Title: Higher versus lower nut consumption and changes in cognitive performance over two years in a population at risk of cognitive decline: a cohort study

Supplementary Data:

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Appendix A: Detailed description of the study methodology

Predimed-Plus study design and setting

PREDIMED-Plus is an ongoing, multicentre, parallel-group, randomized controlled primary intervention trial conducted in 23 Spanish study centres, aimed at evaluating the synergistic effect of three principal lifestyle interventions (i.e., energy-reduced Mediterranean diet (erMedDiet), increased physical activity, and behavioural modification) on a composite cardiovascular primary endpoint (including myocardial infarction, stroke, or cardiovascular mortality), as well as other secondary endpoints and intermediate outcomes (1). From October 2013 to December 2016, 6874 participants who met eligibility criteria were randomly allocated in a 1:1 ratio to the intervention group or to the usual care control group (traditional energy-unrestricted MedDiet), using a centrally controlled, computer-generated random number internet-based system with stratification by centre, sex, and age. Couples sharing the same household were randomized together, using the couple as a unit of randomization. The randomization procedure was blinded to all staff and principal investigators of each recruitment centre.

Outcome assessment: Neuropsychological tests

A Spanish validated version of the Mini-Mental State Examination (MMSE) is a 30-point cognitive screening questionnaire with a value of rest-retest reliability of 0.87 (95%CI: 0.79-0.93) and convergent validity of -0.92 (correlation coefficient with the Alzheimer's Disease Assessment Scale), which is divided into two sections (2,3). The first section requires vocal responses only examining different cognitive functions like orientation, memory, and attention. The second section tests the ability to name, follow verbal and written commands, write a sentence spontaneously and copy a complex polygon. A higher MMSE score indicates better cognitive performance.

The Clock Drawing Test (CDT) is another cognitive screening instrument mainly used to evaluate visuospatial and visuo-constructive capacities, as well as verbal and numerical knowledge, symbolic and conceptual representation, hemi-attention, memory, and executive function (including organization, planning and parallel processing) (4,5). The score ranges from 0 to 7 in the validated Spanish version used (6).

The Spanish Verbal Fluency Tests (VFTs) examine verbal ability and executive function, consisting of two parts: (i) the semantic verbal fluency task-animal category version (VFT-a), in which the participants were requested to name as many different animals as they can during 60 seconds; and (ii) in the phonemic verbal fluency task-letter "p" version (VFT-p), participants were asked to cite, in 60 seconds, as many words as possible that start with the letter P (avoiding names of people or places or repetitions of the same word with different suffixes). The total raw score for each of these tasks corresponds to the number of correct words produced (6,7,8).

The Digit Span Test (DST) of the WAIS-III Spanish version assesses attention and memory (9–12). The DST forward recall (DST-f), being representative of attention and short-term memory capacity, requires participants to repeat orally a series of random single digits in the same order as they heard, the sequence of digits varies in length from three to nine. The DST backward recall (DST-b), considered as a test of working memory capacity, requires participants to repeat a series of random single digits in reverse order, which the sequence varies from two to eight. The performance on the DST was reported by a direct score of the forward performance (ranging from 1 to 16) and the backward performance (ranging from 1 to 14).

The Trail Making Test (TMT), an instrument often used to assess executive function, consists of 25 circles spread out over two sheets of paper (parts A and B). In part A (TMT-A), which assesses attention and processing speed capacities, the

participants were requested to connect consecutive numbers (1–2–3–4-…) in the correct order by drawing a line. In part B (TMT-B), which further examines cognitive flexibility, participants were asked to connect consecutive numbers and letters in an alternating numeric and alphabetic sequence (1-A-2-B-3-C-…). Each part is scored according to the time taken to complete the task (a lower score represents better performance) (11–14).

Covariate assessment

Sociodemographic and lifestyle information were collected by trained personnel via interviewer-administered questionnaires, including age, sex, education level (primary school or lower, secondary school, and college), civil status (single or divorced or separated, married, and widower), smoking status (current smoker, former smoker, and never smoked), physical activity (METs/min/day), and adherence to the erMedDiet (17-point score). Physical activity was estimated using a validated Spanish short version of the Minnesota Leisure Time Physical Activity Questionnaire (the REGICOR questionnaire) (15). Adherence to the erMedDiet was assessed via a validated 17-point scale questionnaire (17-item energy-restricted Mediterranean Adherence Screener, er-MEDAS) (16), where compliance with each of the 17 items was scored with 1 point, therefore, the total er-MEDAS score was ranged between 0 to 17, with 0 meaning null adherence and 17 meaning maximum adherence. Personal medical history (e.g., prevalence of type 2 diabetes, hypertension, and hypercholesterolemia) and medication use were self-reported or collected from the medical records of participants.

Anthropometric variables, such as weight and height, were measured by trained personnel using calibrated scales and wall-mounted stadiometers, respectively, with participants in light clothing and without shoes or accessories. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured using an anthropometric tape midway between the lowest rib and the iliac crest.

Other food consumption information was collected in the same FFQ for nuts, including variables related to vegetables, fruits, legumes, cereals, dairy, meat, fish, other sources of oils and fats (i.e., olive oil, corn oil, sunflower oil, soybean oil, butter, margarine, and lard), biscuits, coffee, tea, and alcohol consumption. The nutrients and energy intakes were subsequently estimated with the Spanish Food Composition Tables (17).

Statistical analyses

For the analyses of the baseline characteristics, participants with insufficient information on civil status (n=21), depressive status (n=22), and medical history of hypertension (n=42) and hypercholesterolemia (n=48) were considered into the category with the greatest frequency for the analysis (18).

