Original Investigation

Mediterranean Diet and Age-Related Cognitive Decline
A Randomized Clinical Trial

Cinta Valls-Pedret, MSc; Aleix Sala-Vila, DPharm, PhD; Mercè Serra-Mir, RD; Dolores Corella, DPharm, PhD; Rafael de la Torre, DPharm, PhD; Miguel Ángel Martínez-González, MD, PhD; Elena H. Martínez-Lapiscina, MD, PhD; Montserrat Fitó, MD, PhD; Ana Pérez-Heras, RD; Jordi Salas-Salvadó, MD, PhD; Ramon Estruch, MD, PhD; Emilio Ros, MD, PhD

IMPORTANCE Oxidative stress and vascular impairment are believed to partly mediate age-related cognitive decline, a strong risk factor for development of dementia. Epidemiologic studies suggest that a Mediterranean diet, an antioxidant-rich cardioprotective dietary pattern, delays cognitive decline, but clinical trial evidence is lacking.

OBJECTIVE To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet.

DESIGN, SETTING, AND PARTICIPANTS Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk were enrolled into the Prevención con Dieta Mediterránea nutrition intervention trial from October 1, 2003, through December 31, 2009. All patients underwent neuropsychological assessment at inclusion and were offered retesting at the end of the study.

INTERVENTIONS Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).

MAIN OUTCOMES AND MEASURES Rates of cognitive change over time based on a neuropsychological test battery: Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trail Test. We used mean *z* scores of change in each test to construct 3 cognitive composites: memory, frontal (attention and executive function), and global.

RESULTS Follow-up cognitive tests were available in 334 participants after intervention (median, 4.1 years). In multivariate analyses adjusted for confounders, participants allocated to a Mediterranean diet plus olive oil scored better on the RAVLT ($P = .049$) and Color Trail Test part 2 ($P = .04$) compared with controls; no between-group differences were observed for the other cognitive tests. Similarly adjusted cognitive composites (mean *z* scores with 95% CIs) for changes above baseline of the memory composite were 0.04 (−0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (−0.05 to 0.23; $P = .04$ vs controls) for the Mediterranean diet plus nuts, and −0.17 (−0.32 to −0.01) for the control diet. Respective changes from baseline of the frontal cognition composite were 0.23 (0.03 to 0.43; $P = .003$ vs controls), 0.03 (−0.25 to 0.31), and −0.33 (−0.57 to −0.09). Changes from baseline of the global cognition composite were 0.05 (−0.11 to 0.21; $P = .005$ vs controls) for the Mediterranean diet plus olive oil, −0.05 (−0.27 to 0.18) for the Mediterranean diet plus nuts, and −0.38 (−0.57 to −0.18) for the control diet. All cognitive composites significantly ($P < .05$) decreased from baseline in controls.

CONCLUSIONS AND RELEVANCE In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Emilio Ros, MD, PhD, Lipid Clinic, Endocrinology and Nutrition Service, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain (eros@clinic.ub.es).

Increased lifespan in developed countries has resulted in a greatly increased frequency of age-related diseases, including Alzheimer disease,[1] the most common type of dementia.[2] The economic and social burden of caring for persons with dementia is increasing, and to date there are no effective pharmacologic agents to prevent or treat the disease[3] or even its precursor stages.[4] The view is emerging that to achieve a benefit an intervention would likely need to be started in the preclinical stage, a situation that applies to a substantial proportion of the elderly population worldwide.[5] Hence, identifying simple and effective interventions to prevent dementia or delay its onset is a major public health priority.

Emerging evidence suggests an association between dietary habits and cognitive performance.[6,7] Oxidative stress has long been considered to play a major role in cognitive decline and neurodegenerative disorders.[8] Thus, it is plausible that, by counteracting oxidative stress, antioxidant-rich foods might afford protection from neurodegenerative diseases. The Mediterranean diet is a plant-based, antioxidant-rich dietary pattern reputed for its many health benefits.[9] As previously reviewed,[10-12] data from large observational studies suggest that increasing adherence to Mediterranean-type diets relates to better cognitive function and a reduced risk of dementia. The observational studies analyzed, however, have many limitations: dietary assessment performed usually only once before outcome ascertainment, heterogeneity of Mediterranean diet scores used to define dietary conformity, diversity of neuropsychological instruments used to assess cognitive function, and residual confounding because individuals with high Mediterranean diet scores tend to have healthier lifestyles. All these reasons highlight the need for randomized clinical trials.[13]

The Prevención con Dieta Mediterránea (PREDIMED) randomized clinical trial reported that, compared with a control diet that consists of advice to reduce dietary fat, a Mediterranean diet supplemented with either extravirgin olive oil or mixed nuts for nearly 5 years reduced the incidence of cardiovascular diseases by 30% in older individuals at high risk.[14] The Mediterranean diet used in the PREDIMED trial in general and the 2 supplemental foods in particular are rich in bioactive phytochemicals with antioxidant and anti-inflammatory properties.[15,16] Thus, it is plausible that, together with the overall dietary pattern, olive oil and nuts might improve or at least delay age-related cognitive decline. In fact, another PREDIMED substudy in which participants underwent neuropsychological testing once at trial's end reported improved cognition in the 2 Mediterranean diet arms, but the lack of baseline evaluation precluded assessment of changes over time.[17,18] To address this issue, we evaluated cognitive changes with repeated measurements using a battery of standard neuropsychological tests in a PREDIMED subcohort of cognitively healthy individuals.

