RESEARCH PAPER

Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

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ABSTRACT

Objective Previous observational studies reported beneficial effects of the Mediterranean diet (MedDiet) on cognitive function, but results were inconsistent. We assessed the effect on cognition of a nutritional intervention using MedDiets in comparison with a low-fat control diet.

Methods We assessed 522 participants at high vascular risk (44.6% men, age 74.6 ± 5.7 years at cognitive evaluation) enrolled in a multicentre, randomised, primary prevention trial (PREDIMED), after a nutritional intervention comparing two MedDiets (supplemented with either extra-virgin olive oil (EVOO) or mixed nuts) versus a low-fat control diet. Global cognitive performance was examined by Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT) after 6.5 years of nutritional intervention. Researchers who assessed the outcome were blinded to group assignment. We used general linear models to control for potential confounding.

Results After adjustment for sex, age, education, *Apolipoprotein E* genotype, family history of cognitive impairment/dementia, smoking, physical activity, body mass index, hypertension, dyslipidaemia, diabetes, alcohol and total energy intake, participants allocated to the MedDiet+EVOO showed higher mean MMSE and CDT scores with significant differences versus control (adjusted differences: +0.62 95% CI +0.18 to +1.05, p=0.005 for MMSE, and +0.51 95% CI +0.20 to +0.82, p=0.001 for CDT). The adjusted means of MMSE and CDT scores were also higher for participants allocated to the MedDiet+Nuts versus control (adjusted differences: +0.57 (95% CI +0.11 to +1.03), p=0.015 for MMSE and +0.33 (95% CI +0.003 to +0.67), p=0.048 for CDT). These results did not differ after controlling for incident depression.

Conclusions An intervention with MedDiets enhanced with either EVOO or nuts appears to improve cognition compared with a low-fat diet.

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INTRODUCTION

Worldwide prevalence of dementia is expected to reach 65.7 million and 115.4 million in 2030 and 2050, respectively.[1] Currently, there is no effective therapy to delay the onset or halt the progression of dementia,[2] a growing public health problem with priority for research.

The potential protection on cognition has been examined for some nutrients such as fatty acids, vitamins, fish, fruit and vegetables but observational and experimental studies have provided inconsistent results.[3] Defining the effect of diet on health by the overall dietary pattern instead of a single or a few nutrients allows to study the synergy among nutrients and avoids problems due to confounding, multiple testing and collinearity among them.[4]

The Mediterranean diet (MedDiet) is characterised by the use of olive oil as the main culinary fat and high consumption of plant-based foods (fruits and nuts, vegetables, legumes and minimally processed cereals). It also includes moderate-to-high consumption of fish and seafood and low consumption of butter or other dairy products and meat or meat products. Regular but moderate intake of alcohol, preferentially red wine during meals, is customary.[5]

The relationship between conformity with the MedDiet and cognition has been assessed in observational studies with promising, though not fully consistent, results.[6–17] The only available trial evaluating this topic found inconsistent results and it had an inordinately short follow-up of only 10 days.[18] We evaluated global cognition among subjects participating in a long-term prevention randomised trial that compared two interventions with MedDiet versus a low-fat diet.

METHODS
Trial design

The PREDIMED (PREvención con DIeta MEDiterránea) study was a randomised, parallel-group, cardiovascular primary prevention trial conducted in Spain from May 2005 to December 2010 which compared two interventions with MedDiet (supplemented with extra virgin olive oil (EVOO) and supplemented with mixed nuts) versus the low-fat diet usually recommended for the primary prevention of cardiovascular disease (CVD) in a high-risk population. The design and methods of the PREDIMED trial have been described in detail elsewhere.[19] The stopping boundary for the benefit of the MedDiets on the primary end point was crossed at the fourth interim evaluation; therefore, on July 2011, the Data Safety Monitoring Boards recommended the trial should be stopped. The results have been recently published.[20] No relevant diet-related adverse effects were reported. The present analysis deals with a subsample from 1 of the 11 recruitment centres (PREDIMED-NAVARRA). This centre was selected

because it completed the recruitment of participants earlier (2005) than the other centres of the trial (2009) and thus allowed for a sufficiently longer intervention period and follow-up time.

