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Original Research Article

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

Jiaqi Ni [1,2,3,†], Stephanie K. Nishi [1,2,3,4,5,†], Nancy Babio [1,2,3,*], Emilio Ros [3,6], F Javier Basterra-Gortari [7,8], Dolores Corella [3,9], Castañer O [10,11], J Alfredo Martínez [3,12,13], Ángel M. Alonso-Gómez [3,14], Julia Wärnberg [3,15], Jesús Vioque [10,16], Dora Romaguera [3,17], José López-Miranda [3,18], Ramon Estruch [3,19,20], Francisco J. Tinahones [3,21], José Manuel Santos-Lozano [3,22], Lluís Serra-Majem [3,23], Naomi Cano-Ibáñez [10,24,25], Josep A. Tur [3,26], José Manuel Fernández-García [27,28], Xavier Pintó [3,29], Miguel Delgado-Rodríguez [13,30], Pilar Matía-Martín [31], Josep Vidal [32,33], Clotilde Vázquez [3,34], Lidia Daimiel [3,35,36], Fernando Fernández-Aranda [3,37,38], Miguel Ruiz-Canela [3,7], Cristina Mestres Solà [39], Olga Portolés [3,9], Aleix Sala-Vila [3,11], Antonio Garcia-Rios [3,18], Laura María Compañ-Gabucio [10,16], Enrique Gómez-Gracia [40,41], M Angeles Zulet [3,12], Alice Chaplin [3,17], Rosa Casas [3,19,20], Silvia Martínez-Diz [42], Lucas Tojal-Sierra [3,14], Ana María Gómez-Pérez [3,21], Estefanía Toledo [3,7], Santiago Rios [1,2,3], Carolina Ortega-Azorín [3,9], Rafael de la Torre [3,43,44], Patricia J. Peña-Orihuela [3,18], Manuela Garcia-de la Hera [10,16], Carmen Sayón-Orea [3,7], Mireia Malcampo [11], Jordi Salas-Salvadó [1,2,3], the PREDIMED-Plus investigators

[1] *Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Alimentació, Nutrició, Desenvolupament i Salut Mental (ANUT-DSM), Unitat de Nutrició Humana, Reus, Spain;* [2] *Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain;* [3] *Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain;* [4] *Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Toronto, ON, Canada;* [5] *Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Unity Health Toronto, ON, Canada;* [6] *Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain;* [7] *Department of Preventive Medicine and Public Health, Universidad de Navarra, IdiSNA, Pamplona, Spain;* [8] *Department of Endocrinology and Nutrition, Hospital Universitario de Navarra, IdiSNA, Universidad Pública de Navarra, Pamplona, Spain;* [9] *Department of Preventive Medicine, University of Valencia, Valencia, Spain;* [10] *Centro de Investigación Biomédica en Red Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain;* [11] *Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d`Investigació Médica (IMIM), Barcelona, Spain;* [12] *Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, IdiSNA, Pamplona, Spain;* [13] *Precision Nutrition and Cardiometabolic Health Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain;* [14] *Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic Area; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain;* [15] *EpiPHAAN research group, School of Health Sciences, University of Malaga - Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain;* [16] *Instituto de Investigación Sanitaria y Biomédica de Alicante. Universidad Miguel Hernández (ISABIAL-UMH). Alicante, Spain;* [17] *Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain;* [18] *Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain;* [19] *Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain;* [20] *Institut de Recerca en Nutrició i Seguretata Alimentaria (INSA-UB). University of Barcelona, Barcelona, Spain;* [21] *Virgen de la Victoria Hospital, Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA). University of Málaga, Málaga, Spain;* [22] *Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain;* [23] *Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain;* [24] *Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain;* [25] *Instituto de Investigación Biosanitaria de Granada*

Abbreviations used: BDI-II, Beck Depression Inventory; CDT, Clock Drawing Test; CI, Confidence Intervals; DST-b, Digit Span Test Backward; DST-f, Digit Span Test Forward; En, Energy; erMedDiet, energy-reduced Mediterranean diet; GCF, Global Cognitive Function; IQR, Interquartile Range; MedDiet, Mediterranean diet; MET, metabolic equivalent; PREDIMED-Plus, the PREvención con DIeta MEDiterránea study; RCT, randomized clinical trial; s/wk, serving(s) per week; 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.