Multivariable linear regression models were adjusted for potentially related confounders for cognitive function. Basic model was adjusted for age (years), sex, and respective baseline cognitive function score. The fully-adjusted multivariable model was further adjusted education level (primary or less, secondary, college), civil status (single, divorced or separated, married, widower), treatment groups (intervention or control), centre size (≤200, 200 to 300, 300 to 400, >400 participants), BMI (kg/m^2), physical activity (METs/min/day), smoking status (current, former, never), alcohol consumption in g/day (and adding the quadratic term), energy intake (kcal/day), presence of depressive symptomatology (yes/no), diabetes (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no), and dietary factors (i.e., consumption of vegetables, fruits, legumes, cereals, dairy, meat, fish, other sources of oils and fats, biscuits in g/day, coffee and tea in mL/day). All covariates were determined at baseline visit (initial cognitive interview), and the multicollinearity among the variables was assessed using variance inflation factor (VIF) and/or tolerance (1/VIF). Penalized splines were used to explore

the potential nonlinearity association using the continuous variable of nut consumption (19). In all models, we used robust variance estimators to account for intra-cluster correlations considering there were couples of the same household who were randomized together. Median values of nut groups were treated as a continuous variable to assess the linear trend across categories of nut consumption and 2-year changes in cognitive function.

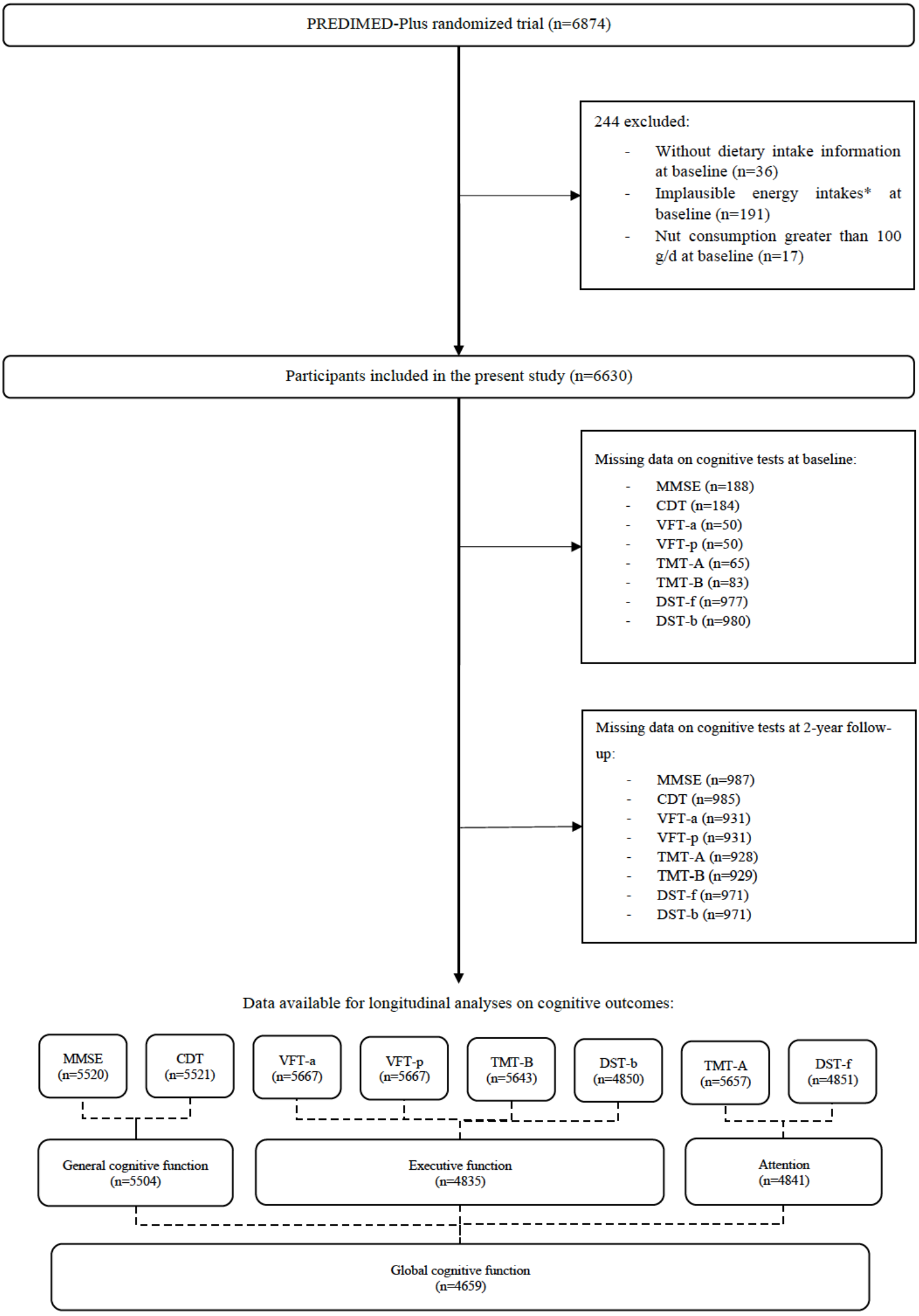
Potential effect modification by sex, education level, treatment group, smoking status, presence of type 2 diabetes, hypertension, and hypercholesterolemia, and depressive symptomatology was explored with the likelihood ratio test by comparing models with and without the multiplicative interaction term between these variables and nut consumption categories in the fully adjusted models. When a significant interaction was detected (P value <0.05), analyses were performed separately in each stratum and a command (marginsplot) was used to visualize the interaction. To test the robustness of the results, several sensitivity analyses were conducted by removing participants with baseline MMSE <24 (20) or by removal of participants with extreme percentiles of GCF z-scores at baseline (<5% and >95%).

All analyses were performed with Stata/SE version 14.2 (StataCorp LLC, College Station, TX, USA) using the PREDIMED-Plus study dataset updated to December 22, 2020. Statistical significance was set at a two-tailed P value <0.05.

Appendix B: Table 1. Composite cognitive assessment equations[1].