Study population

Participants were community-dwelling men (55–80 years) and women (60–80 years), initially free of CVD but at high vascular risk because of the presence of either type-2 diabetes or at least three of the following major risk factors: current smoking, hypertension, dyslipidaemia, overweight or family history of premature CVD. Exclusion criteria included previous history of CVD, any severe chronic illness, illiteracy, or other conditions, as described.[19]

General practitioners (GPs) extracted names of potential participants from the clinical records of the primary care practices. Once the GPs had ensured agreement with the eligibility criteria, potential participants were approached by a telephone call or during their clinical visits. If they showed interest in the study, a screening interview was scheduled to inform them about the study.[19] All procedures followed the Declaration of Helsinki. The Institutional Review Board of the Navarra recruitment centre approved the study protocol (protocol 50/2005). All participants signed an informed consent.

The PREDIMED-NAVARRA centre recruited 1055 participants between 2003 and 2005.

The neuropsychological study was conducted over 8 months in the primary care centres in the same day that the nurse performed the blood tests for the PREDIMED trial. We established this routine to promote compliance and to allow participants to complete several tasks on the same day. Participants who did not attend the visits on their scheduled days were considered non-eligible for neuropsychological testing. Those who attended the visits but did not accept undergoing neuropsychological testing were also excluded. Finally, among 969 participants who were then alive, 522 participants underwent a neuropsychological testing after a mean 6.5 years of follow-up.

Randomisation and blinding

After the screening visit, eligible participants were randomly (allocation ratio 1:1:1) assigned to one of three diet groups by using a computer-generated random-number sequence. Tables of random allocation were centrally elaborated. We concealed allocation into the intervention groups by using closed envelopes with correlative numbers by prespecified subgroups of sex and age.

The study nurses in charge of the random allocation were independent of the nursing staff of the primary care practices. At baseline, GPs were not informed of the allocation of participants. Researchers who assessed the outcome were also blinded to group assignment.[19]

Sample size

An individually randomised trial would require 132 participants per group to detect a 1-unit mean difference in Mini-Mental State Examination (MMSE) between each of the MedDiet groups and the control group assuming a SD of 2.5 units for a two-sided 5% α error with 90% power.

Nutrition interventions and dietary assessment

As previously described, a behavioural intervention promoting the MedDiet was implemented.[19 21] Briefly, participants received intensive education and advice to increase adherence to the MedDiet or the low-fat diet, according to group allocation. At inclusion and quarterly thereafter, dietitians administered group sessions, separately for each group. Sessions consisted of informative talks and delivery of written material with descriptions of typical foods for each dietary pattern, seasonal shopping lists, meal plans and recipes. Participants allocated the MedDiet groups received free allotments of either EVOO (1 l/week) or 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts). In the control group, participants received advice to reduce all types of fat and non-food gifts as an incentive to improve compliance. Energy restriction was not advised, nor physical activity promoted. At baseline and yearly thereafter, a trained dietitian administered a validated 137-item food-frequency questionnaire and a 14-item short questionnaire of adherence to the MedDiet.[22 23]

Primary outcome: cognitive assessment

Two neuropsychological tests were administered after a mean follow-up of 6.5 years: the Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT). MMSE assesses orientation to time and place, registration, attention and calculation, recall, language, and visual construction[24] and the score ranges from 0 to 30. The MMSE has been shown to be a valid indicator of cognitive impairment.[25] There is a validated Spanish version.[26] CDT is a neuropsychological tool to assess a wide range of higher-level cognitive abilities required simultaneously for its successful completion, including language comprehension, visuospatial abilities, working memory, attention and abstract thinking.[27] CDT is a useful instrument to identify subjects at risk of cognitive decline and dementia.[28] We used a validated Spanish version ranging from 0 to 7.[29]

The effect of an intervention with MedDiet on cognition has not been previously explored in any long-term randomised clinical trial. Considering the disappointing experience from some earlier interventions (vitamin E, omega-3 fatty acids) that showed no protective effect in randomised clinical trials,[30 31] in spite of the extensive evidence of beneficial effects from large longitudinal studies,[32 33] it seems prudent to explore the effect of MedDiet on cognition, first assessing global cognition. As the neuropsychological battery is limited, it is not possible to analyse the effect of diet on different cognitive domains or determine the nature of cognitive impairment (neurodegenerative/vascular).