* Corresponding author

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(ibs.GRANADA), Granada, Spain; [26] Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma de Mallorca, Spain; [27] Medicina Familiar y Comunitaria. Grupo de trabajo de Nutrición, Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Centro de Salud de Valga, Pontevedra, Spain; [28] Department of Psychiatry, Radiology, Public Health, Nursing and Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain; [29] Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona Spain; [30] Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain; [31] Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; [32] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain; [33] Department of Endocrinology, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [34] Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz. Instituto de Investigaciones Biomédicas IISFJD. University Autonoma, Madrid, Spain; [35] Nutritional Control of the Epigenome Group. Precision Nutrition and Obesity Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain; [36] Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Urbanización Montepríncipe, 28660 Boadilla del Monte, Spain; [37] Clinical Psychology Unit, University Hospital of Bellvitge-Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Barcelona, Spain; [38] Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain; [39] Medico Família CAP Vandellos -Hospitalet, Hospitalet de L'Infant, Spain; [40] Preventive Medicine and Public Health Department, School of Medicine, University of Málaga, 29010 Malaga, Spain; [41] Biomedical Research Institute of Malaga-IBIMA Plataforma BIONAND, 29010 Malaga, Spain; [42] Service of Preventive Medicine and Public Health, Hospital Universitario Clínico San Cecilio, 18016 Granada, Spain; [43] Integrative Pharmacology and Systems Neurosciences Research Group, Hospital del Mar Medical Research Institute, Barcelona, Spain; [44] Department of Medicine and Life Sciences (MELIS), Universitat Pompeu Fabra, Barcelona, Spain

A B S T R A C T

Background: Tree nuts and peanuts (henceforth, nuts) are nutrient-dense foods rich in neuroprotective components; thus, their consumption could benefit cognitive health. However, evidence to date is limited and inconsistent regarding the potential benefits of nuts for cognitive function.

Objective: To prospectively evaluate the association between nut consumption and 2-y changes in cognitive performance in older adults at cognitive decline risk.

Methods: A total of 6,630 participants aged 55 to 75 y (mean age 65.0±4.9 y, 48.4% women) with overweight/obesity and metabolic syndrome completed a validated semi-quantitative food frequency questionnaire and a comprehensive battery of neuropsychological tests at baseline and a 2-y follow-up. Composite cognitive scores were used to assess global, general, attention, and executive function domains. Nut consumption was categorized as <1, ≥1 to <3, ≥3 to <7, and ≥7 servings/wk (1 serving=30 g). Multivariable-adjusted linear regression models were fitted to assess associations between baseline nut consumption and 2-y cognitive changes.

Results: Nut consumption was positively associated with 2-y changes in general cognitive function (*P*-trend <0.001). Compared with participants consuming <1 serving/wk of nuts, those categorized as consuming ≥3 to <7 and ≥7 servings/wk showed more favorable changes in general cognitive performance (β z-score [95% CI] = 0.06 [0.00,0.12] and 0.13 [0.06,0.20], respectively). No significant changes were observed in the multivariable-adjusted models for other cognitive domains assessed.

Conclusion: Frequent nut consumption was associated with a smaller decline in general cognitive performance over 2 y in older adults at risk of cognitive decline. Randomized clinical trials to verify our findings are warranted.

Keywords: aging, nuts, unsaturated fatty acids, cognitive decline, cognition, older people

Introduction

Beyond the usual consequences of biological aging, a decline of cognitive function is a common harbinger of dementia, including Alzheimer's disease, which is recognized as a public health priority [1]. By 2050, dementia prevalence is estimated to triple, and currently, there are no effective curative treatments available [1,2]. Therefore, proactive strategies targeting modifiable risk factors to prevent or delay the onset or progression of cognitive decline are imperative [2]. Diet is considered an important modifiable lifestyle factor and plays a pivotal role in controlling other modifiable risk factors shared by cardiovascular and neurodegenerative diseases, such as hypertension, obesity, and diabetes [2].

Tree nuts and peanuts (henceforth, nuts), characteristic components of commonly recommended healthy dietary patterns for sustaining optimal cognitive function [3–6], are nutrient-dense foods with antioxidant and anti-inflammatory properties [7]. The myriad of nutrients and biologically active compounds that nuts contain, such as unsaturated fatty acids, high-quality vegetable protein, an array of vitamins and beneficial minerals, dietary fiber, phenolic compounds, and phytosterols, appear to have neuroprotective effects [7,8]. In addition to the established associations of nut consumption with reduced cardiovascular [9,10] and cardiometabolic [11] disease outcomes and its potentially beneficial relationship with body weight and body fat reduction [12], diabetes [13,14], hypertension [15], and depression [16], nuts may also benefit brain health.

Epidemiological evidence for the association between nut consumption and cognitive performance is limited. Most cross-sectional studies have supported a positive relationship between nut consumption and cognitive function [7,17,18]. However, results from prospective studies of the association between nut consumption and cognitive decline or changes in cognitive performance over time have been inconsistent [7,17,18]. Similarly, randomized clinical trials (RCTs) examining the effects of nut intake on cognitive outcomes are few, and results have been inconsistent, showing either beneficial or no effects on cognitive decline [7,17,18].