Methods

Participants

This clinical trial was conducted in a subcohort of the PREDIMED trial (http://www.predimed.es). The protocol has been described in detail elsewhere.[19] The text of the study protocol can be found in the trial protocol in Supplement 1. For this analysis, we asked 578 individuals consecutively recruited in the Barcelona-North PREDIMED center from October 1, 2003, through December 31, 2009, to undergo neuropsychological tests to assess cognition at 2 time points, as previously described.[20] Study participants were men aged 55 to 80 years and women aged 60 to 80 years at high cardiovascular risk but no cardiovascular disease at enrollment. Criteria for eligibility were the presence of either type 2 diabetes mellitus or at least 3 of 5 cardiovascular risk factors: smoking, hypertension, dyslipidemia, overweight or obesity, and family history of early-onset coronary heart disease. Exclusion criteria were prior cardiovascular disease, any severe chronic illness, substance abuse, illiteracy, and history of allergy or intolerance to the supplemental foods olive oil or nuts. Exclusion criteria specific for this substudy were difficulty in expression or comprehension of the Spanish language, depression (defined as a score >13 on the Hamilton Depression Rating Scale), and mild cognitive impairment (defined according to the Petersen diagnostic criteria, which include memory symptoms, scores <1.5 SDs of the mean of a reference population on an episodic memory test, preserved activities of daily living, and absence of dementia).[21]

We obtained baseline and yearly data on medical history, medication use, lifestyle, and adiposity. Fasting venous blood and morning urine samples were obtained at baseline, 1 year, 3 years, 5 years, and the trial's termination, whichever came first. The study protocol was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by the Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona (Clinical Research Ethics Committee of Hospital Clínic of Barcelona). Written informed consent was obtained from all participants.

Eligible candidates were randomly assigned to 1 of 3 intervention groups: a Mediterranean diet supplemented with extravirgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce all dietary fat). Randomization was performed centrally by means of a computer-generated random-number sequence in blocks of 50 participants balanced by sex and age (<70 and ≥70 years).[19]

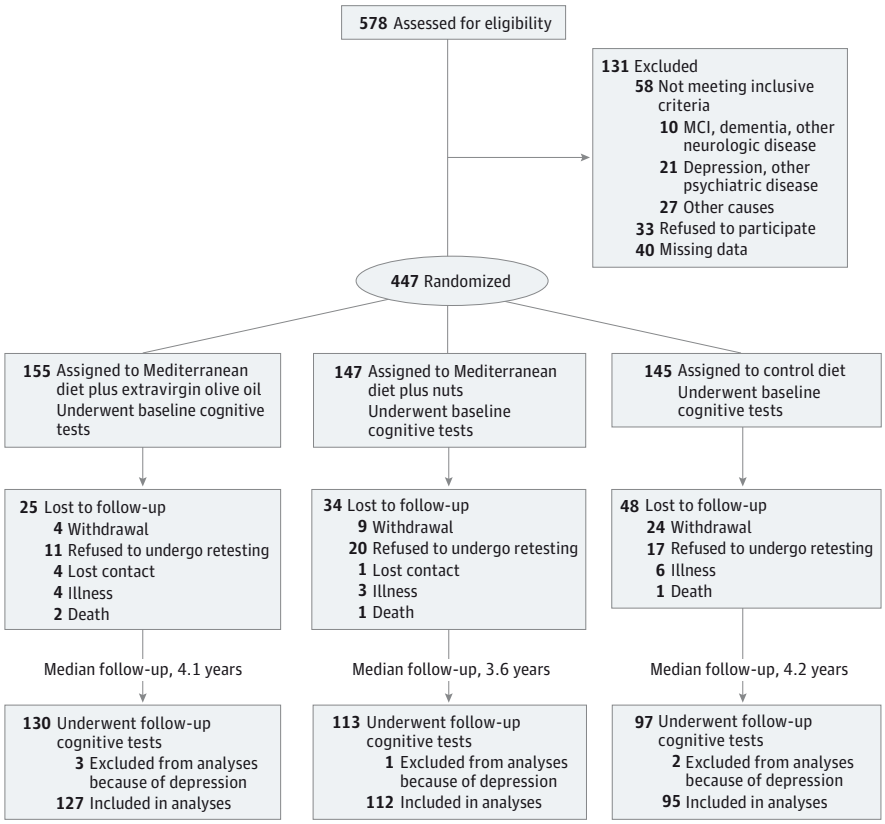
Assessment of Risk Factors

Participants were considered to have diabetes, hyperlipidemia, or hypertension if they had a previous diagnosis of these conditions or were treated with antidiabetic, cholesterol-lowering, or antihypertensive agents, respectively. Anthropometric measurements were performed by standard methods, as previously described.[19] 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 Leisure Time Physical Activity Questionnaire and expressed in minutes at a given metabolic equivalent per day.[22]

Dietary Assessment and Nutritional Interventions

Dietary data were collected during a face-to-face interview with a trained dietitian using a validated 137-item food-frequency

Figure 1. Flow Diagram of the Study



MCI indicates mild cognitive impairment.

questionnaire.[23] Nutrient intakes were computed using Spanish food composition tables and adjusted for energy intake. Candidates were randomly assigned to 1 of 3 interventions: Mediterranean diet plus olive oil, Mediterranean diet plus nuts, or control diet. Quarterly sessions were scheduled for the 2 Mediterranean diet groups; in them, they were educated on how to follow the Mediterranean diet and received supplemental foods at no cost. Olive oil (1 L/wk) was provided to one group and 30 g/d of mixed nuts (15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds) to the other group. During the first 3 years of the trial, participants in the control diet group were scheduled for yearly visits in which they were given a leaflet explaining the low-fat diet. The realization that the more infrequent visits for this group might be a limitation of the trial prompted a protocol amendment in October 2006. Thereafter, participants allocated to the control diet received personalized advice and group sessions with the same frequency and intensity as those in the Mediterranean diet groups. In them, participants were educated on how to follow a low-fat diet and received small nonfood gifts. In each session, a validated 14-item screener of adherence to the Mediterranean diet was used to track diet changes.[24] Neither energy restriction nor increased physical activity was advised for any treatment arm.