Secondary outcome: incidence of dementia and MCI in the PREDIMED-NAVARRA RCT

At the end of the nutritional intervention and thus, coinciding with the cognitive study, medical records of all participants were checked to collect incidence events including mild cognitive impairment (MCI), dementia and depression. This information was sent to The Adjudication Committee. This Committee reviewed the suitability of diagnoses according to the available information. Additionally, participants with a pathological cognitive screening test were re-evaluated by a neurologist to determine the presence or absence of MCI or dementia.

Diagnoses of dementia or MCI from the Adjudication Committee were based on assessments recorded in clinical records and usually made by neurologists upon the request of either GPs or participants. Our participants had a high vascular risk so they were regularly monitored by GPs. In addition in another subsample of 268 participants, we performed a comprehensive cognitive evaluation to identify MCI or dementia. The use of both methods (review of medical record based on referrals by GPs and personalised comprehensive neuropsychiatric assessment) are likely to have increased the sensitivity in detecting MCI and dementia. However, it seems logical to think that

the sensitivity for a MCI diagnosis would be higher for the personalised and comprehensive cognitive assessment.

Covariate assessment

The baseline questionnaire included questions about sociodemographic characteristics, lifestyle and health-related habits, medical history and family history of cognitive impairment or dementia. Anthropometric measurements were taken by trained personnel using standard methods.[19] 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.[34 35] Apolipoprotein E (APOE) genotype was determined with the method of Hixson and Vernier.[36] Only three participants of the 522 analysed were homozygous for E4, so APOE genotype was considered dichotomously: presence of at least one E4 allele (sum of E4/3 and E4/4 genotypes) versus absence of E4 allele. APOE E2/4 genotype was excluded.

Statistical analyses

Quantitative data were shown as means and SDs. Bivariate analyses were done with the χ^2 test or the Fisher test for categorical variables. Bivariate comparisons among groups for continuous variables were done by using one-way analysis of variance. Analyses were performed on an intention-to-treat principle. First, we explored differences in baseline characteristics of participants according to the allocated intervention groups. Then, we estimated unadjusted mean scores in neuropsychological tests according to the intervention groups. Finally, multivariable-adjusted mean scores of cognitive function tests and differences versus control (95% CIs) in each intervention group were estimated using general linear models adjusting for sex, age, education, family history of cognitive impairment or dementia, ApoE4 genotype, hypertension, dyslipidaemia, diabetes, smoking status, alcohol intake, body mass index, physical activity and total energy intake. All p values were two-tailed at the <0.05 level. Statistics were performed with SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA) software.

RESULTS

Study population

The PREDIMED-NAVARRA centre recruited 1055 participants between 2003 and 2005.

Among 969 participants who were alive, 522 participants underwent neuropsychological testing after a mean follow-up of 6.5 years. Figure 1 shows the flow of participants throughout the study.

A comparison of baseline characteristics of the analysed cohort with that of the participants not included in the PREDIMED-NAVARRA cognition study is shown in table 1. The analysed cohort had on average a higher educational level and was less often diagnosed as having hypertension and diabetes but more often as having dyslipidaemia compared with the participants not included in this cognition study. Participants who underwent cognitive assessment were less often current smokers and had a slightly lower body mass index.