Overall, evidence to date regarding the beneficial impact of nut consumption on cognitive function and/or cognitive decline remains inconclusive, though more favorable outcomes tend to be observed in populations at a higher risk of cognitive decline and dementia (e.g., older age, less education, obesity, cardiometabolic risk, etc.) [18,19]. Therefore, to establish nut-related dietary strategies to prevent or delay cognitive decline and eventually dementia, further investigation targeting populations at high risk is warranted.

[†] JN and SKN contributed equally to this work.

Considering the limitations of the evidence from current cross-sectional studies and challenges associated with conducting RCTs, long-term and large-scale prospective cohort studies are needed to reduce the knowledge gaps previously mentioned [5]. Therefore, this study aimed to prospectively investigate the association between nut consumption and 2-y changes in cognitive performance in older Spanish adults with overweight/obesity harboring the metabolic syndrome, thus being at risk of cognitive decline, in the large cohort of the PREDIMED-Plus (PREvención con DIeta MEDiterránea) trial.

Methods

Study design and participants

The present longitudinal cohort study was conducted within the framework of the PREDIMED-Plus trial, based on the assessment of baseline nut consumption and measures of cognitive function assessed at baseline and 2 y of follow-up. Detailed information about the PREDIMED-Plus study protocol is available at https://www.predimedplus.com/en/, Appendix A, and elsewhere [20,21]. The research ethics committees of all centers approved the study protocol, and participants provided written informed consent. The trial was registered in 2014 at: [www.isrctn.com/ISRCTN89898870]. Eligible participants were community-dwelling adults aged 55 to 75 y, with overweight or obesity (BMI 27 to 40 kg/m^2), who at baseline met at least 3 criteria for the metabolic syndrome [22]. For the present study, participants who had not completed the baseline dietary questionnaire had reported energy intakes outside predefined limits ($\geq$800 to $\leq$ 4000 kcal/d for men, $\geq$500 to $\leq$3500 kcal/d for women) [23] or had reported nut consumption of $\geq$100g/d [24] were excluded.

Exposure: nut consumption

A validated semi-quantitative FFQ [25] was administered by trained dietitians in individual interviews to assess the habitual consumption of 143 food items during the previous year. Nut consumption at baseline was considered the exposure variable in the present study. The FFQ contained 4 questions related to nuts (i.e., almonds, pistachios, walnuts, and other nuts) with 9 possible frequency categories ranging from 'never to almost never' to '$>$ 6 servings/day' (serving size = 30 g). Intraclass correlation coefficients for relative reproducibility and validity for nut intake were 0.80 and 0.55, respectively [25]. Information collected from the FFQ was converted to grams per day by multiplying the numerical value of each frequency category by the nut serving size (30 g/serving) and was further recoded into 4 categories based on the distribution of the original nut consumption measure (right-skewed) of the study population, globally recommended quantities of nut intake [26], and prior studies [24,27]: $<$1 serving/wk, $\geq$1 to $<$3 servings/wk, $\geq$3 to $<$7 servings/wk, and $\geq$7 servings/wk.

Outcome: cognitive performance

Cognitive performance was assessed by trained personnel at baseline and at the 2-y follow-up visit. A battery of 8 neuropsychological tests, validated for the Spanish population, including MMSE, the Clock Drawing Test (CDT), the Verbal Fluency Tests (VFTs), the forward and backward version of the Digit Span Test (DST-f and DST-b, respectively) of the Wechsler Adult Intelligence Scale-III (WAIS-III), and the Trail Making Test part A (TMT-A) and B (TMT-B), were administered in personal interviews. Appendix A provides a detailed description of the neuropsychological tests assessed.

Each cognitive test at baseline and at 2-y follow-up was standardized for each participant to a z-score using the mean and SD of baseline data, and the difference between the standardized scores at 2 timepoints was calculated to examine changes in cognitive performance over time [28,29]. Composite measures for 3 cognitive domains (attention, executive function, and general cognition) and one global assessment of cognitive function (GCF) were calculated for each participant. Composite cognitive assessments were determined by adding or subtracting each individual test z-score based on whether a higher score indicates higher or lower cognitive performance, respectively, as shown in Appendix B. Following this, these 4 composite scores were further re-standardized to z-scores using the mean and SD of baseline composite score data. The 2-y change in the 4 composite scores was considered the primary outcome of interest in the present study.

Covariate assessment

Sociodemographic, lifestyle, medical history, food consumption, and anthropometric information were collected by trained personnel at baseline. Depressive symptomatology was evaluated by the Beck Depression Inventory (BDI-II) with the cut-off point established for depressive status risk as a score $\geq$14 [30,31]. Appendix A provides a detailed description of the covariate assessment.