Composite cognitive domain	Composite component score
Attention[2]	$= \frac{(-zTMT{-}A) + zDST{-}f}{2}$
Executive Function[3]	$= \frac{zVFT{-}a + zVFT{-}p + (-zTMT{-}B) + zDST{-}b}{4}$
General Cognitive Function[4]	$= \frac{zMMSE + zCDT}{2}$
Global Cognitive Function[5]	$= \frac{zMMSE + zCDT + zVFT{-}a + zVFT{-}p + (-zTMT{-}A) + (-zTMT{-}B) + zDST{-}f + zDST{-}b}{8}$

[1]Standardized scores of the TMT-A and TMT-B were inverted, so that higher scores would represent better cognitive performance.
[2]The attention composite included the mean standardized individual scores of the TMT-A score and the DST-f score.
[3]The executive function composite included the VFT-a score, VFT-p score, TMT-B score, and DST-b score.
[4]The general cognitive function composite included the MMSE score and the CDT score.
[5]The global cognitive function (GCF) was determined by computing the mean standardized individual scores of all neuropsychological tests.
Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test - backward; DST-f, Digit Span test - forward; MMSE, Mini-Mental State Examination; s/wk, serving(s) per week (one serving was considered 30 grams); TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.


PREDIMED-Plus randomized trial (n=6874)
244 excluded:
- Without dietary intake information at baseline (n=36)
- Implausible energy intakes* at baseline (n=191)
- Nut consumption greater than 100 g/d at baseline (n=17)
Participants included in the present study (n=6630)
Missing data on cognitive tests at baseline:
- MMSE (n=188)
- CDT (n=184)
- VFT-a (n=50)
- VFT-p (n=50)
- TMT-A (n=65)
- TMT-B (n=83)
- DST-f (n=977)
- DST-b (n=980)
Missing data on cognitive tests at 2-year follow-up:
- MMSE (n=987)
- CDT (n=985)
- VFT-a (n=931)
- VFT-p (n=931)
- TMT-A (n=928)
- TMT-B (n=929)
- DST-f (n=971)
- DST-b (n=971)
Data available for longitudinal analyses on cognitive outcomes:
MMSE (n=5520)
CDT (n=5521)
VFT-a (n=5667)
VFT-p (n=5667)
TMT-B (n=5643)
DST-b (n=4850)
TMT-A (n=5657)
DST-f (n=4851)
General cognitive function (n=5504)
Executive function (n=4835)
Attention (n=4841)
Global cognitive function (n=4659)

Appendix C: Figure 1. Flowchart of the study population. CDT, Clock Drawing Test; DST-b, Digit Span test backward; DST-f, Digit Span test forward; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological. General cognitive function = ($_{Z}$MMSE + $_{Z}$CDT) / 2; Executive function = ($_{Z}$VFT-a + $_{Z}$VFT-p + (–$_{Z}$TMT-B) + $_{Z}$DST-b) / 4; Attention = ((–$_{Z}$TMT-A) + $_{Z}$DST-f) / 2; Global cognitive function = ($_{Z}$MMSE + $_{Z}$CDT + $_{Z}$VFT-a + $_{Z}$VFT-p + (–$_{Z}$TMT-A) + (–$_{Z}$TMT-B) + $_{Z}$DST-f + $_{Z}$DST-b) / 8.

*Daily energy intakes for men <800 kcal or >4000 kcal and women <500 kcal or >3500 kcal (21).

Appendix D: Table 2. Baseline dietary-intake characteristics of the participants by categories of total nut consumption.

		Total Nut Consumption					
		Total	**<1 s/wk[1]**	**≥1 to <3 s/wk**	**≥3 to <7 s/wk**	**≥7 s/wk**	**P value[2]**
Frequency, n		6,630	2,432	1,796	1,306	1,096	
Total nuts, g/day		14.6 ± 16.2	1.7 ± 1.8	9.3 ± 2.8	21.7 ± 5.1	43.7 ± 14.5	**<0.001**
	Walnuts	7.0 ± 9.4	0.9 ± 1.3	4.2 ± 4.0	10.2 ± 6.8	21.2 ± 11.9	**<0.001**
	Almonds	3.7 ± 6.3	0.4 ± 0.9	2.4 ± 2.4	5.8 ± 5.6	10.8 ± 10.4	**<0.001**
	Other nuts	3.9 ± 7.0	0.4 ± 1.0	2.7 ± 2.6	5.7 ± 6.1	11.6 ± 12.1	**<0.001**
Dietary variables							
Total energy intake, kcal/day		2363 ± 551	2221 ± 559	2355 ± 516	2438 ± 524	2605 ± 518	**<0.001**
Carbohydrates, En%		40.6 ± 6.9	41.7 ± 7.4	40.8 ± 6.5	39.7 ± 6.3	38.7 ± 6.4	**<0.001**
Protein, En%		16.8 ± 2.8	16.9 ± 3.0	16.8 ± 2.7	16.8 ± 2.7	16.5 ± 2.6	**<0.001**
Total fat, En%		39.6 ± 6.5	38.1 ± 6.9	39.3 ± 6.1	40.6 ± 6.1	42.0 ± 6.1	**<0.001**
Fibre, g/day		26.1 ± 8.7	23.0 ± 7.7	25.5 ± 7.8	28.0 ± 8.4	31.7 ± 9.2	**<0.001**
Vegetables, g/day		327.9 ± 139.7	303.8 ± 136.6	324.5 ± 131.9	346.8 ± 139.2	364.2 ± 148.7	**<0.001**
Fruits, g/day		358.8 ± 206.4	327.3 ± 198.5	354.8 ± 199.4	375.8 ± 197.1	415.2 ± 230.4	**<0.001**
Legumes, g/day		20.7 ± 11.2	19.1 ± 11.0	20.7 ± 10.3	21.5 ± 11.5	23.4 ± 12.4	**<0.001**
Cereals, g/day		150.3 ± 78.2	149.8 ± 83.0	151.7 ± 76.2	148.9 ± 74.0	150.7 ± 75.7	0.773
Total meat, g/day		147.7 ± 58.3	146.4 ± 59.7	150.3 ± 57.2	147.7 ± 55.7	146.6 ± 60.0	0.154
Total fish, g/day		102.2 ± 47.6	93.7 ± 46.6	104.3 ± 47.7	108.6 ± 47.2	110.0 ± 47.3	**<0.001**
Total dairy, g/day		346.2 ± 200.9	350.1 ± 202.5	337.3 ± 195.3	345.3 ± 196.2	353.1 ± 211.4	0.124