The analysed cohort had a mean age of 74.6 (SD:5.7) years at cognitive evaluation and 44.6% were men. By study design, we found a high prevalence of hypertension, dyslipidaemia and type-2 diabetes. Table 2 shows baseline characteristics of participants by intervention group. As expected from the randomised design, the groups were well balanced with respect to all these baseline characteristics.
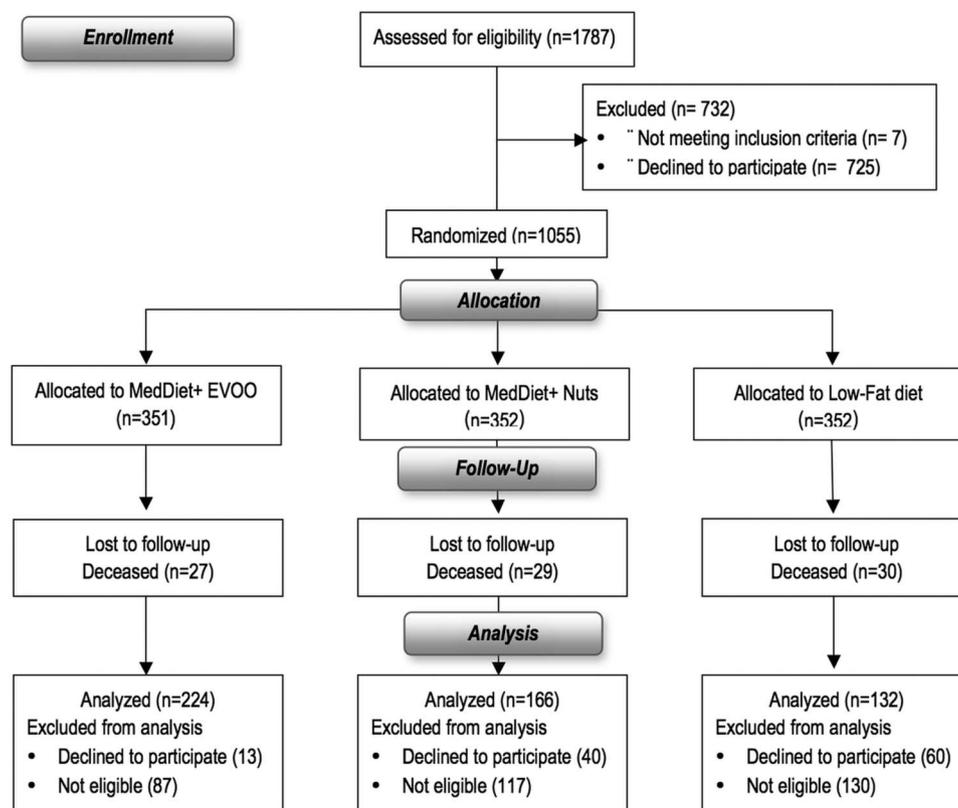
Figure 1 Flow chart of participants.

Table 1 Comparison of baseline characteristics* of the analysed cohort with that of the participants not included in PREDIMED-NAVARRA cognition study

Variables	Participants not included (n=533)	Participants included (n=522)	p Value†
Apolipoprotein E4 genotype‡, n (%)	85 (15.9)	70 (13.4)	0.244
Sex male, n (%)	239 (44.8)	233 (44.6)	0.947
Age (years)	67.77±6.68	67.38±5.65	0.302
Education only primary§, n (%)	413 (77.5)	371 (71.1)	0.017
Hypertension, n (%)	456 (85.6)	420 (80.5)	0.028
Dyslipidaemia, n (%)	331 (62.1)	362 (69.3)	0.013
Diabetes, n (%)	232 (43.5)	183 (35.1)	0.005
Body mass index (kg/m²)	29.7±3.4	29.1±3.3	0.002
Smoking			
Current smoker, n (%)	105 (19.7)	78 (14.9)	0.041
Former smoker, n (%)	118 (22.1)	109 (20.9)	0.619
Alcohol intake (g/day)	12±19	13±19	0.445
Physical activity (MET-min/day)¶	276±217	274±197	0.848
Total energy intake (kcal/day)	2242±539	2257±536	0.648

*Mean and SD unless otherwise stated.
†χ^2 Test (percentages) or one-way analysis of variance (means).
‡Sum of E4/3 and E4/4 genotypes (E2/4 excluded).
§Education categorised as having only primary education ($\leq$8 years of education in Spain) or having a higher education level (original data of PREDIMED Study).
¶Minutes at a given metabolic equivalent level (units of energy expenditure in a physical activity, 1 MET-min roughly equivalent to 1 kcal).

Diet intervention compliance

The intervention in the PREDIMED-NAVARRA centre achieved a substantial contrast between the two groups allocated to the MedDiet and the control group. The average values for the 14-item short questionnaire after a 5-year intervention were 10.5 (SD:3.3) in MedDiet+EVOO, 9.1 (SD:4.9) in MedDiet+Nuts and 5.8 (SD:4.7) in the control group (p<0.001). After a 6-year intervention, these figures were 10.8 (SD:2.7) in MedDiet+EVOO; 10.1 (SD:4.0) in MedDiet+Nuts and 6.3 (SD:4.7) in the control group (p<0.001).