Statistical analyses

Baseline characteristics of the study population were presented and compared by nut consumption categories as means $\pm$ SD using one-way ANOVA for continuous variables and numbers (percentages) using the chi-square test for categorical variables. The associations between nut consumption (exposure) either as continuous or categorical (with the first group [$<$1 serving/wk] as the reference category) and 2-y changes in each of the cognitive function measurements (outcome) were analyzed fitting multivariable linear regression models and presented as β-coefficients and 95% confidence intervals (CI). If a given cognitive function assessment was missing, this test was not included in the analysis for that participant. Models are presented and fully adjusted for potential confounders. Interaction, stratified, and sensitivity analyses were further performed as appropriate. Appendix A provides a detailed description of the statistical analyses.

Results

A total of 6,630 participants (mean age 65.0 $\pm$ 4.9 y, 48.4% women) were included in the study. For details regarding the number of individuals assessed in each cognitive outcome analysis, see Appendix C. Baseline sociodemographic, anthropometric, and lifestyle factors, medical history, and cognitive performance were similar between the primary and analyzed samples (Appendix G).

Baseline characteristics of the study population overall and by categories of total nut consumption at baseline are presented in Table 1 and Appendix D. At baseline, the mean daily nut consumption ranged from 1.7 $\pm$ 1.8 g in the lowest to 43.7 $\pm$ 14.5 g in the highest category (overall mean: 14.6 $\pm$ 16.2 g/d). Walnuts were the most consumed nut among the considered nut types (overall mean: 7.0 $\pm$ 9.4 g/d). Participants in the highest category of nut consumption were more likely to have higher education levels, to partake in more physical activity, and to show better adherence to the Mediterranean diet (MedDiet) with greater consumption of vegetables, fruits, legumes, fish, and olive oil, compared to those in the lowest category. A lower BMI, waist circumference, and a lower percentage of current smokers and

TABLE 1
Baseline characteristics of the PREDIMED-Plus participants according to categories of total nut consumption