Oils and fats, g/day	42.8 ± 17.3	41.9 ± 17.4	43.7 ± 16.8	43.4 ± 17.4	42.8 ± 17.8	**0.005**
Olive oils, g/day	39.9 ± 17.0	38.8 ± 17.1	40.9 ± 16.7	40.4 ± 16.7	40.2 ± 17.6	**<0.001**
Biscuits, g/day	26.9 ± 29.8	26.9 ± 31.3	26.4 ± 28.4	27.7 ± 30.4	26.6 ± 27.9	0.649
Coffee and tea, mL/day	88.6 ± 60.0	89.3 ± 59.3	89.1 ± 61.4	89.4 ± 58.0	85.0 ± 61.3	0.190
Total alcohol, g/day	11.0 ± 15.0	11.1 ± 15.7	11.2 ± 14.7	10.7 ± 14.0	11.1 ± 154.1	0.800
MedDiet score (17-points)	8.5 ± 2.7	7.8 ± 2.6	8.5 ± 2.6	9.0 ± 2.6	9.6 ± 2.7	**<0.001**
MedDiet score (16-points without nuts-item)	8.1 ± 2.5	7.7 ± 2.5	8.1 ± 2.5	8.3 ± 2.5	8.8 ± 2.6	**<0.001**

Data are presented as mean ± standard deviation.

Abbreviations: En, energy; MedDiet, Mediterranean diet; s/wk, serving(s) per week.

[1] 1 serving=30 g.

[2] *p*-value for differences between categories of total nut consumption was calculated by one-way ANOVA.

Appendix E: Table 3. Longitudinal association between baseline total nut consumption and changes in cognitive performance after 2-years of follow-up in the PREDIMED-Plus cohort.

	Continuous		**Categories of Nut Consumption**				
	Nut consumption (servings/day)		**<1 s/wk**	**≥1 to <3 s/wk**	**≥3 to <7 s/wk**	**≥7 s/wk**	
	β (95% CI)	**p-value**	**Reference**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**P-trend**
Global Cognitive Function[1] (n=4,659)							
Basic model	**0.03 [0.00,0.06]**	**0.025**	reference	0.02 [-0.02,0.06]	0.02 [-0.02,0.07]	**0.06 [0.01,0.10]**	**0.015**
Multivariable-adjusted model	0.02 [-0.02,0.05]	0.351	reference	0.00 [-0.04,0.04]	0.01 [-0.03,0.06]	0.03 [-0.02,0.08]	0.170
General Cognitive Function[2] (n=5,504)							
Basic model	**0.07 [0.04,0.11]**	**<0.001**	reference	0.04 [-0.01,0.10]	0.05 [-0.01,0.11]	**0.13 [0.07,0.19]**	**<0.001**
Multivariable-adjusted model	**0.07 [0.03,0.12]**	**0.001**	reference	0.04 [-0.02,0.09]	0.06 [-0.00,0.12]	**0.13 [0.06,0.20]**	**<0.001**
Attention[3] (n=4,841)							
Basic model	0.02 [-0.02,0.06]	0.400	reference	0.03 [-0.02,0.09]	0.03 [-0.03,0.08]	0.03 [-0.03,0.10]	0.324
Multivariable-adjusted model	-0.01 [-0.05,0.04]	0.670	reference	0.01 [-0.05,0.06]	0.01 [-0.05,0.07]	-0.00 [-0.07,0.07]	0.981
Executive Function[4] (n=4,835)							
Basic model	**0.03 [0.00,0.06]**	**0.047**	reference	0.01 [-0.03,0.05]	0.02 [-0.02,0.07]	**0.05 [0.00,0.10]**	**0.046**
Multivariable-adjusted model	0.00 [-0.03,0.04]	0.864	reference	-0.01 [-0.05,0.03]	0.00 [-0.05,0.05]	0.01 [-0.05,0.06]	0.686
MMSE (n=5,520)							
Basic model	**0.06 [0.02,0.10]**	**0.004**	reference	**0.07 [0.01,0.13]**	**0.09 [0.03,0.15]**	**0.10 [0.03,0.16]**	**0.003**
Multivariable-adjusted model	0.03 [-0.01,0.08]	0.161	reference	0.05 [-0.00,0.11]	**0.08 [0.02,0.14]**	0.06 [-0.01,0.13]	0.078