Primary outcome: cognitive test

Table 3 shows the mean MMSE and CDT scores at the end of follow-up by the intervention arm. Mean MMSE and CDT scores were significantly higher for participants allocated to the MedDiet+EVOO group in comparison with the control group, while crude differences were not significant for the MedDiet+Nuts group versus the control group.

In multivariate regression analyses, participants allocated to the MedDiet+EVOO group showed mean global cognitive function scores with significant differences versus the control group (adjusted differences: +0.62 95% CI +0.18 to +1.05, p=0.005 for MMSE, and +0.51 95% CI +0.20 to +0.82, p=0.001 for CDT). The adjusted means of MMSE and CDT scores were also higher for participants allocated to the MedDiet+Nuts group versus the control group (adjusted differences: +0.57 95% CI +0.11 to +1.03, p=0.015 for MMSE and +0.33 95% CI +0.003 to +0.67, p=0.048 for CDT) (Table 4)

The presence of *ApoE4* genotype (B=−0.804 95% CI −1.315 to -0.294), female sex (B=−0.562 95% CI −1.067 to −0.058)

and older age (B=−0.087 95% CI −0.120 to −0.055 per 1-year of increase) were associated with a lower MMSE score whereas more years of education (B=0.156 95% CI 0.096 to 0.215 per 1-year of increase) was associated with a better MMSE score. Similar results were found in relation to the CDT outcome: *ApoE4* genotype (B=−0.535 95% CI −0.899 to −0.171), female sex (B=−0.485 95% CI −0.845 to −0.125), age (B=−0.071 95% CI −0.094 to −0.048 per 1-year of increase) and education (B=0.118 95% CI 0.076 to 0.161). None of the other potential confounders included as covariates were independently associated with cognitive outcomes in multivariable analyses.

Secondary outcome: incidence of dementia and MCI in PREDIMED-NAVARRA RCT

After 6.5 years of nutritional intervention, 60 cases of incident MCI (18 in MedDiet+EVOO; 19 in MedDiet+Nuts; 23 low-fat) and 35 cases of incident dementia (12 in MedDiet+EVOO; 6 in MedDiet+Nuts; 17 in low-fat) were diagnosed in the PREDIMED-NAVARRA centre.

Within the subgroup of 268 participants undergoing comprehensive cognitive assessment, 34 (12.7%) participants were diagnosed with MCI and 5 (1.9%) with dementia. These data suggest that the case-ascertainment method based on the review of medical records may be similarly sensitive than the personalised cognitive assessment for dementia diagnosis but sensitivity of medical records review was clearly lower than that for a complete neurological examination for a MCI diagnosis.

DISCUSSION

To the best of our knowledge, this is the first study evaluating the effect of a long-term randomised intervention aimed to change the overall dietary pattern on global cognitive function. Our trial suggests that nutritional intervention with MedDiet supplemented with either EVOO or nuts is associated with improved global cognition. The benefit of MedDiet was independent of potential confounders such as age, family history of cognitive impairment or dementia, *ApoE* genotype, education, physical activity, vascular risk factors and energy intake.

Our longitudinal results concur with the recent findings from a cross-sectional analysis at baseline in another PREDIMED subgroup (Barcelona) whereby increased consumption of EVOO and walnuts were independently related to better cognition.[37] They are also consistent with the weak but not significant association observed for olive oil, monounsaturated fatty acids and the MedDiet in the European Prospective Investigation into Cancer and Nutrition-Greek (EPIC-Greek) study,[6] with a similar but stronger association observed in a large Italian cohort[38] and with a slightly improved cognitive performance in the Three-City French cohort.[7]