Total Nut Consumption						P [2]
	Total	<1 s/wk[1]	≥1 to <3 s/wk	≥3 to <7 s/wk	≥7 s/wk	
Frequency, *n*	6,630	2,432	1,796	1,306	1,096	
Total nuts, g/day, median [IQR]	9 [2, 24]	2 [0, 4]	9 [6, 13]	21 [17, 26]	39 [32, 51]	<0.001
Walnuts	2 [0, 13]	0 [0, 0]	2 [2, 4]	13 [4, 13]	24 [13, 30]	<0.001
Almonds	2 [0, 4]	0 [0, 0]	2 [0, 4]	4 [2, 13]	13 [0, 13]	<0.001
Other nuts	2 [0, 4]	0 [0, 0]	2 [0, 4]	4 [0, 9]	13 [0, 17]	<0.001
Sociodemographic variables						
Age, y	65.0 ± 4.9	65.0 ± 4.9	64.8 ± 5.0	64.9 ± 4.9	65.4 ± 4.7	0.022
Women, n (%)	3,210 (48.4)	1,203 (49.5)	873 (48.6)	618 (47.3)	516 (47.1)	0.473
Education level, n (%)						
Primary or less	3,266 (49.3)	1,233 (50.7)	874 (48.7)	664 (50.8)	495 (45.2)	0.006
Secondary	1,913 (28.9)	717 (29.5)	517 (28.8)	352 (27.0)	327 (29.8)	
College	1,451 (21.9)	482 (19.8)	405 (22.6)	290 (22.2)	274 (25.0)	
Civil status, n (%)						
Single, divorced, or separated	854 (12.9)	341 (14.0)	208 (11.6)	154 (11.8)	151 (13.8)	0.109
Married	5,088 (76.7)	1,833 (75.4)	1,391 (77.5)	1,030 (78.9)	834(76.1)	
Widower	688 (10.4)	258 (10.6)	197 (11.0)	122 (9.3)	111 (10.1)	
Disease present at recruitment						
Type 2 diabetes, n (%)	2,041 (30.8)	778 (32.0)	533 (29.7)	398 (30.5)	332 (30.3)	0.411
Hypertension, n (%)	5,570 (84.0)	2,078 (85.4)	1,494 (83.2)	1,091 (83.5)	907 (82.8)	0.105
Hypercholesterolemia, n (%)	4,637 (69.9)	1,661 (68.3)	1,269 (70.7)	934 (71.5)	773 (70.5)	0.152
Medication use, n (%)						
Insulin or other antidiabetic drugs	1,768 (26.7)	659 (27.1)	476 (26.5)	350 (26.8)	283 (25.8)	0.881
Antihypertensive agents	5,204 (78.5)	1,947 (80.1)	1,395 (77.7)	1,015 (77.7)	847 (77.3)	0.129
Statins or other hypolipidemic drugs	3,453 (52.1)	1,253 (51.5)	945 (52.6)	678 (51.9)	577 (52.7)	0.881
Depressive symptomatology, n (%)	1,366 (20.6)	547 (22.5)	368 (20.5)	239 (18.3)	212 (19.3)	0.014
Anthropometric variables						
BMI, kg/m^2	32.6 ± 3.4	32.9 ± 3.5	32.6 ± 3.4	32.4 ± 3.5	32.0 ± 3.2	<0.001
Waist circumference, cm						
Women	104.0 ± 9.2	105.0 ± 9.2	103.9 ± 9.3	103.1 ± 8.9	102.7 ± 9.2	<0.001
Men	110.9 ± 8.8	111.8 ± 9.1	110.8 ± 8.4	110.5 ± 8.7	109.9 ± 8.5	<0.001
Lifestyle variables						
Smoking status, n (%)						
Current smoker	821 (12.4)	349 (14.4)	203 (11.3)	143 (11.0)	126 (11.5)	0.029
Former smoker	2,865 (43.2)	1,030 (42.4)	789 (43.9)	567 (43.4)	479 (43.7)	
Never smoked	2,944 (44.4)	1,053 (43.3)	804 (44.8)	596 (45.6)	491 (44.8)	
Physical activity, METs/min/day	352.0 ± 329.3	326.8 ± 330.2	343.9 ± 310.2	379.7 ± 339.4	388.2 ± 340.2	<0.001
Cognitive performance assessment, raw scores						
Mini-Mental State Examination (MMSE)	(*n* = 6,442) 28.2 ± 1.9	(*n* = 2,358) 28.1 ± 2.0	(*n* = 1,752) 28.3 ± 1.9	(*n* = 1,274) 28.3 ± 1.8	(*n* = 1,058) 28.2 ± 1.9	0.021
Clock Drawing Test (CDT)	(*n* = 6,446) 5.9 ± 1.2	(*n* = 2,358) 5.9 ± 1.3	(*n* = 1,753) 6.0 ± 1.2	(*n* = 1,274) 5.9 ± 1.2	(*n* = 1,061) 6.0 ± 1.2	0.495
Verbal Fluency tasks semantical (VFT-a)	(*n* = 6,580) 16.0 ± 4.9	(*n* = 2,416) 16.0 ± 5.0	(*n* = 1,782) 15.9 ± 4.8	(*n* = 1,295) 16.1 ± 4.8	(*n* = 1,087) 16.2 ± 4.9	0.374
Verbal Fluency tasks phonological (VFT-p)	(*n* = 6,580) 12.2 ± 4.5	(*n* = 2,416) 12.1 ± 4.6	(*n* = 1,782) 12.1 ± 4.6	(*n* = 1,295) 12.3 ± 4.4	(*n* = 1,087) 12.4 ± 4.4	0.198
Trail Making Test Part A[3] (TMT-A)	(*n* = 6,565) 52.8 ± 28.6	(*n* = 2,414) 53.8 ± 30.0	(*n* = 1,779) 53.2 ± 29.3	(*n* = 1,294) 52.2 ± 27.4	(*n* = 1,078) 50.9 ± 25.2	0.038
Trail Making Test Part B[3] (TMT-B)	(*n* = 6,547) 130.1 ± 72.4	(*n* = 2,403) 131.4 ± 73.6	(*n* = 1,774) 131.0 ± 73.2	(*n* = 1,293) 128.6 ± 70.1	(*n* = 1,077) 127.5 ± 70.9	0.389
Digit Span test forward (DST-f)	(*n* = 5,653) 8.8 ± 2.5	(*n* = 2,092) 8.8 ± 2.5	(*n* = 1,516) 8.7 ± 2.5	(*n* = 1,118) 8.9 ± 2.5	(*n* = 927) 8.9 ± 2.4	0.322
Digit Span test backward (DST-b)	(*n* = 5,650) 5.1 ± 2.2	(*n* = 2,090) 5.1 ± 2.2	(*n* = 1,516) 5.0 ± 2.2	(*n* = 1,118) 5.1 ± 2.3	(*n* = 926) 5.2 ± 2.2	0.441

Data are presented as n (%) and mean ± SD or median [IQR] for categorical and continuous variables, respectively.
Abbreviations: IQR, interquartile range; METs, metabolic equivalents; 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 Pearson's Chi-square test or one-way ANOVA, as appropriate.
[3] Inverse neuropsychological assessment score, lower scores represent better cognitive performance.

participants with depressive symptoms, were also observed in the highest compared with the lowest nut consumption category.