CDT (n=5,521)							
Basic model	**0.07 [0.02,0.11]**	**0.003**	reference	0.01 [-0.06,0.07]	0.00 [-0.07,0.07]	**0.12 [0.06,0.19]**	**0.001**
Multivariable-adjusted model	**0.09 [0.04,0.14]**	**0.001**	reference	0.01 [-0.05,0.08]	0.02 [-0.05,0.09]	**0.15 [0.07,0.23]**	**<0.001**
VFT-a (n=5,667)							
Basic model	0.03 [-0.0011,0.07]	0.120	reference	0.04 [-0.02,0.09]	0.01 [-0.05,0.07]	0.06 [-0.00,0.12]	0.129
Multivariable-adjusted model	-0.02 [-0.06,0.02]	0.372	reference	0.01 [-0.04,0.06]	-0.03 [-0.09,0.03]	-0.01 [-0.08,0.06]	0.553
VFT-p (n=5,667)							
Basic model	0.03 [-0.01,0.07]	0.154	reference	-0.01 [-0.06,0.04]	0.02 [-0.04,0.08]	0.04 [-0.02,0.10]	0.158
Multivariable-adjusted model	0.02 [-0.02,0.07]	0.307	reference	-0.02 [-0.07,0.03]	0.02 [-0.04,0.08]	0.02 [-0.04,0.09]	0.271
TMT-A[5] (n=5,657)							
Basic model	-0.02 [-0.06,0.02]	0.289	reference	-0.01 [-0.07,0.04]	-0.01 [-0.07,0.05]	-0.04 [-0.10,0.03]	0.304
Multivariable-adjusted model	-0.01 [-0.06,0.03]	0.569	reference	0.00 [-0.05,0.06]	-0.00 [-0.06,0.06]	-0.02 [-0.09,0.05]	0.576
TMT-B[5] (n=5,643)							
Basic model	0.00 [-0.04,0.04]	0.897	reference	0.01 [-0.04,0.07]	0.02 [-0.04,0.07]	-0.02 [-0.08,0.04]	0.597
Multivariable-adjusted model	0.03 [-0.01,0.08]	0.134	reference	0.04 [-0.02,0.09]	0.03 [-0.03,0.09]	0.02 [-0.05,0.09]	0.578
DST-f (n=4,851)							
Basic model	0.01 [-0.03,0.05]	0.606	reference	0.03 [-0.02,0.09]	0.03 [-0.03,0.09]	0.03 [-0.04,0.10]	0.476
Multivariable-adjusted model	-0.01 [-0.06,0.03]	0.558	reference	0.01 [-0.05,0.07]	0.02 [-0.05,0.08]	-0.01 [-0.08,0.07]	0.899
DST-b (n=4,850)							
Basic model	**0.04 [0.00,0.09]**	**0.046**	reference	0.02 [-0.03,0.08]	0.05 [-0.01,0.11]	0.04 [-0.03,0.10]	0.194
Multivariable-adjusted model	0.03 [-0.02,0.08]	0.188	reference	-0.00 [-0.06,0.05]	0.04 [-0.03,0.10]	0.01 [-0.06,0.09]	0.482

Sensitivity analyses[6]							
Removal of participants with baseline MMSE <24 (n=202)							
Global Cognitive Function[1] (n=4,543)							
Basic model	**0.03 [0.00,0.06]**	**0.038**	reference	0.01 [-0.03,0.06]	0.01 [-0.03,0.06]	**0.06 [0.01,0.10]**	**0.024**
Multivariable-adjusted model	0.01 [-0.02,0.05]	0.474	reference	-0.00 [-0.04,0.04]	0.00 [-0.04,0.05]	0.03 [-0.02,0.08]	0.248
General Cognitive Function[2] (n=5,346)							
Basic model	**0.06 [0.02,0.10]**	**0.001**	reference	0.03 [-0.02,0.09]	0.03 [-0.03,0.09]	**0.12 [0.06,0.17]**	**<0.001**
Multivariable-adjusted model	**0.06 [0.02,0.11]**	**0.005**	reference	0.03 [-0.02,0.09]	0.04 [-0.02,0.11]	**0.12 [0.05,0.18]**	**0.001**
Attention[3] (n=4,720)							
Basic model	0.01 [-0.03,0.05]	0.541	reference	0.02 [-0.03,0.08]	0.01 [-0.04,0.07]	0.03 [-0.03,0.09]	0.456
Multivariable-adjusted model	-0.01 [-0.06,0.03]	0.574	reference	0.00 [-0.05,0.06]	-0.00 [-0.06,0.06]	-0.01 [-0.08,0.06]	0.858
Executive Function[4] (n=4,715)							
Basic model	**0.03 [0.00,0.07]**	**0.036**	reference	0.01 [-0.03,0.05]	0.02 [-0.03,0.07]	**0.05 [0.00,0.10]**	**0.038**
Multivariable-adjusted model	0.00 [-0.03,0.04]	0.816	reference	-0.01 [-0.06,0.03]	-0.00 [-0.05,0.05]	0.01 [-0.05,0.06]	0.655
MMSE (n=5,361)							
Basic model	**0.05 [0.01,0.09]**	**0.013**	reference	**0.07 [0.01,0.12]**	**0.07 [0.02,0.13]**	**0.08 [0.02,0.15]**	**0.010**
Multivariable-adjusted model	0.02 [-0.02,0.07]	0.284	reference	0.05 [-0.00,0.11]	**0.07 [0.01,0.13]**	0.05 [-0.02,0.12]	0.164
CDT (n=5,362)							
Basic model	**0.05 [0.01,0.10]**	**0.017**	reference	-0.00 [-0.06,0.06]	-0.02 [-0.09,0.05]	**0.11 [0.04,0.18]**	**0.005**
Multivariable-adjusted model	**0.08 [0.03,0.13]**	**0.003**	reference	0.01 [-0.05,0.07]	0.01 [-0.06,0.08]	**0.14 [0.07,0.22]**	**0.001**
VFT-a (n=5,504)							
Basic model	0.03 [-0.01,0.07]	0.108	reference	0.04 [-0.02,0.09]	0.00 [-0.06,0.06]	**0.06 [0.00,0.12]**	0.125
Multivariable-adjusted model	-0.02 [-0.06,0.03]	0.475	reference	0.01 [-0.04,0.06]	-0.03 [-0.09,0.03]	-0.00 [-0.07,0.07]	0.662