Our findings are consistent with previous, but not all, observational studies conducted outside the Mediterranean basin. In a community-based American cohort study, a higher adherence to the MedDiet was associated with slower rates of cognitive decline after a 7.6-year follow-up.[8] Another American cohort study found that a higher adherence to the MedDiet was associated with a lower risk of developing MCI[9] and AD (Alzheimer's disease)[10–12] as well as lower risk of MCI conversion to AD.[9] Scarmeas *et al*[10 11] found a protective effect of MedDiet pattern on incidence of dementia in two studies with larger sample sizes of 2258 and 1880 and higher incidences of dementia, 262 and 282 cases, respectively. Subsequently, Gu *et al*[12] found similar results in a study with 1219 participants and 118 cases of incident dementia. In the total sample of participants from the PREDIMED-NAVARRA centre, we observed

Table 2 Baseline characteristics* of participants according to intervention group

Variables	MedDiet+EVOO (n=224)	MedDiet+Nuts (n=166)	Control (low-fat diet) (n=132)	p Value†
Family history of cognitive decline‡, n (%)	42 (18.8)	37 (22.8)	27 (20.8)	0.691
Apolipoprotein E4 genotype§, n (%)	28 (12.5)	23 (13.9)	19 (14.4)	0.861
Sex male, n (%)	102 (45.5)	71 (42.8)	60 (45.5)	0.842
Age (years)	67.35±5.65	67.30±5.77	67.55±5.54	0.925
Education (years)	8.50±2.79	8.45±3.00	8.54±3.38	0.966
Hypertension, n (%)	174 (77.7)	138 (83.1)	108 (81.8)	0.366
Dyslipidaemia, n (%)	158 (70.5)	115 (69.3)	89 (67.4)	0.827
Diabetes, n (%)	83 (37.1)	58 (34.9)	35 (26.5)	0.117
Body mass index (kg/m^2)	29.30±3.4	28.96±3.1	29.94±3.4	0.494
Smoking				
Current smoker, n (%)	33 (14.7)	20 (12.0)	25 (18.9)	0.251
Former smoker, n (%)	46 (20.5)	35 (21.1)	28 (21.2)	0.986
Alcohol intake (g/day)	14±20	13±19	11±17	0.450
Physical activity (MET-min/day)¶	282±200	280±194	253±197	0.356
Total energy intake (Kcal/day)	2276±543	2290±538	2184±519	0.185

The PREDIMED-NAVARRA trial.
*Mean and SD unless otherwise stated.
†χ^2 Test (percentages) or one-way analysis of variance (means).
‡Cognitive impairment or dementia in first degree relatives.
§Sum of E4/3 and E4/4 genotypes (E2/4 excluded).
¶Minutes at a given metabolic equivalent level (units of energy expenditure in a physical activity, 1 MET-min roughly equivalent to 1 kcal).
EVOO, extra virgin olive oil; MedDiet, Mediterranean diet.

a lower incidence of dementia (35/1055), so even admitting that case-ascertainment for dementia incidence maybe more accurate, it is probable that our study was underpowered to address a protective effect of MedDiet on dementia development, given the small number of total cases observed. On the other hand, the results observed in our trial in terms of MMSE score changes are also of relatively small magnitude but our study was adequately powered to detect them and our findings support a beneficial effect. The fact that our study was a randomised controlled trial with a long follow-up period may account for a relatively greater magnitude of effect than in some shorter previous observational studies which reported a smaller benefit or null results. Thus, an Australian cohort with a 4-year[13] and 8-year[14] follow-up and another American cohort with 5.4-year[15] follow-up found no association between higher adherence to the MedDiet and cognitive decline or MCI. Recently, results from French participants who agreed to participate in a postsupplementation observational follow-up of the SU.VI.MAX [Supplementation en Vitamines et Mineraux Antioxydants] trial and results from participants from the Nurses Health Study who performed a telephone-based cognitive evaluation have been published. None of them supports a global protective effect of the MedDiet on cognitive decline.[16 17] These heterogeneous findings can be explained by several reasons, including the probably long induction period for the effect of nutritional changes on cognition, the use of a definition for the MedDiet in observational epidemiology which is highly dependent on sample-specific cut-off points for food consumption, and the intake of other foods or supplements not included in the score used to appraise adherence to the MedDiet. These other nutritional factors can be responsible for residual confounding. More importantly, nutritional assessment tools used in observational epidemiology are prone to measurement errors that usually may lead to null associations. Another reason that may explain these heterogeneous findings may be related to characteristics of study populations. Some demographic factors and comorbidities should be also taken into account in order to evaluate the effect of the MedDiet on cognition. Most studies have evaluated participants with a mean age ≥75 years.[6–12 15] Since the MedDiet may exert its protective effect relatively early on the neurodegeneration process, this may minimise the effective size of the Mediterranean diet. Vascular, inflammatory and oxidative mechanisms are involved in the pathogenesis of dementia. In populations with high vascular risk, a more important vascular contribution to dementia can be expected. It would be interesting to address if the effect of the MedDiet is different in these populations. Unfortunately, only one of the cohorts mentioned above, evaluated the effect of diet on a population with a high vascular comorbidity and provided negative results.[15]