Figure 1 and Appendix E show the associations (β coefficients and 95% CI) between baseline nut consumption and changes in cognitive performance over the 2-y follow-up period. After adjusting for potential confounding factors, nut consumption was positively associated with 2-y changes in cognitive performance, as assessed by the general cognitive function composite score (*P*-trend<0.001) and the CDT score (*P*-trend <0.001). In particular, in the multivariable-adjusted models where nut consumption was treated as a continuous variable, a 1-serving/day higher

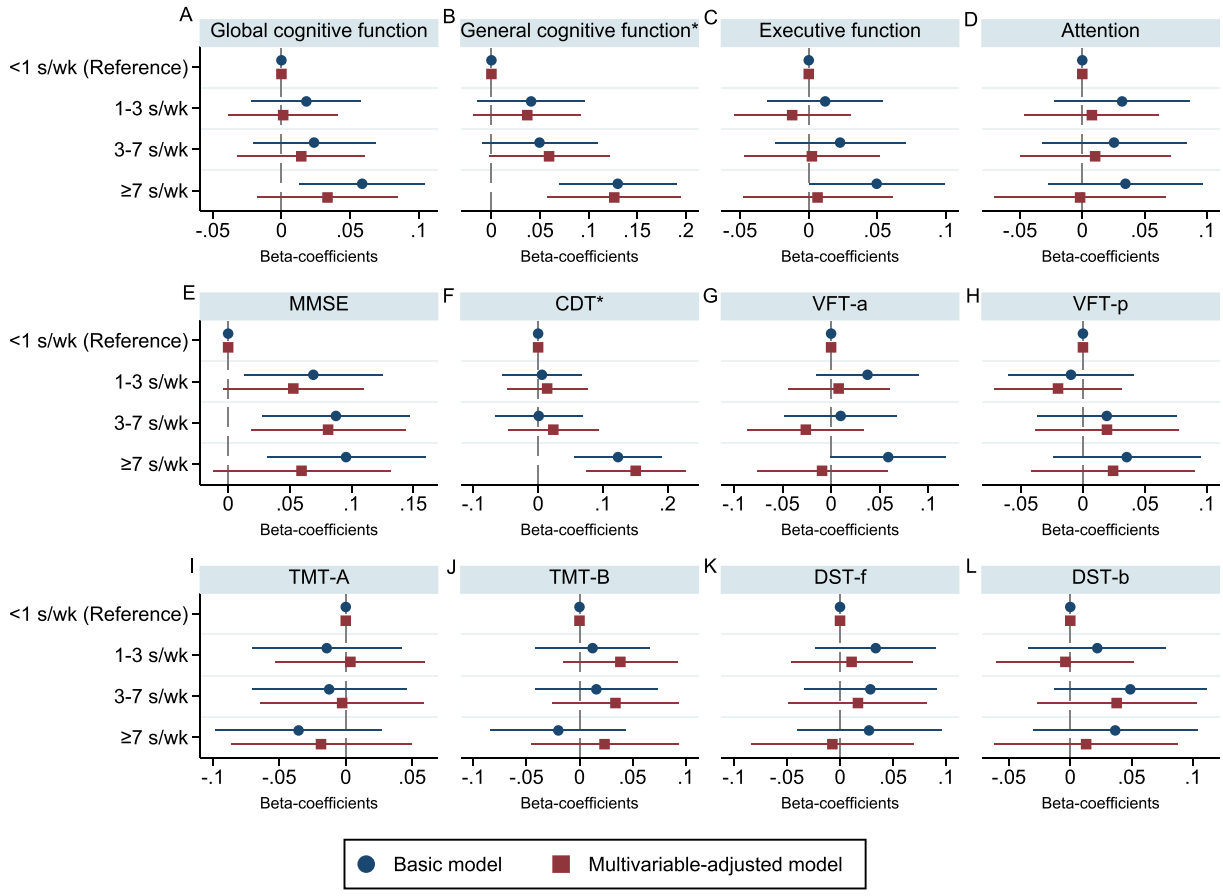

FIGURE 1. Beta coefficients and 95% CI of 2-y changes in cognitive performance (i.e. global cognitive function (A), general cognitive function (B), executive function (C), attention (D), MMSE score (E), CDT score (F), VFT-a score (G), VFT-p score (H), TMT-A score (I), TMT-B score (J), DST-f score (K), DST-b score (L)) according to categories of baseline nut consumption. The blue circles and red boxes represent the point estimates of the beta coefficients, and the blue and red lines indicate the CIs of the basic and multivariable-adjusted models, respectively. Basic models were adjusted for respective cognitive test scores at baseline, age (years), and sex. Multivariable-adjusted models were further adjusted for intervention PREDIMED-Plus randomized groups, and participating center (≤200, 200 to 300, 300 to 400, >400 participants), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), BMI (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]). * indicates *P*-trend across 4 groups <0.05. 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; 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. CDT, Clock Drawing Test; DST-b, Digit Span test - backward; DST-f, Digit Span test - forward; 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.