Evaluation of Cognitive Function

An experienced neuropsychologist (C.V.-P.) who was masked to the participants' diet and cardiovascular risk factors conducted the cognitive examinations. Neuropsychological tests were performed at baseline and repeated at the date closest to the study's termination that was most convenient for participants. Thus, follow-up time was not the same for all study participants. The instruments used were the Mini-Mental State Examination to assess global cognitive function, the Rey Auditory Verbal Learning Test (RAVLT) to rate immediate (sum of words recalled on the 5 learning trials) and delayed episodic verbal memory, and the verbal paired associates test, a subtest of Wechsler Memory Scale, to evaluate episodic memory performance. While recruitment was ongoing, we added tests to assess changes in language and frontal functions as well. To this end, we included the animal fluency test to evaluate semantic fluency, the Digit Span subtest of the Wechsler Adult Intelligence Scale to assess immediate memory (forward digits) and working memory (backward digits), and the Color Trail Test (parts 1 and 2) to measure attention, visuomotor speed, and cognitive flexibility.

Participants' raw test changes were standardized to z scores, and 3 composite scores of cognitive function were calculated for each participant. First, the memory composite included the mean standardized individual change scores of the RAVLT and Wechsler Memory Scale paired associates subtest. The second composite score related to frontal functions, including tests measuring attention, cognitive flexibility and working memory, and was constructed by averaging standardized change scores of the Wechsler Adult Intelligence Scale Digit

Table 1. Baseline Characteristics of Participants by Study Group[a]

Characteristic	Mediterranean Diet Plus Extravirgin Olive Oil (n = 127)	Mediterranean Diet Plus Nuts (n = 112)	Control Diet (n = 95)	*P* Value[b]
Men	60 (47.2)	58 (51.8)	46 (48.4)	.77
Age, mean (SD), y	67.9 (5.4)[c]	66.7 (5.3)	65.5 (5.8)	.005
Body mass index, mean (SD)	28.5 (3.3)	28.4 (3.2)	28.5 (3.3)	.95
Educational level, mean (SD), y	6.8 (3.0)	7.6 (3.3)	7.1 (2.8)	.13
Married	101 (79.5)	89 (79.5)	74 (77.9)	.47
Family history of early-onset CHD	40 (31.5)	23 (20.5)	32 (33.7)	.07
Ever smoker	54 (42.5)	47 (42.0)	44 (46.3)	.79
Dyslipidemia	96 (75.6)	83 (74.1)	68 (71.6)	.80
Total cholesterol, mean (SD), mg/dL	220.7 (32.1)[c]	217.1 (37.6)	209.4 (33.6)	.051
LDL-C, mean (SD), mg/dL	136.4 (31.2)	137.0 (33.7)	129.3 (28.4)	.15
HDL-C, mean (SD), mg/dL	57.5 (16.5)[c]	54.7 (13.9)	51.6 (12.0)	.01
Triglycerides, mean (SD), mg/dL	134.4 (99.5)	128.7 (65.9)	146.1 (87.7)	.34
Ratio of total cholesterol to HDL-C	4.1 (0.99)	4.1 (0.95)	4.2 (0.97)	.54
Use of hypolipidemic drugs	67 (52.8)	53 (47.3)	47 (49.5)	.70
Hypertension	98 (77.2)	77 (68.8)	73 (76.8)	.26
Use of antihypertensive agents	86 (67.7)	71 (63.4)	63 (66.3)	.78
Type 2 diabetes mellitus	70 (55.1)	66 (58.9)	48 (50.5)	.48
Use of antidiabetic medication	34 (26.8)	41 (36.6)	36 (37.9)	.20
Use of anticholinergic drugs	20 (15.7)	13 (11.6)	15 (15.8)	.59
Physical activity, mean (SD), MET-min/d	541 (358)	554 (339)	516 (349)	.73
APOE ε4 genotype	24 (18.9)	14 (12.5)	14 (14.7)	.38
Hamilton Depression Rating Scale score, mean (SD)	2.1 (2.5)	2.2 (2.6)	2.4 (2.6)	.68

Abbreviations: CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET-min, minutes at a given metabolic equivalent level (units of energy expenditure in physical activity, 1 MET-min roughly equivalent to 1 Kcal).

SI conversion factors: To convert cholesterol values to millimoles per liter, multiply by 0.0259; triglyceride levels to millimoles per liter, multiply by 0.0113.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] *P* value for comparisons across groups with the Pearson χ^2 test for categorical variables or 1-way analysis of variance for continuous variables.

[c] Significantly different from control diet group (Bonferroni post hoc test).