Table 3 Unadjusted means (95% CI) in cognitive tests after a 6½-year follow-up according to the intervention group

	MedDiet+EVOO (n=224) (1) Mean (95% CI)	MedDiet+Nuts (n=166) (2) Mean (95% CI)	Control (low-fat diet) (n=132) (3) Mean (95% CI)	Analysis of variance p value	Bonferroni (1) vs (3)	Bonferroni (2) vs (3)
MMSE	28.00 (27.72 to 28.29)	27.96 (27.64 to 28.29)	27.40 (26.99 to 27.81)	0.030	0.037	0.085
CDT	5.45 (5.25 to 5.65)	5.27 (5.01 to 5.52)	4.95 (4.67 to 5.24)	0.020	0.016	0.299

The PREDIMED-NAVARRA trial.
CDT, Clock Drawing Test; EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.

Table 4 Multivariable-adjusted means after a 6½-year follow-up and differences versus control (95% CIs) in each intervention group

	MedDiet+EVOO (n=224)		MedDiet+Nuts (n=166)		Control (low-fat diet) (n=132)
	Mean (95% CI)	p Value (vs control)	Mean (95% CI)	p Value (vs control)	Mean (95% CI)
MMSE	27.73 (27.27 to 28.19)		27.68 (27.20 to 28.16)		27.11 (26.61 to 27.61)
Adjusted diff. versus control (95% CI)	+0.62 (+0.18 to +1.05)	0.005	+0.57 (+0.11 to +1.03)	0.015	0 (reference)
CDT	5.31 (4.98–5.64)		5.13 (4.78–5.47)		4.80 (4.44–5.16)
Adjusted diff. versus control (95% CI)	+0.51 (+0.20 to +0.82)	0.001	+0.33 (+0.003 to +0.67)	0.048	0 (reference)

General Linear Models. The PREDIMED-NAVARRA trial.
CDT, Clock Drawing Test; EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.
Adjusted for sex, age, education, family history of cognitive impairment or dementia, *ApoE4* genotype, hypertension, dyslipidaemia, diabetes, smoking status, alcohol intake, body mass index, physical activity and total energy intake.

Finally, the only randomised controlled trial to date assessing the very short-term effect of MedDiet on cognition found that participants allocated to a diet change (to a MedDiet pattern) improved only visuospatial working memory while participants allocated to the control group (no change) improved numerical working memory and word recognition. It is possible that some limitations of that previous trial such as small sample size (27 subjects), young age (19–30 years) of the studied population and the extremely short duration of the intervention (10 days) could be partly responsible for these inconsistent results.[18]

There are mechanisms that can explain the protective effect of MedDiet on cognitive status, including antioxidative and anti-inflammatory effects and reduced vascular comorbidities. Oxidative stress has been associated with neurodegeneration.[39] The main components of the MedDiet intervention in the PREDIMED trial, EVOO and nuts, have antioxidant properties[19] and, together with other polyphenol-rich foods in the MedDiet, are suggested to relate to improved cognitive function.[37] In fact, a previous assessment from the PREDIMED-NAVARRA trial found that the intervention in this subgroup of the trial was able to increase after 3 years the total plasma antioxidant capacity.[40] Further evidence suggests that inflammation could play a role in the pathogenesis of dementia.[41] The MedDiet and especially the typical traditional Mediterranean components such as EVOO and nuts have been associated with lower serum concentrations of different inflammatory markers.[42] The protective effect of the MedDiet on vascular comorbidities also supports the biological plausibility of our results. Compliance with the MedDiet is inversely associated with vascular risk factors.[42] At the same time, there is increasing evidence that major vascular risk factors are associated with a higher risk of cognitive decline and dementia.[43] Therefore, the protective effect of the MedDiet on cognition might be related in part to improvements in underlying vascular risk factors. Due to the randomised design of the study, vascular risk factors at baseline were well-balanced among the three groups, a reason why the results did not materially change after adjusting for vascular risk factors.

