during these two years. However, no linear trend was observed, suggesting that a threshold effect may exist. When we studied this association separately for each of the 9 component of the MedDiet score, only the MUFA:SFA ratio was associated with better cognition in the final examination and with improved changes

Table 2
Baseline characteristics of the participants across categories of Mediterranean dietary score (MDS) [a]

	MDS (Trichopoulou 0 to 9 score)			
	Low	Moderate	High	p value
MDS cutoff	<4	4-6	>6	
n	275	435	113	
Male (%)	73	72	74	0.877
ApoE4 genotype (%)	18.6	20.5	16.8	0.630
Age at baseline (y)	61.6 ± 6.1	61.9 ± 5.8	62.5 ± 6.2	0.347
Age at initial cognitive evaluation (y)	67.4 ± 5.7	67.4 ± 5.7	67.3 ± 5.9	0.997
Age at final cognitive evaluation (y)	69.4 ± 5.8	69.4 ± 5.7	69.4 ± 5.8	0.996
University education (y)	5.6 ± 2.0	5.3 ± 1.8	5.4 ± 1.9	0.248
Initial TICS-m score	34.0 ± 2.5	34.0 ± 2.5	33.8 ± 2.5	0.753
Immediate memory	4.7 ± 1.5	4.7 ± 1.4	4.7 ± 1.5	0.337
Delayed recall	2.7 ± 1.6	2.8 ± 1.6	2.5 ± 1.6	0.322
Orientation	9.7 ± 0.8	9.7 ± 0.8	9.6 ± 0.8	0.241
Attention/calculation	6.2 ± 1.2	6.1 ± 1.2	6.1 ± 1.2	0.807
Language	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	0.955
Final TICS-m score	34.4 ± 2.4	34.2 ± 2.4	34.7 ± 2.4	0.081
Immediate memory	5.0 ± 1.6	4.8 ± 1.6	4.8 ± 1.6	0.253
Delayed recall	3.4 ± 1.8	3.3 ± 1.8	3.1 ± 1.8	0.246
Orientation	9.8 ± 0.6	9.8 ± 0.6	9.7 ± 0.6	0.828
Attention/calculation	6.3 ± 1.1	6.2 ± 1.1	6.4 ± 1.2	0.336
Language	3.8 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	0.376
Difference (Final-Initial)	0.3 ± 2.6	0.2 ± 2.6	0.9 ± 2.6	0.032
Body mass index (kg/m^2)	26.0 ± 3.2	25.9 ± 3.1	25.3 ± 2.7	0.113
Physical activity (METs-h/week)	19.2 ± 17.2	22.2 ± 22.4	25.9 ± 21.8	0.012
Smoking status				
Current smoker, n (%)	41 (14.9)	55 (12.6)	14 (12.4)	
Former smoker, n (%)	136 (49.5)	231 (53.1)	58 (57.3)	0.533
Energy intake (kcal/d)	2094 ± 668	2300 ± 652	2405 ± 553	<0.001
Total fat (% of energy)	36.9 ± 6.8	33.6 ± 6.7	31.6 ± 5.5	<0.001
Proteins (% of energy)	19.3 ± 4.3	18.5 ± 3.7	17.9 ± 2.8	0.001
Carbohydrates (% of energy)	40.8 ± 8.7	44.8 ± 8.2	47.2. ± 6.6	<0.001
Dietary intake (g/day) [b]				
MUFAs	36 ± 10	37 ± 10	39 ± 10	<0.001
PUFAs	13 ± 4	13 ± 5	13 ± 4	<0.001
n-3 PUFAs	3 ± 1	3 ± 1	3 ± 1	<0.001
SFAs	35 ± 7.8	27 ± 7.7	21 ± 7.8	<0.001
MUFA: SFA Ratio	1.2 ± 0.7	1.4 ± 0.4	1.8 ± 0.6	<0.001
Fiber	24 ± 11	32 ± 10	40 ± 11	<0.001
Alcohol	9 ± 13	10 ± 13	10 ± 13	<0.001
Olive oil	15 ± 16	19 ± 15	23 ± 16	<0.001
Cereals	87 ± 73	108 ± 73	118 ± 73	<0.001
Vegetables	413 ± 378	602 ± 375	712 ± 376	<0.001
Fruits	283 ± 287	456 ± 284	590 ± 285	<0.001
Legumes	20 ± 20	25 ± 20	29 ± 17	<0.001
Fish	96 ± 71	122 ± 71	161 ± 71	<0.001
Meat/meat products	174 ± 61	154 ± 66	109 ± 66	<0.001
Dairy products	227 ± 169	133 ± 168	52 ± 169	<0.001
Fast food [c]	12 ± 13	9 ± 13	6 ± 13	0.009

a. Values are mean ± SD unless otherwise stated, MET: metabolic equivalent task. Continuous variables were compared using ANOVA. Categorical variables were compared using Chi-squared tests. b. Adjusted for total energy intake (kcal/day). The total energy intake (kcal/day) was included in the analysis of covariance ANCOVA model. c. Hamburgers, sausages, and pizza. MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; SFAs: Saturated fatty acids.