Backward Test and Color Trail Test (parts 1 and 2). Third, a global cognition composite was generated by computing the mean standardized changes of all neuropsychological tests, including the Mini-Mental State examination. These 3 composite scores were prespecified as the primary outcomes of the study. Incident cases of mild cognitive impairment were recorded as well.

Laboratory Determinations

To determine adherence to supplemental foods, we measured urinary hydroxytyrosol (the main phenolic compound in extravirgin olive oil) and plasma proportions of α-linolenic acid (a fatty acid characteristic of walnuts) at baseline and the closest time point to the second cognitive evaluation in a random subsample of participants, as described.[14] The *APOE* ε4 genotype was determined with the method of Hixson and Vernier.[25]

Statistical Analyses

Baseline imbalances in demographic variables and cardiovascular risk factors among treatment groups were assessed by analysis of variance (ANOVA) or χ^2 tests, as appropriate. Differences between the participants who withdrew from and those who remained in the study were assessed by the *t* test or χ^2 tests, as appropriate. Baseline and postintervention (the time point closest to the second cognitive evaluation) food and nutrient consumption and biomarkers of adherence were assessed by ANOVA. Between-group differences in baseline neuropsychological test scores were assessed by ANOVA and in addition by analysis of covariance (ANCOVA) with adjustment for sex, baseline age, years of education, *APOE* ε4 genotype, smoking, body mass index, energy intake, physical activity, diabetes, hyperlipidemia, the ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, and use of anticholinergic drugs. Postintervention changes for each cognitive test and test composites were assessed by ANOVA and additionally by ANCOVA, adjusting for the variables listed above plus follow-up time. Between-group differences in incident mild cognitive impairment were analyzed by logistic regression adjusting for the confounders listed above. Bonferroni post hoc tests were used for all comparisons. Statistical significance was set at the $P < .05$ level. Analyses were performed using SPSS statistical software, version 16.0 (SPSS Inc).

Results

Participants

The baseline neuropsychological evaluation was completed by 447 participants, but 113 (25.3%) refused to undergo a second procedure or abandoned the study for different reasons (**Figure 1**). No significant differences were observed between participants who withdrew from and those who remained in the study in terms of age, sex, years of education, or cardiovascular risk factors (data not shown). However, there were more *APOE* ε4 alleles (24.8% and 15.6%, respectively; $P = .004$) and worse cognitive scores on the Mini-Mental State Examination

Table 2. Baseline Energy and Nutrient Consumption and Changes by Study Group[a]

Variable	Mean (95% CI) Mediterranean Diet Plus Extravirgin Olive Oil (n = 127)	Mediterranean Diet Plus Nuts (n = 112)	Control Diet (n = 95)	*P* Value[a]
Energy, kcal				
Baseline	2453 (2339 to 2566)	2505 (2403 to 2608)	2398 (2275 to 2521)	.44
Change	−309 (−411 to −206)	−271 (−371 to −171)	−345 (−456 to −233)	.64
Energy from protein, %				
Baseline	17.0 (16.5 to 17.5)	16.5 (16.0 to 17.0)	16.6 (16.0 to 17.1)	.34
Change	0.52 (0.10 to 0.95)	0.31 (−0.14 to 0.75)	0.10 (−0.51 to 0.71)	.48
Energy from carbohydrate, %				
Baseline	41.8 (40.5 to 43.0)	41.4 (40.3 to 42.6)	41.8 (40.4 to 43.2)	.90
Change	−4.59 (−5.72 to −3.47)	−5.01 (−6.05 to −3.97)[b]	−2.61 (−4.03 to −1.18)	.02
Fiber, g/1000 kcal				
Baseline	12.3 (11.7 to 13.0)	11.6 (11.0 to 12.2)	11.7 (10.9 to 12.4)	.22
Change	0.14 (−0.43 to 0.71)	0.82 (0.35-1.29)	−0.07 (−0.68 to 0.54)	.07
Energy from fat, %				
Baseline	38.3 (37.2 to 39.4)	38.7 (37.7 to 39.7)	38.2 (36.9 to 39.4)	.79
Change	3.51 (2.46 to 4.55)	4.52 (3.52 to 5.52)[b]	1.97 (0.69 to 3.25)	.008
Saturated fatty acids, %				
Baseline	10.2 (9.8 to 10.6)	10.4 (10.0 to 0.8)	10.1 (9.6 to 10.6)	.61
Change	−0.29 (−0.64 to 0.05)	−0.59 (−0.89 to −0.28)	−0.20 (−0.69 to 0.29)	.33
Monounsaturated fatty acids, %				
Baseline	18.7 (18.1 to 19.3)	18.6 (18.0 to 19.3)	18.8 (18.0 to 19.6)	.95
Change	3.66 (3.00 to 4.33)[b]	3.40 (2.68 to 4.12)	2.17 (1.32 to 3.03)	.02
Polyunsaturated fatty acids, %				
Baseline	6.1 (5.7 to 6.4)	6.4 (6.0 to 6.8)	6.1 (5.7 to 6.5)	.30
Change	−0.02 (−0.44 to 0.40)	1.49 (1.09 to 1.88)[c]	−0.14 (−0.61 to 0.33)	<.001
Cholesterol, mg				
Baseline	413 (393 to 434)	405 (384 to 426)	399 (374 to 425)	.66
Change	−48.0 (−68.1 to −28.0)	−41.0 (−60.3 to −21.7)	−71.2 (−92.9 to −49.5)	.12

[a] *P* value for comparisons across groups with 1-way analysis of variance.