There are limitations to our study. First, the most important limitation is that cognitive function of participants was not assessed at baseline. Cognitive status assessment was not initially included in the protocol since the study was primarily designed to assess the effect of MedDiet on incident CVD. The randomised design of the trial and the similarity of the three groups in all other baseline characteristics, however, are reasons to hold the assumption that cognitive performance at baseline was well balanced as well. Beyond the randomised design, another reason

to accept the appropriate comparability of the groups is that our comparisons were fully-adjusted for a wide array of potential confounders. Even if small between-group differences in cognition might have existed at baseline, it would be very unlikely that they may remain after conditioning on all these covariates. Second, we did not control for depressive symptoms at baseline nor during the cognitive assessment. Similarly, considering the even distribution of other confounders at baseline among groups, it should not undermine the validity of the results. A mood disorder may affect the assessment of cognitive performance and some authors have noted a favourable effect of the Mediterranean diet on mood[44] so it is possible that this effect could also be observed in our patients. However, in the substudy with 268 participants from the same cohort in whom we assessed the effect of the MedDiet on cognitive domains, and the incidence of MCI and dementia, the results did not significantly change after controlling for depressive symptoms at the time of cognitive assessment. The adjudication committee obtained information on the incidence of depression at the end of the study coinciding with the cognitive evaluation. Having a new medical diagnosis of depression or a new antidepressant drug prescription was used for case ascertainment of depression in the PREDIMED study. It is possible that milder cases of depression might have gone undetected. However, most severe ones and all cases with a severity significant enough as to require treatment were identified. Our results were similar when we adjusted for incident depression. For the MedDiet+EVOO group, the adjusted differences versus the control group were +0.63 95% CI +0.20 to +1.06, p=0.004 for MMSE and +0.51 95% CI +0.20 to +0.81, p=0.001 for CDT. For the MedDiet+Nuts group versus the control group, the adjusted differences were +0.56 95% CI +0.10 to +1.01, p=0.017 for MMSE, and +0.33 95% CI (+0.008 to +0.66), p=0.045 for CDT. This suggests that the effect of the Mediterranean diet on cognitive function is independent of its potential effect on mood.

We acknowledge that our sample size was relatively small with respect to the observed effect size; therefore our estimates have wide CIs. Another limitation of the study is its single blinded nature, but there is no possibility of conducting true double-blind long-term trials in nutrition. Finally, by study design, we included participants at high risk of CVD, thus the generalisation of our findings to the average general population is uncertain.

Our study also has strengths. First, the study was a long-term randomised controlled trial where MedDiets were supplemented with hallmark food components such as EVOO and mixed nuts, both with strong antioxidant and anti-inflammatory properties. Second, we controlled for several potential confounders and

randomisation allows us to rule out residual confounding as an alternative explanation of our results. Third, previous observational studies have considered the changes in dietary habits in the prodromal phase of dementia as a reverse causation bias.[7 9] A synchronous timing of dietary and cognitive assessments or a short follow-up period render a study more vulnerable to reverse causation bias.[7 9] Our long follow-up period helps to avoid this potential bias. Fourth, as we performed our analyses on an intention-to-treat principle, the presence of participants who failed to comply with the proposed dietary intervention due to an undiagnosed cognitive decline would bias the effect of the MedDiet on cognitive function toward the null. Even considering this possibility, we found an association of the MedDiet with better cognitive scores.

In conclusion, an intervention with MedDiet supplemented with either EVOO or mixed nuts was associated with a better global cognitive performance after 6.5 years of follow-up compared with a control group who received advice on a lower-fat diet. Our findings support increasing evidence on the protective effects of the MedDiet on cognitive function. Future interventional research including both baseline and follow-up assessments of global and multiple domains of cognition is needed to obtain firmer evidence regarding potential benefits of MedDiet on cognition.

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Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

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