Table 3
Adjusted differences in cognitive change according to baseline adherence to the Mediterranean diet. The SUN Project, 2008-2012

	MDS (Trichopoulou 0 to 9 score)		
	Low <4	**Moderate 4-6**	**High >6**
Initial TICS-m (range 0 to 54 points)			
Means, points (95% CI)	34.10 (33.80-34.40)	33.98 (33.75-34.22)	33.73 (33.27-34.20)
Final TICS-m after 2 years (range 0 to 54)			
Means, points (95% CI)	34.39 (34.13-34.64)	34.19 (33.99-34.39)	34.81 (34.41-35.21)
Difference (Final-Initial)			
Means, points (95% CI)	0.40 (0.14-0.66)	0.20 (0.01-0.40)	0.82 (0.42-1.22)
Adjusted differences, points (95% CI)	-0.43 (-0.92 to 0.05)	-0.62 (-1.07 to -0.18)	0 (ref.)
p value (vs. higher category)	0.080	0.006	
Low+moderate vs. high, (95% CI)	-0.56 (-0.99 to -0.13)		0 (ref.)
p value (vs. higher category)	0.011		

Adjusted for age, sex, *ApoE* genotype, follow-up time between baseline and cognitive evaluation, total energy intake (kcal/day), body mass index (kg/m²), smoking status (current, former, never smoker), physical activity (METs-h/week), diabetes, hypertension, hypercholesterolemia, history of CVD, and years of university education. Final TICS-m was adjusted for the TICS-m score at the initial evaluation. The difference (Final-Initial) was also adjusted for the TICs-m score at the initial evaluation. We considered the higher category group as the reference group.

during follow-up. With this regard, when we excluded from the Trichopoulou MedDiet score the MUFA:SFA ratio, no association was observed. A high consumption of olive oil seems to be the key element to explain the high MUFA:SFA ratio in Mediterranean populations. This is in agreement with the findings of the PREDIMED-NAVARRA randomized trial for the group that used extra-virgin olive oil in the intervention (15, 16).

The MedDiet has been shown to have beneficial effects on cardiovascular risk factors and its related mechanisms (4, 37-39). Very importantly, a recent large randomized trial showed that the MedDiet reduced the incidence of hard cardiovascular end-points (3, 40). The biological mechanisms underlying these protective effects could also influence cognitive function (41, 42). Cerebrovascular disease is a common finding in elderly population and a major cause for dementia (43). Several studies have appraised the association between adherence to the MedDiet with cognitive status or cognitive decline, however, results are controversial.

In this context, the first study reporting a beneficial association between adherence to the MedDiet and Alzheimer's disease refers to the WHICAP (Washington Heights-Inwood Columbian Aging Project) cohort. After a 4-y follow-up period, a 40% relative reduction in the risk of Alzheimer's disease was observed among participants with a high adherence to the MedDiet (21). The Three-City Study also reported that participants with moderate or intensive use of olive oil showed lower risk of cognitive deficit after 4-year follow-up than those who never used olive oil (10). Samieri et al. also reported that the MUFA:SFA ratio was strongly associated with lower cognitive decline (18) and Scarmeas et al. related a high MedDiet adherence to a lower risk for mild cognitive impairment (20). A similar inverse association between cognitive decline and adherence to MedDiet has been reported by other studies (12, 22), supporting our observations. However, other studies did not been replicate this association (11, 24). Also, Samieri et al. (18) observed in 16,058 women from the NHS (Nurses' Health Study) that a high adherence to the MedDiet did not benefit cognitive decline but it was associated with better cognitive function.

Interestingly, Martinez-Lapiscina et al. concluded that MedDiet, especially if it was supplemented with a free provision of extra virgin olive oil, slightly improved cognitive status in the PREDIMED-NAVARRA randomized intervention study (15, 16) We acknowledge that in our study we did not observe a linear association between MedDiet adherence and cognitive function. This could be partially explained by a threshold effect.

The MedDiet pattern allows an integrative approach of the overall food pattern considering the additive and/or synergistic effects of each food component (44-47). On the other hand, a dietary low intake of SFA replaced by MUFA has been related with a better lipid profile, insulin sensitivity, and glycemic control and decreased blood pressure (48). Olive oil is the major component and the main source of MUFA of the MedDiet and as previously stated, some studies have described a direct association between olive oil consumption and cognitive function or reduced cognitive decline (10, 17). Olive oil has been presumed to have a protective effect on cognitive function (18, 49). It contains many biological components with antioxidant properties (50), that may reduce neuronal damage (51, 52). A recent study has provided evidence that oleocanthal, a phenolic component of extra-virgin olive oil, enhances amyloid-β clearance from the brain (53).