[b] Significantly different from control group (Bonferroni post hoc test).

[c] Significantly different from the other intervention groups (Bonferroni post hoc test).

(27.7 and 28.1, respectively; *P* = .006) and Wechsler Memory Scale (14.2 and 15.1, respectively; *P* = .02) among participants who withdrew from the study compared with those who completed the study. Dropouts were unevenly distributed among groups (18.1% Mediterranean diet plus olive oil, 28.8% Mediterranean diet plus nuts, and 34.5% control diet; *P* = .004).

Table 1 gives the baseline demographic and clinical characteristics for the 334 participants who completed the study (median follow-up, 4.1 years; range, 1.0-8.8 years). The mean age of the participants was 66.8 years, and 170 (50.9%) were women. The characteristics of participants in the 3 intervention groups were well balanced except for age and lipid values because participants in the Mediterranean diet plus olive oil group were a mean of 2 years older than those allocated to the control group, and total and high-density lipoprotein cholesterol levels were lower in the control group.

Dietary Changes

Participants assigned to the Mediterranean diet plus olive oil group significantly increased consumption of extravirgin olive oil while reciprocally decreasing consumption of common olive oil. Expectedly, those allocated to the Mediterranean diet plus nuts group increased nut consumption (eTable 1 in Supplement 2). The main nutrient changes in the Mediterranean diet groups reflected the fat composition of the supplemental foods because energy supplied as monounsaturated and polyunsaturated fatty acids significantly increased in the Mediterranean diet plus olive oil and Mediterranean diet plus nuts groups, respectively (**Table 2**).

Participants in the 3 groups reported similar baseline adherence to the Mediterranean diet, as assessed by the 14-item screener. Compared with the control group, both Mediterranean diet groups had increased adherence to the Mediterranean diet at the end of follow-up. Changes in biomarkers were mean increases of 0.19% for plasma α-linolenic acid in the Mediterranean diet plus nuts group and of 49.6 μg/L in urinary hydroxytyrosol in the Mediterranean diet plus olive oil group, indicating good adherence with the supplemental foods (eTable 2 in Supplement 2).

Table 3. Baseline Cognitive Test Scores and Changes by Study Group

Variable	Mean (95% CI) Mediterranean Diet Plus Extravirgin Olive Oil (n = 127)	Mediterranean Diet Plus Nuts (n = 112)	Control Diet (n = 95)	*P* Value[a]
MMSE[b]				
Baseline	28.01 (27.79 to 28.24)	28.11 (27.87 to 28.35)	28.38 (28.12 to 28.65)	.10
Change	0.16 (−0.12 to 0.44)	−0.07 (−0.36 to 0.23)	−0.26 (−0.57 to 0.06)	.15
RAVLT, total learning[b]				
Baseline	39.31 (37.92 to 40.70)	39.46 (37.98 to 40.94)	39.24 (37.63 to 40.85)	.98
Change	4.50 (3.24 to 5.77)[c]	4.26 (2.91 to 5.60)	2.10 (0.64 to 3.57)	.04
RAVLT, delayed recall[b]				
Baseline	6.61 (6.09 to 7.13)	6.48 (5.93 to 7.03)	6.37 (5.77 to 6.96)	.83
Change	1.47 (1.02 to 1.92)	1.80 (1.32 to 2.28)	0.95 (0.43 to 1.47)	.06
Paired associates[b]				
Baseline	15.25 (14.69 to 15.82)	15.25 (14.65 to 15.85)	14.89 (14.24 to 15.54)	.66
Change	0.25 (−0.33 to 0.83)	0.41 (−0.21 to 1.03)	−0.09 (−0.76 to 0.58)	.56
Verbal fluency[d]				
Baseline	18.44 (17.18 to 19.70)	20.33 (18.86 to 21.79)	19.02 (17.53 to 20.51)	.16
Change	0.53 (−0.78 to 1.84)	−1.51 (−3.08 to 0.06)	0.30 (−1.27 to 1.87)	.13
Digit Span Forward[d]				
Baseline	5.33 (5.03 to 5.63)	5.20 (4.85 to 5.56)	5.23 (4.89 to 5.57)	.85
Change	0.11 (−0.16 to 0.38)	0.36 (−0.01 to 0.73)	−0.08 (−0.40 to 0.25)	.28
Digit Span Backward[d]				
Baseline	3.76 (3.49 to 4.02)	3.83 (3.52 to 4.14)	3.95 (3.66 to 4.25)	.63
Change	0.25 (−0.10 to 0.59)	0.34 (−0.12 to 0.81)	−0.24 (−0.64 to 0.17)	.14
Color Trail Test part 1[d,e]				
Baseline	62.60 (56.29 to 68.91)	61.15 (53.56 to 68.74)	57.00 (49.61 to 64.38)	.53
Change	−5.77 (−11.25 to −0.28)	2.48 (−5.29 to 10.26)	4.53 (−2.11 to 11.17)	.045
Color Trail Test part 2[d,e]				
Baseline	136.55 (123.19 to 149.90)	131.59 (115.13 to 148.05)	129.99 (114.39 to 145.60)	.81
Change	5.66 (−10.23 to 21.55)[c]	24.23 (1.36 to 47.10)	37.56 (18.14 to 56.97)	.045

Abbreviations: MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test.

[a] *P* value by analysis of covariance adjusted for sex, baseline age, years of education, marital status, *APOE* ε4 genotype, ever smoking, baseline body mass index, energy intake, physical activity, type 2 diabetes mellitus, hyperlipidemia, ratio of total cholesterol to HDL-C, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up (not in baseline, only in change).