VFT-p (n=5,504)							
Basic model	0.02 [-0.01,0.06]	0.207	reference	-0.01 [-0.06,0.04]	0.02 [-0.04,0.07]	0.03 [-0.03,0.09]	0.211
Multivariable-adjusted model	0.02 [-0.03,0.06]	0.401	reference	-0.02 [-0.07,0.03]	0.02 [-0.04,0.08]	0.02 [-0.05,0.09]	0.348
TMT-A[5] (n=5,495)							
Basic model	-0.01 [-0.05,0.03]	0.511	reference	-0.01 [-0.06,0.04]	0.00 [-0.05,0.06]	-0.03 [-0.09,0.04]	0.538
Multivariable-adjusted model	-0.01 [-0.05,0.04]	0.705	reference	0.00 [-0.05,0.05]	0.01 [-0.05,0.07]	-0.02 [-0.08,0.05]	0.739
TMT-B[5] (n=5,486)							
Basic model	-0.00 [-0.04,0.04]	0.971	reference	0.01 [-0.04,0.07]	0.02 [-0.03,0.08]	-0.03 [-0.09,0.04]	0.481
Multivariable-adjusted model	0.03 [-0.02,0.08]	0.193	reference	0.04 [-0.01,0.09]	0.04 [-0.02,0.10]	0.02 [-0.05,0.08]	0.697
DST-f (n=4,730)							
Basic model	0.01 [-0.04,0.05]	0.742	reference	0.03 [-0.03,0.09]	0.02 [-0.04,0.09]	0.02 [-0.05,0.09]	0.620
Multivariable-adjusted model	-0.02 [-0.06,0.03]	0.542	reference	0.01 [-0.05,0.07]	0.01 [-0.05,0.08]	-0.01 [-0.09,0.07]	0.846
DST-b (n=4,729)							
Basic model	0.04 [-0.00,0.08]	0.060	reference	0.02 [-0.04,0.08]	0.05 [-0.02,0.11]	0.04 [-0.03,0.11]	0.205
Multivariable-adjusted model	0.03 [-0.02,0.08]	0.209	reference	-0.00 [-0.06,0.05]	0.04 [-0.03,0.10]	0.02 [-0.06,0.09]	0.448
Removal of participants with extreme GCF z-score at baseline (<5% and >95%) (n=465)							
Global Cognitive Function[1] (n=4,194)							
Basic model	**0.04 [0.00,0.07]**	**0.023**	reference	0.01 [-0.03,0.05]	0.02 [-0.03,0.06]	**0.06 [0.01,0.11]**	**0.020**
Multivariable-adjusted model	0.02 [-0.01,0.06]	0.239	reference	-0.00 [-0.05,0.04]	0.01 [-0.04,0.05]	0.04 [-0.02,0.09]	0.152
General Cognitive Function[2] (n=5,039)							
Basic model	**0.07 [0.03,0.11]**	**<0.001**	reference	0.04 [-0.01,0.10]	0.05 [-0.01,0.11]	**0.12 [0.06,0.18]**	**<0.001**
Multivariable-adjusted model	**0.07 [0.03,0.12]**	**0.001**	reference	0.04 [-0.02,0.09]	**0.07 [0.01,0.13]**	**0.13 [0.06,0.20]**	**<0.001**

Attention[3] (n=4,376)							
Basic model	0.02 [-0.02,0.06]	0.288	reference	0.03 [-0.03,0.08]	0.02 [-0.04,0.08]	0.04 [-0.03,0.10]	0.315
Multivariable-adjusted model	-0.01 [-0.05,0.04]	0.820	reference	0.00 [-0.05,0.06]	0.01 [-0.06,0.07]	-0.00 [-0.07,0.07]	0.980
Executive Function[4] (n=4,370)							
Basic model	**0.03 [0.00,0.07]**	**0.040**	reference	0.01 [-0.04,0.05]	0.01 [-0.04,0.06]	**0.05 [0.00,0.10]**	0.058
Multivariable-adjusted model	0.01 [-0.03,0.05]	0.596	reference	-0.02 [-0.06,0.03]	-0.01 [-0.06,0.04]	0.01 [-0.04,0.07]	0.602
MMSE (n=5,055)							
Basic model	**0.05 [0.01,0.09]**	**0.007**	reference	**0.07 [0.01,0.12]**	**0.09 [0.03,0.15]**	**0.09 [0.02,0.15]**	**0.006**
Multivariable-adjusted model	0.04 [-0.01,0.08]	0.121	reference	0.05 [-0.00,0.11]	**0.09 [0.02,0.15]**	0.06 [-0.01,0.13]	0.066
CDT (n=5,056)							
Basic model	**0.06 [0.01,0.10]**	**0.010**	reference	0.01 [-0.05,0.07]	0.00 [-0.07,0.07]	**0.11 [0.05,0.18]**	**0.003**
Multivariable-adjusted model	**0.09 [0.03,0.14]**	**0.001**	reference	0.02 [-0.05,0.08]	0.03 [-0.04,0.10]	**0.15 [0.07,0.23]**	**<0.001**
VFT-a (n=5,202)							
Basic model	0.03 [-0.01,0.06]	0.137	reference	0.03 [-0.02,0.09]	-0.00 [-0.06,0.06]	0.05 [-0.01,0.11]	0.237
Multivariable-adjusted model	-0.01 [-0.05,0.03]	0.557	reference	0.01 [-0.05,0.06]	-0.03 [-0.09,0.03]	-0.01 [-0.08,0.06]	0.558
VFT-p (n=5,202)							
Basic model	0.03 [-0.01,0.07]	0.102	reference	-0.01 [-0.06,0.05]	0.01 [-0.05,0.07]	0.05 [-0.02,0.11]	0.129
Multivariable-adjusted model	0.03 [-0.01,0.08]	0.158	reference	-0.01 [-0.07,0.04]	0.01 [-0.05,0.07]	0.04 [-0.03,0.11]	0.163
TMT-A[5] (n=5,192)							
Basic model	-0.03 [-0.07,0.01]	0.147	reference	-0.02 [-0.08,0.04]	-0.01 [-0.07,0.05]	-0.05 [-0.11,0.01]	0.192
Multivariable-adjusted model	-0.02 [-0.06,0.02]	0.289	reference	-0.00 [-0.06,0.06]	0.00 [-0.06,0.06]	-0.03 [-0.10,0.03]	0.363
TMT-B[5] (n=5,178)							
Basic model	0.00 [-0.04,0.05]	0.898	reference	0.02 [-0.04,0.07]	0.03 [-0.03,0.09]	-0.02 [-0.08,0.05]	0.670
Multivariable-adjusted model	0.03 [-0.01,0.08]	0.181	reference	0.05 [-0.01,0.10]	0.05 [-0.02,0.11]	0.02 [-0.05,0.09]	0.597