nut consumption was associated with a 0.07 z-score more favorable change in general cognitive function (95% CI: 0.03 to 0.12, $p<0.001$), and a 0.09 z-score more favorable change in CDT (95% CI: 0.04 to 0.14, $P<0.001$ (Appendix E). In addition, nut consumption was also significantly associated with a lower cognitive decline for the GCF (*P*-trend=0.015) in the basic model (Appendix E). This association attenuated after additional adjustment for cardiovascular disease risk factors. Furthermore, results in relation to the MMSE screening test showed that participants who consumed ≥3 to <7 servings per wk of nuts had better cognitive performance evolution after the 2-y follow-up than those who consumed less than 1 serving per wk of nuts (β=0.08 z-score, 95% CI: 0.02 to 0.14, $P=0.011$). This significant finding did not extend to the highest category (≥7 servings per wk) of nut consumption, and no overall trend between MMSE score changes and nut consumption was observed (*P*-trend=0.078).

The associations of nut consumption with 2-y changes in cognitive function remained similar in all sensitivity analyses (Appendix E). We found no significant interactions between nut consumption and sex, education level, smoking status, randomized intervention group, or the presence of type 2 diabetes, hypertension, and hypercholesterolemia (all p for interaction values >0.05; data not shown). Conversely, there were significant synergistic multiplicative interactions between nut consumption and depressive status in relation to changes in GCF ($p=0.041$), general cognitive function ($p=0.013$), attention ($p=0.043$), MMSE ($p=0.013$), and DST-f ($p=0.004$) (Appendix F). In the stratified analysis, we also observed that over the 2-y follow-up, higher nut consumption was significantly associated with less cognitive decline in individuals with depression at baseline but not in those without depression (data not shown).

Discussion

The present study provides novel prospective findings of the associations between nut consumption at baseline and subsequent changes in cognitive function. Our results show that a higher frequency of nut consumption is associated with favorable changes in the general cognitive function composite and CDT score, suggesting a potential dose-response relationship between nut consumption and a delay in cognitive decline over the period of 2 y, regardless of the baseline cognitive status, sociodemographic, cardiometabolic, and lifestyle factors including diet, in older adults with overweight/obesity, metabolic syndrome, and at risk of cognitive decline. These findings were robust in the sensitivity analyses performed. We also found a potential synergistic interaction between nut consumption and depression, suggesting that participants with depressive symptomatology at baseline tended to benefit more from the consumption of nuts than those without depression.

The observed positive association between nut consumption and cognitive performance is in line with findings from most existing cross-sectional studies, in which nut consumption has been associated with better cognitive performance and a lower risk of cognitive impairment [18]. Our findings concur in part with the results of prior prospective studies conducted in different middle-aged and older populations, showing that nut consumption was associated with less cognitive decline [32], better cognitive performance [32,33], and related to a lower risk of cognitive impairment [34–36]. Yet, in some of these prospective studies, the sample size was limited [32]; the temporal relationship could not be determined since no cognitive assessment was conducted at baseline when collecting nut consumption data [34]; and in one study, the associations between nut consumption and the trend in delayed cognitive decline weakened after additional adjustment for cardiovascular disease risk factors [33]. In 2 prospective cohort studies involving 15,467 US female nurses aged 70 y and older [37] and a population-weighted sample of 3,632 older US adults [38], cross-sectional associations between nut consumption and better cognitive performance were consistently observed. Still, unlike what was revealed in our study, none of them found an association between nut consumption and potential cognitive decline postponement over time. The weakened variability in cognitive change that could be attributed to nut consumption in these studies may be due to various factors, such as the advanced age of the participants (mean age 74 y), i.e., many older adults might have already experienced cognitive decline before inclusion in these studies [37,38]; the relative homogeneity and high education level of the population studied [37] since higher former education levels and lifelong higher educational attainment is a strong protective factor against cognitive decline and dementia risk [2]; and the use of telephone-based assessments for cognitive outcomes, which were more prone to measurement bias and less accurate to detect cognitive changes [37,38].

Evidence from clinical trials assessing the effects of nut intake on cognitive function is limited. Two PREDIMED sub-studies reported improvements in cognitive function in those participants randomized to a MedDiet intervention supplemented with 30 g/d mixed nuts after a mean of 6.5 y or 4.1 y, compared with those in the low-fat control diet arm [39,40]. The effects of different types of nut consumption (e.g., almonds [41,42], walnuts [19], and peanuts [43]) on cognitive performance and cognitive decline in middle-aged and older adults were inconsistent, either showing improvements in cognitive function [42,43] or no effect in delaying cognitive decline [19,41], but in no case was worse cognitive status observed compared with control diets. Some possible reasons for this inconsistency might be due to the duration of the interventions, the sample size studied, the background diets, the sociodemographic-economic and health status of the study populations, and most importantly, the overall risk of cognitive impairment/dementia, as persons at a higher risk (such as the PREDIMED-Plus population) are those that can benefit most from an intervention with neuroprotective agents such as certain nut components [18,19,39,40].