[b] Measured in 334 participants (127, 112, and 95 participants, respectively).

[c] Significantly different from control group (Bonferroni post hoc test).

[d] Measured in 96 participants (41, 25, and 30 participants, respectively).

[e] Lower scores indicate improvement.

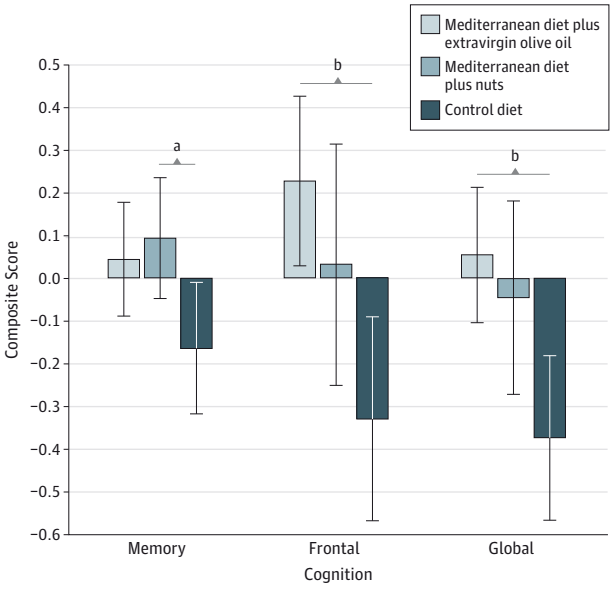
Cognitive Function

The interventions had no significant effect on depression scores. Mean changes after the Mediterranean diet plus olive oil, Mediterranean diet plus nuts, and control diet were 0.1, −1.6, and 0.3, respectively (*P* = .49).

eTable 3 in Supplement 2 gives the baseline cognitive scores and changes at the end of the trial. **Table 3** gives the fully adjusted values for the same variables. No baseline differences existed among study groups in the adjusted model. Improved 4-year scores in the 2 RAVLTs were observed in all groups, with significant differences in the RAVLT for the participants in the Mediterranean diet plus olive oil group vs the control group. Participants in the Mediterranean diet plus olive oil group also had improved scores on the Color Trail Test part 1, but the adjusted changes were not significant compared with those in the control group (*P* = .06). The Color Trail Test part 2 scores worsened in all groups, although less in the Mediterranean diet plus olive oil group, with adjusted changes significantly different from those in the control group (Table 3).

Figure 2 and **Table 4** report adjusted changes in composite scores for memory, frontal functions, and global cognition. Table 4 also reports unadjusted values, which differed little from those in the fully adjusted model. Participants in the control group had a significant decrease from baseline in all composites. Compared with the control group, the memory composite improved significantly in the Mediterranean diet plus nuts group, whereas the frontal and global cognition composites improved in the Mediterranean diet plus olive oil group. Figure 2 also shows that the changes for the 2 Mediterranean diet arms in each composite were more like each other than when comparing those of the individual Mediterranean diet arms with the control arm.

Figure 2. Changes in Cognitive Function Measured With Composites by Intervention Group



Error bars indicate 95% CIs. *P* values by analysis of covariance were adjusted for sex, baseline age, years of education, marital status, *APOE* ε4 genotype, ever smoking, baseline body mass index, energy intake, physical activity, type 2 diabetes mellitus, hyperlipidemia, ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up, with the Bonferroni post hoc test. For each cognitive composite, the changes between the 2 Mediterranean arms were not statistically different (*P* >.99 for all). The changes for memory between the Mediterranean diet plus olive oil and control groups and for frontal and global cognition between the Mediterranean diet plus nuts and control groups had values of *P* < .25.

[a] *P* < .05.

[b] *P* < .01.

At the end of follow-up, we identified 37 cases of incident mild cognitive impairment: 17 (13.4%) in the Mediterranean diet plus olive oil group, 8 (7.1%) in the Mediterranean diet plus nuts group, and 12 (12.6%) in the control group (adjusted *P* = .28). No dementia cases were documented in participants completing follow-up.

Discussion

The PREDIMED study is a 5-year randomized clinical trial of nutrition intervention with the Mediterranean diet vs a control diet for primary cardiovascular prevention in older individuals at high cardiovascular risk.[14] In a PREDIMED substudy, we assessed cognitive performance by various neuropsychological tests at baseline and after a median follow-up of 4.1 years. Results revealed cognitive improvement in participants allocated the Mediterranean diet and cognitive decline in those allocated the control diet. The benefit of the Mediterranean diet was independent of sex, age, energy intake, and cognition-related variables, including educational level, *APOE* ε4 genotype, and vascular risk factors. These findings are novel because, to our knowledge, no prior long-term clinical trial has assessed cognitive changes in response to dietary patterns.