DST-f (n=4,386)							
Basic model	0.01 [-0.04,0.05]	0.695	reference	0.02 [-0.03,0.08]	0.03 [-0.03,0.10]	0.01 [-0.06,0.08]	0.692
Multivariable-adjusted model	-0.02 [-0.07,0.03]	0.494	reference	-0.00 [-0.06,0.06]	0.02 [-0.05,0.08]	-0.03 [-0.10,0.05]	0.658
DST-b (n=4,385)							
Basic model	**0.04 [0.00,0.09]**	**0.049**	reference	0.02 [-0.04,0.08]	0.05 [-0.02,0.11]	0.04 [-0.03,0.11]	0.210
Multivariable-adjusted model	0.04 [-0.01,0.09]	0.164	reference	-0.01 [-0.07,0.05]	0.03 [-0.03,0.10]	0.01 [-0.06,0.09]	0.476

Basic models were adjusted for respective cognitive test score at baseline, age (years), and sex. Multivariable-adjusted models were further adjusted for intervention PREDIMED-Plus randomized groups, and participating centre (≤200, 200 to 300, 300 to 400, >400 participants), education level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), body mass index (kg/m^2), physical activity (METs/min/day), smoking status (current, former, or never), alcohol consumption in g/day (and adding the quadratic term), energy intake (kcal/day), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension prevalence (yes/no), and hypercholesterolemia prevalence (yes/no), and dietary factors (consumption of vegetables, fruits, legumes, cereals, oils and fats, biscuits, dairy, meat, fish [g/day], coffee and tea [mL/day]).

β-coefficients were estimated using linear regression models with robust standard errors to account for intracluster correlations. Linear trend was calculated by assigning the median values to each category of nut consumption groups and treating these values across groups as a continuous variable in the linear regression models. Significant values (p<0.05) were highlighted in bold type.

Abbreviations: CDT, Clock Drawing Test; CI, confidence interval; DST-b, Digit Span test backward; DST-f, Digit Span test forward; MMSE, Mini-Mental State Examination; s/wk, serving(s) per week (1 serving=30 g); TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

[1] Global cognitive function (GCF) was calculated using the formula GCF= ($_Z$MMSE + $_Z$CDT + $_Z$VFT-a + $_Z$VFT-p + (–$_Z$TMT-A) + (–$_Z$TMT-B) + $_Z$DST-f + $_Z$DST-b) / 8.

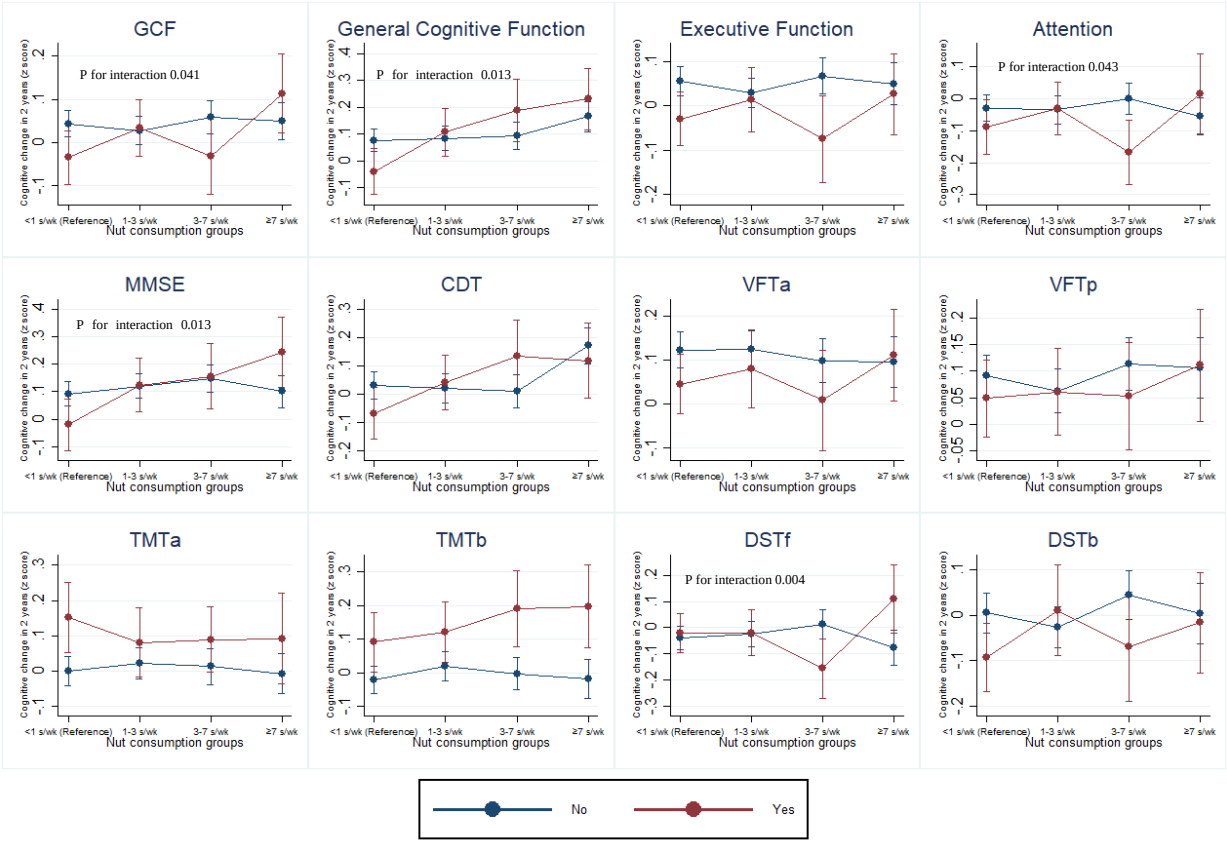
[2] General cognitive function was calculated using the formula General cognitive function= ($_Z$MMSE + $_Z$CDT) / 2.