Several potential mechanisms underlying the associations between nut intake and cognitive function have been proposed. Oxidative stress, neuroinflammation, and reduced blood flow are considered crucial mechanisms that trigger the formation of arterial plaques, induce cell death and organic dysfunction, leading to cognitive decline and neurodegenerative diseases [17]. Evidence has accumulated on the beneficial role of nuts in improving antioxidant status, endothelial function, peripheral inflammation [7,18,44], and of nut constituents in reducing amyloid-beta (Aβ) production, aggregation, and Aβ-induced toxicity [8]. Moreover, nut consumption has also been associated with reduced incidence of, and mortality from, different cardiovascular diseases [7,10] and reductions in body weight and adiposity gain [12]. Moreover, clinical trials with nuts have demonstrated beneficial effects on blood pressure [15], blood lipid profile [7], and insulin sensitivity [13]. Given that cardiometabolic disorders and cognitive decline share similar vascular risk factors [2,7,18], nut consumption might benefit cognitive function via modulation of most vascular risks. In the present study, nut consumption was significantly associated with a more favorable change in GCF; however, this association weakened after further adjustment for cardiovascular disease risk factors, suggesting that nut consumption may partially postpone cognitive decline by reducing the cardiovascular disease risk profile. The neurological and cardiometabolic benefits of nuts may be explained by their nutrient-dense profile and high content of bioactive compounds. Nuts are rich in nutrients like vitamin E, folate, carotenoids, and selenium, as well as different phenolic compounds, which are potent antioxidant and anti-inflammatory agents [7,8]. Nuts also contain a high amount of unsaturated fatty acids (particularly, linoleic and α-linolenic acids in walnuts) that have vasculo-protective and anti-inflammatory effects, besides their indispensable roles in maintaining neuronal structure and function, modulating neuronal plasticity and various metabolic processes [8,45,46]. The high-quality vegetable protein and amino acids found in nuts, like L-arginine, can exert neuroprotective effects via anti-atherosclerotic and antioxidative mechanisms, modulating neuroinflammation and improving endothelial function [7,8]. The optimal mineral composition of nuts, being high in calcium, magnesium, and potassium but devoid of sodium, has demonstrated beneficial effects on blood pressure and insulin sensitivity [15,47]. Furthermore, the high content of dietary fiber, along with unsaturated fat and polyphenols, may potentially modulate gut microbiota and, subsequently, cognitive function through the "gut-brain axis" [7,48].

The major strengths of our study include: 1) its prospective study design with a 2-y follow-up period, whereby beneficial associations between nut consumption and cognitive function were observed in a relatively short time frame in a population at high risk; 2) the nut intake categorization in the analysis is based on common nut recommendations, hence facilitating the ability to interpret study findings; 3) the measurement of different cognitive domain changes by using a comprehensive neuropsychological battery with the construction of composite scores; 4) the control of covariables by adjusting the statistical models for several potential relevant confounders, and 5) the robustness of our results after performing several sensitivity and stratified analyses. Our study also has limitations. Firstly, due to the inherent characteristics of observational

studies, the possibility of reverse causality and residual confounding from factors not assessed in our analyses (e.g., apoE carrier status) cannot be discounted; therefore, a cause-effect relationship could not be determined. Secondly, nut consumption was assessed once at baseline from a single FFQ, which may be prone to measurement error, misclassification, and recall bias as it relies on individuals' memory; this may result in an underestimation of the associations. Lastly, the observed results in an older sample of overweight/obese individuals with cardiovascular disease risk factors may not be extended to the general population and should be interpreted with caution; however, the present findings support that the consumption of nuts might benefit cognitive performance in individuals at high risk of cognitive decline.

In conclusion, frequent nut consumption may help to delay cognitive decline in older adults with overweight/obesity, metabolic syndrome, and at risk of cognitive decline, even over a relatively short 2-y period. This finding needs to be reproduced in further epidemiological and clinical studies before dietary recommendations to delay cognitive decline and prevent or delay the onset or progression of cognitive impairment and dementia may be made.

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Author responsibilities

JS-S, DC, JAM, ÁMA-G, JW, JeV, DR, JL-M, RE, FJT, LS-M, JAT, XP, MD-R, PM-M, JoV, CV, LD, and ER contributed to study concept and design, conducting the study and to data collection and management from the participants of PREDIMED-Plus study. JN, SKN, NB and JS-S contributed to the present study concept and design, and drafted the manuscript. JN and SKN performed the statistical analyses. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available in a controlled data-sharing collaboration model. Investigators who are interested in this study can contact the PREDIMED Steering Committee by sending a request letter to predimed_scommittee@googlegroups.com. A data-sharing agreement indicating the characteristics of the collaboration and data management will be completed for the proposals that are approved by the Steering Committee.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.05.032.

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