Our results extend those of prior PREDIMED substudies wherein cognitive performance was better after the intervention in the 2 Mediterranean diet groups[17] or in the Mediterranean diet plus olive oil group,[18] but changes over time were not assessed. Inasmuch as the main food changes were increased intakes of the supplemental foods olive oil and nuts in the corresponding Mediterranean diet groups, our findings also concur with those of the cross-sectional analysis at baseline of the same cohort, in which higher consumption of olive oil and walnuts was independently related to better cognition.[20] The data are consistent as well with large observational studies[10-12] providing longitudinal evidence of a moderate protective effect of the Mediterranean diet against cognitive decline and Alzheimer disease. Our findings, however, derive from a randomized clinical trial with baseline and post-intervention assessments, thus providing a stronger level of scientific evidence.[13]

In our study, participants allocated to the Mediterranean diet plus nuts had improvement in the memory composite compared with those ascribed the control diet. Thus far, scientific evidence is limited on the association between nut consumption and cognition. Two observational studies, the Doetinchem Cohort[26] and the Nurses' Health Study,[27] found that long-term nut consumption was related to overall cognition at older age but not to cognitive decline during follow-up for 5 to 6 years. On the other hand, a randomized clinical trial in young adults found no effect of walnut supplementation for 8 weeks on cognitive function.[28] Results from experimental studies[29,30] have also linked dietary supplementation with nuts, particularly walnuts, to improved cognitive outcomes in aged animals. A prior PREDIMED substudy[31] with a larger sample size indicated that the Mediterranean diet plus nuts reduced incident depression among diabetic participants. In our study, with lower statistical power, we observed no effect of the intervention on depression scores.

Participants in the Mediterranean diet plus olive oil group had improved frontal function and global cognition composites in our study. There is also little evidence on the association between olive oil consumption and cognition. In the prospective Three-City Study in France,[32] a weak association between increased olive oil intake and risk of cognitive decline during a 4-year follow-up was described. Greater intake of monounsaturated fatty acids, abundant in olive oil, also related to better cognitive function in the Italian Longitudinal Study on Aging after an 8-year follow-up.[33] In the same line, a PREDIMED substudy[18] reported decreased rates of mild cognitive impairment in participants allocated to the Mediterranean diet plus olive oil compared with those in the control group.

The beneficial effect of Mediterranean diets on cognition probably stems from the abundance of antioxidants and anti-inflammatory agents that they provide. The supplemental foods, extravirgin olive oil and nuts, are particularly rich in phenolic compounds[15,16] that might counteract oxidative processes in the brain, leading to neurodegeneration. Polyphe-

Table 4. Baseline Cognitive Function Measured With Composites and Changes by Intervention Group

Variable	Mean (95% CI)			*P* Value
	Mediterranean Diet Plus Extravirgin Olive Oil	Mediterranean Diet Plus Nuts	Control Diet	
Memory[a]				
Unadjusted model[b]				
Baseline	−0.06 (−0.02 to 0.08)	0.04 (−0.12 to 0.20)	0.04 (−0.14 to −0.23)	.56
Change	0.04 (−0.10 to 0.17)	0.08 (−0.06 to 0.22)	−0.14 (−0.29 to 0.004)	.08
Fully adjusted model[c]				
Baseline	0.02 (−0.11 to 0.15)	0.013 (−0.13 to 0.16)	−0.04 (−0.20 to −0.11)	.82
Change	0.04 (−0.09 to 0.18)	0.09 (−0.05 to 0.23)[d]	−0.17 (−0.32 to −0.01)	.04
Frontal Cognition[e]				
Unadjusted model[b]				
Baseline	0.06 (−0.10 to 0.23)	0.02 (−0.16 to 0.21)	−0.10 (−0.33 to 0.12)	.41
Change	0.23 (0.07 to 0.38)[d]	−0.02 (−0.27 to 0.22)	−0.28 (−0.53 to −0.03)	.002
Fully adjusted model[c]				
Baseline	−0.06 (−0.25 to 0.13)	0.04 (−0.20 to 0.27)	0.12 (−0.11 to −0.34)	.50
Change	0.23 (0.03 to 0.43)[d]	0.03 (−0.25 to 0.31)	−0.33 (−0.57 to −0.09)	.003
Global Cognition[e]				
Unadjusted model[b]				
Baseline	0.06 (−0.06 to 0.18)	0.21 (0.06 to 0.36)	0.22 (0.06 to 0.39)	.17
Change	0.05 (−0.08 to 0.18)[d]	−0.06 (−0.24 to 0.11)	−0.36 (−0.56 to −0.15)	.001
Fully adjusted model[c]				
Baseline	−0.07 (−0.17 to 0.04)	−0.05 (−0.16 to 0.06)	−0.07 (−0.19 to 0.05)	.97
Change	0.05 (−0.11 to 0.21)[d]	−0.05 (−0.27 to 0.18)	−0.38 (−0.57 to −0.18)	.005

[a] Measured in 334 participants (127, 112, and 95 participants, respectively).

[b] Comparisons across groups by 1-way analysis of variance.

[c] Comparisons across groups by analysis of covariance adjusted for sex, baseline age, years of education, marital status, *ApoE4* genotype, ever smoking, baseline body mass index, energy intake, physical activity, diabetes mellitus, hyperlipidemia, ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up (not in baseline, only in change).

[d] Significantly different from control group (Bonferroni post hoc test).