[3] Attention domain was calculated using the formula Attention = ((–$_Z$TMT-A) + $_Z$DST-f) / 2.

[4] Executive function domain was calculated using the formula Executive function = ($_Z$VFT-a + $_Z$VFT-p + (–$_Z$TMT-B) + $_Z$DST-b) / 4.

[5] Inverse neuropsychological assessment score.

[6] In the sensitivity analyses, the multivariable-adjusted models were additionally performed with removal of participants with baseline MMSE <24 (mild dementia and poorer) or removal of participants with extreme GCF z-score at baseline (<5% and >95%).



Appendix F: Figure 2. Interaction between nut consumption and depressive status in relation to cognitive performance assessments. Multivariable-adjusted models were adjusted for respective cognitive test score at baseline, age (years), sex, intervention PREDIMED-Plus randomized groups, and participating centre (≤200, 200 to 300, 300 to 400, >400 participants), education level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), body mass index (kg/m^2), physical activity (METs/min/day), smoking status (current, former, or never), alcohol consumption in g/day (and adding the quadratic term), energy intake (kcal/day), diabetes prevalence (yes/no), hypertension prevalence (yes/no), and hypercholesterolemia prevalence (yes/no), and dietary factors (consumption of vegetables, fruits, legumes, cereals, oils and fats, biscuits, dairy, meat, fish [g/day], coffee and tea [mL/day]). CDT, Clock Drawing Test; DST-b, Digit Span test backward; DST-f, Digit Span test forward; MMSE, Mini-Mental State Examination; s/wk, serving(s) per week (1 serving=30 g); TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological. General cognitive function = (zMMSE + zCDT) / 2; Executive function = (zVFT-a + zVFT-p + (–zTMT-B) + zDST-b) / 4; Attention = ((–zTMT-A) + zDST-f) / 2; Global cognitive function = (zMMSE + zCDT + zVFT-a + zVFT-p + (–zTMT-A) + (–zTMT-B) + zDST-f + zDST-b) / 8.

Appendix G: Table 4. Baseline characteristics comparison between PREDIMED-Plus randomized participants and those analysed in the present study for examining changes in global cognitive function (GCF).

	Randomized PREDIMED-Plus participants (n=6,874)	Participants included in the present analyses (n=4,659 for GCF)	P value[1]
Socio-demographic variables			
Women, n (%)	3,335 (48.5)	2,239 (48.1)	0.629
Age, years	64.9 ± 4.9	65.0 ± 4.9	0.704
Education level, n (%)			
Primary or less	3,362 (48.9)	2,278 (48.9)	
Secondary	1,986 (28.9)	1,355 (29.1)	0.963
College	1,526 (22.2)	1,026 (22.0)	
Civil status, n (%)			
Single, divorced or separated	897 (13.1)	590 (12.7)	
Married	5,261 (76.5)	3,589 (77.0)	0.801
Widower	716 (10.4)	480 (10.3)	
Lifestyle variables			
Smoking status, n (%)			
Current smoker	857 (12.5)	604 (13.0)	0.625
Former smoker	2,983 (43.4)	1,987 (42.7)	

Never smoked	3,034 (44.1)	2,068 (44.4)	
Physical activity, METs/min/day	351.8 ± 328.7	360.8 ± 333.3	0.154
Anthropometric variables			
BMI, kg/m^2	32.6 ± 3.5	32.5 ± 3.4	0.094
Waist circumference, cm			
Women	104.0 ± 9.2	103.7 ± 9.2	0.254
Men	111.0 ± 8.8	110.7 ± 8.8	0.127
Disease present at recruitment			
Type 2 diabetes, n (%)	2,093 (30.5)	1,325 (28.4)	0.020
Hypertension, n (%)	5,758 (83.8)	3,912 (84.0)	0.773
Hypercholesterolemia, n (%)	4,813 (70.0)	3,240 (69.5)	0.586
Cognitive performance			
Global Cognitive Function[2]	0.02 ± 0.64 (n=4,803)	0.02 ± 0.64 (n=4,659)	0.999
General Cognitive Function[3]	0.00 ± 0.79 (n=5,669)	0.02 ± 0.78 (n=4,659)	0.352
Attention[4]	0.01 ± 0.79 (n=5,006)	0.02 ± 0.78 (n=4,659)	0.669
Executive Function[5]	0.03 ± 0.75 (n=5,000)	0.03 ± 0.75 (n=4,659)	0.974

Data are presented as n (%) and mean ± standard deviation for categorical and continuous variables, respectively

Abbreviations: BMI, body mass index; GCF, global cognitive function; METs, metabolic equivalent.

[1] p-value for differences between two groups was calculated by Pearson's Chi-square test or unpaired Student t-test, as appropriate.

[2] Global cognitive function (GCF) was calculated using the formula GCF= (ZMMSE + ZCDT + ZVFT-a + ZVFT-p + (–ZTMT-A) + (–ZTMT-B) + ZDST-f + ZDST-b) / 8.

[3] General cognitive function was calculated using the formula General cognitive function= (ZMMSE + ZCDT) / 2.

[4] Attention domain was calculated using the formula Attention = ((–ZTMT-A) + ZDST-f) / 2.

[5] Executive function domain was calculated using the formula Executive function = (ZVFT-a + ZVFT-p + (–ZTMT-B) + ZDST-b) / 4.

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