Inconsistency among studies may be due to several sources. Disparities in the MedDiet assessment as well as in cognitive function evaluation are major issues. For example, the French three-city study (12) assessed cognitive function with the MMSE test (Mini Mental State Examination) (54) and Samieri et al. (18) measured cognitive function with TICS. Both studies

Table 4
Adjusted differences in cognitive function changes according to baseline intake of each of the 9 items included in the Mediterranean Diet Score and olive oil consumption. The higher consumption category was considered as the reference

	Cut-off (sex-specific median)		Difference (Final-Initial) [a]	
	Women	**Men**	**Adjusted difference (points) for ≤ cut-off**	**p**
Olive oil, g/d	14.4	11.8	-0.37 (-0.68 to -0.06)	0.020
MUFA:SFA ratio	1.38	1.27	-0.53 (-0.84 to -0.22)	0.001
Fruits and nuts, g/d	435	317	-0.03 (-0.32 to 0.32)	0.985
Vegetables, g/d	598	452	-0.02 (-0.33 to 0.29)	0.917
Cereals, g/d	77	77	-0.01 (-0.33 to 0.32)	0.972
Legumes, g/d	17	21	0.16 (-0.14 to 0.47)	0.297
Fish, g/d	110	106	0.01 (-0.29 to 0.31)	0.961
Meats/meat products, g/d	139	150	0.16 (-0.48 to 0.15)	0.320
Dairy, g/d	73	92	-0.11 (-0.243 to 0.21)	0.500
Alcohol, g/d	5-25	10-50	0.17 (-0.16 to 0.49)	0.315

a. Differences adjusted for age, sex, *ApoE* genotype, and TICS-m score at final cognitive evaluation, follow-up time between baseline and second cognitive evaluation total energy intake (kcal/day), body mass index (kg/m^2), tobacco use status (current, former, never smoker), physical activity (METs-h/week), diabetes, hypertension, hypercholesterolemia, history of CVD, years of university education, and all other items in the MedDiet score.

assessed MedDiet adherence with the Trichopoulou score (5). However, the modest association observed by Samieri et al. could be due to the low adherence to a MedDiet style pattern in U.S. population (18). In this context of inconsistency between studies, a randomized clinical trial could be the ideal tool to uncover a clear benefit of the MedDiet on cognitive function (23). The available large randomized trial by Martinez-Lapiscina et al. supports the potential of a MedDiet to help preserve cognitive function but it lacks the baseline cognitive assessment (15, 16).

A potential limitation in this work is the self-reported nature of exposure (MedDiet), even if validity and reliability of the FFQ used in our cohort has been extensively evaluated (32). On the other hand, the TICS-m test has been widely used and it has been shown to reduce selection bias in epidemiological studies. It facilitates follow-up in longitudinal studies and allows including people over large areas. Nevertheless, a recent review revealed considerable heterogeneity in the ways that telephone instruments have been used for evaluating cognitive function (55). However, the opportunity to reduce selection bias may outweigh its limitations. Moreover, the TICS-m test has been validated in French women (55) and in a German population (56), evidencing that the TICS-m is a useful tool for assessing overall cognitive status. Nevertheless, this has not already been validated in Spanish and more studies are necessary, albeit, a Spanish study reported that it was a useful test in dementia (33). Moreover, it should be also stated that the psychometric properties of the TICS-m are a limitation. Another limitation is the lack of a complete battery of neuropsychological test and the lack of functional measurements and clinical-neurological assessment procedures, precluding conclusions regarding dementia, mild cognitive impairment and subtypes thereof. A potential weakness of the SUN cohort is that all participants were university graduates, thus, they cannot be considered as a representative sample of the general population. Our participants were more likely to be homogeneous in terms of their background diet than participants would be if a similar study were conducted in a representative sample of the general population. This homogeneity regarding their educational level, background diet and other aspects can limit the generalizability of our findings and also may have reduced the between-subject variability in dietary exposures, because they belong to a single educational and socioeconomic stratum. However, this fact can be also viewed as an advantage. This homogeneity could also have enhanced the validity of our study, by reducing the potential confounding related to socioeconomic level, educational status and variability in participants background diet. In any case, we adjusted our results for major potential confounders and this adjustment enhances also the internal validity of our results.

On the other hand, over-adjustment cannot be disregarded because if the association between MedDiet and cognition is due to vascular factors, adjusting for cardiovascular risk factors, as we have done, may substantially reduce or even nullify the association. On the other hand, the MedDiet might be a marker of a healthier lifestyle which should be taken into account since the magnitude of association could be overestimated if confounding is not adequately controlled for (18).

One strength of our design is that the higher educational level of the participants in the cohort ensures a higher validity of self-reported information (57-59). Nevertheless, all our estimates are also adjusted for years of university education. This is important because education has been inversely associated with cognitive decline (60-63).

The consistency between our results and those related to depression (64, 65) also reinforces the potential neuro-protection by and olive oil-rich MedDiet.

In summary, our results support the presumed neuroprotective effects of the MedDiet on cognitive decline. This finding seem to be mainly explained by a high MUFA:SFA ratio which at the same time could be influenced by the high extra virgin olive oil consumption.

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Ethical standards: This study complies with the current laws of the country in which they were performed.

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