[e] Measured in 96 participants (41, 25, and 30 participants, respectively).

nols can ameliorate neurologic health by additional mechanisms, including improved cerebrovascular blood flow, modulation of neuronal signaling, enhanced synthesis of neurotrophic factors, and stimulation of neurogenesis.[34] Diabetes is an established link with cognitive decline, and a variety of polyphenols also disclose an antidiabetic effect.[35] In this regard, results from the cross-sectional evaluation at baseline of the present cohort, whereby urinary polyphenol excretion (an objective biomarker of intake) was linearly associated with better memory scores,[20] reinforce the notion that phenolic compounds protect brain function.[6] On the other hand, nuts, particularly walnuts given in one arm of the trial, contain sizeable amounts of α-linolenic acid, the vegetable ω3 fatty acid. Administration of this fatty acid has been found to enhance brain plasticity and exert an antidepressant effect in experimental animals.[36]

A consistent body of evidence supports a high effect of vascular risk factors on cognitive decline and dementia[37]; hence, another mechanism through which the Mediterranean diet might promote brain health is vascular improvement. Brain magnetic resonance imaging investigations have found a strong beneficial effect of high adherence to the Mediterranean diet on white matter hyperintensities[38] and subclinical brain infarcts.[39] Furthermore, prospective studies have suggested that the Mediterranean diet[40,41] and the use of olive oil[42] reduce the incidence of stroke. In the PREDIMED study,[14] the 2 Mediterranean diet interventions reduced the incidence of cardiovascular diseases by 30% compared with the control diet, whereas the risk of stroke was reduced by 34% in the Mediterranean diet plus olive oil group and by 49% in the Mediterranean diet plus nuts group. Besides vascular brain damage, other strong associations of cognitive impairment and Alzheimer disease are hypertension[37] and diabetes,[43] and the PREDIMED Mediterranean diets also had a beneficial effect on blood pressure[44] and diabetes risk.[45]

There are still other possible mechanisms of brain protection by Mediterranean diets, such as increase of neurotrophic factors related to neurotransmission, synaptic plasticity, and elimination of β-amyloid from the brain. Thus, a report from a 3-year PREDIMED substudy[46] found increased plasma concentrations of brain-derived neurotrophic factor in the Mediterranean diet plus nuts group. Finally, an experimental study[47] found that oleocanthal, a phenolic component of extravirgin olive oil, enhances brain β-amyloid clearance, suggesting a link between olive oil consumption and reduced risk of Alzheimer disease.

Our study has limitations. First, this is a post hoc analysis of a subsample in a larger clinical trial that was not specifically designed to examine cognition. Second, the overall sample size is small, and the subsample receiving tests of frontal functions and language is even smaller. Nonetheless, the results of all composite cognitive scores were statistically significant in favor of the Mediterranean diets, with little differences before and after adjusting for confounders. Third, because of our differential results for the Mediterranean diet on cognitive composites, depending on whether it included olive oil or nuts, it is difficult to precisely delineate what part of the diet was associated with preventing cognitive decline. However, changes in the 2 Mediterranean diet groups were more like each other than when compared with those in the control

arm, from which it can be inferred that the 2 Mediterranean diets were protective. Fourth, we had losses to follow-up, predominantly in the control group, probably because participants did not receive food incentives. Nevertheless, dropout rates per group followed a pattern similar to that of the main trial[14] and were not unexpected given the older age of participants and the trial's duration. Fifth, participants who withdrew had worse baseline cognition and more *APOE* ε4 genotypes than completers, thus being more likely to disclose cognitive impairment during follow-up. The fact that there were more dropouts in the control group suggests a bias toward a benefit in this group. Sixth, given the long recruitment period, intervals of follow-up cognitive assessments were unavoidably unequal. For this reason, follow-up time was entered as a confounder in the multivariable models. Finally, our cohort was selected for high vascular risk, which prevents generalizing the results to the average elderly population. There are also strengths to our study, such as the randomized design, long duration of the intervention, assessment of diet adherence by objective biomarkers, and use of a comprehensive battery of standardized neuropsychological tests to assess cognitive function.

Conclusions

Our results suggest that in an older population a Mediterranean diet supplemented with olive oil or nuts may counteract age-related cognitive decline. The lack of effective treatments for cognitive decline and dementia points to the need of preventive strategies to delay the onset and/or minimize the effects of these devastating conditions. The present results with the Mediterranean diet are encouraging, but further investigation is warranted.

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Author Affiliations: Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer, Hospital Clínic, Barcelona, Spain (Valls-Pedret, Sala-Vila, Serra-Mir, Pérez-Heras, Ros); Ciber Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain (Valls-Pedret, Sala-Vila, Serra-Mir, Corella, de la Torre, Martínez-González, Martínez-Lapiscina, Fitó, Pérez-Heras, Salas-Salvadó, Estruch, Ros); Department of Preventive Medicine, University of Valencia, Valencia, Spain (Corella); Cardiovascular and Nutrition Research Group, Institut de Recerca Hospital del Mar, Barcelona, Spain (de la Torre, Fitó); Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain (Martínez-González, Martínez-Lapiscina); Human Nutrition Department, Hospital Universitari Sant Joan, Institut d'Investigació Sanitaria Pere Virgili, Universitat Rovira i Virgili, Reus, Spain (Salas-Salvadó); Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer, Hospital Clínic, Barcelona, Spain (Estruch).

Author Contributions: Dr Ros had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Valls-Pedret, Serra-Mir, Corella, Martínez-González, Martínez-Lapiscina, Pérez-Heras, Salas-Salvadó, Estruch, Ros.
Acquisition, analysis or interpretation of data: Valls-Pedret, Sala-Vila, Corella, de la Torre, Martínez-González, Martínez-Lapiscina, Fitó, Salas-Salvadó.
Drafting of the manuscript: Valls-Pedret, Sala-Vila, Ros.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Valls-Pedret, Sala-Vila, Martínez-Lapiscina.
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Supervision: Valls-Pedret, Corella, Martínez-González, Martínez-Lapiscina, Fitó, Estruch, Ros.

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