GeroScience
https://doi.org/10.1007/s11357-025-01670-1

ORIGINAL ARTICLE

Dietary vitamin D intake and 2-year changes in cognitive function in older adults with overweight or obesity and metabolic syndrome

Héctor Vázquez-Lorente · Jiaqi Ni · Indira Paz-Graniel · Estefanía Toledo · Dolores Corella · Olga Castañer · J. Alfredo Martínez · Ángel M. Alonso-Gómez · Julia Wärnberg · Jesús Vioque · Dora Romaguera · José López-Miranda · Ramon Estruch · Francisco J. Tinahones · José Lapetra · Lluís Serra-Majem · Amira Bouzalmate-Hajjaj · Josep A. Tur · Rafael M. Micó Pérez · Marta Fanlo · Miguel Delgado-Rodríguez · Ana Barabash Bustelo · Josep Vidal · Clotilde Vázquez · Lidia Daimiel · Emili Ros · Fernando Fernández-Aranda · Teresa Rognoni · Nancy Babio · Eva M. Asensio · Karla-Alejandra Pérez-Vega · Antonio Garcia-Rios · Laura Compañ-Gabucio · Raquel Cueto-Galán · M. Angeles Zulet · Mar Nafria · Rosa Casas · Naomi Cano-Ibáñez · Luis Tojal-Sierra · Ana María Gómez-Pérez · Nuria Goñi · José V. Sorli · María Dolores Zomeño · Antonio P. Arenas-Larriva · Pedro Jiménez-Sellés · Javier Basterra-Gortari · Montserrat Fitó · Jordi Salas-Salvadó

Received: 6 March 2025 / Accepted: 15 April 2025

Abstract The protective role of dietary vitamin D intake on cognitive function is of interest, but evidence remains inconsistent. We aimed to evaluate the association between dietary vitamin D intake and 2-year cognitive changes in older adults at risk of cognitive decline. This longitudinal study comprised 5454 individuals (aged 55–75 years in men and 60–75 years in women) who exhibited overweight/obesity and metabolic syndrome. Data on dietary vitamin D intake was assessed using a validated 143-item food frequency questionnaire. Cognitive function was assessed through five composite scores derived from a comprehensive battery of eight neuropsychological tests, encompassing

---

Héctor Vázquez-Lorente and Jiaqi Ni contributed equally to this work and share first authorship.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-025-01670-1.

H. Vázquez-Lorente (✉) · J. Ni · I. Paz-Graniel (✉) ·
E. Toledo · D. Corella · O. Castañer · J. A. Martínez ·
Á. M. Alonso-Gómez · J. Wärnberg · D. Romaguera ·
J. López-Miranda · R. Estruch · F. J. Tinahones ·
J. Lapetra · L. Serra-Majem · A. Bouzalmate-Hajjaj ·
J. A. Tur · M. Fanlo · C. Vázquez · L. Daimiel ·
E. Ros · F. Fernández-Aranda · N. Babio ·
E. M. Asensio · K.-A. Pérez-Vega · A. Garcia-Rios ·
M. A. Zulet · R. Casas · A. M. Gómez-Pérez ·
J. V. Sorli · M. D. Zomeño · A. P. Arenas-Larriva ·
J. Basterra-Gortari · M. Fitó · J. Salas-Salvadó
Centro de Investigación Biomédica en Red Fisiopatología de La Obesidad y La Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain
e-mail: hector.vazquez@urv.cat

I. Paz-Graniel
e-mail: indiradelsocorro.paz@urv.cat

H. Vázquez-Lorente · J. Ni · I. Paz-Graniel · N. Babio ·
J. Salas-Salvadó
Unitat de Nutrició Humana, Departament de Bioquímica I Biotecnologia, Grup Alimentació, Nutrició, Desenvolupament i Salut Mental ANUT-DSM, Universitat Rovira I Virgili, Reus, Spain

H. Vázquez-Lorente · J. Ni · I. Paz-Graniel · N. Babio ·
J. Salas-Salvadó
Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain

E. Toledo · N. Goñi · J. Basterra-Gortari
Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdiSNA), University of Navarra, Pamplona, Spain

E. Toledo
Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

D. Corella · E. M. Asensio · J. V. Sorli
Department of Preventive Medicine, University of Valencia, Valencia, Spain

O. Castañer · J. Vioque · L. Compañ-Gabucio · N. Cano-Ibáñez
CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

J. A. Martínez · M. A. Zulet
Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, IdiSNA, University of Navarra, Pamplona, Spain

J. A. Martínez · M. Delgado-Rodríguez
Precision Nutrition and Cardiometabolic Health Program, IEA Food, CEI UAM + CSIC, Madrid, Spain

J. A. Martínez
Departamento de Medicina y Endocrinología, Universidad de Valladolid, Valladolid, Spain

Á. M. Alonso-Gómez · L. Tojal-Sierra
Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic AreaOsakidetza Basque Health Service, Araba University HospitalUniversity of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain

J. Wärnberg
EpiPHAAN Research Group, School of Health Sciences, University of Málaga – Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain

J. Vioque · L. Compañ-Gabucio
Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernández (ISABIAL-UMH), Alicante, Spain

D. Romaguera · M. Nafria
Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain

J. López-Miranda · A. Garcia-Rios · A. P. Arenas-Larriva
Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain

R. Estruch · R. Casas
Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain

R. Estruch · R. Casas
Institut de Recerca en Nutrició I Seguretat Alimentaria (INSA-UB), University of Barcelona, Barcelona, Spain

F. J. Tinahones · A. M. Gómez-Pérez
Department of Endocrinology, Virgen de La Victoria Hospital, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Málaga, Málaga, Spain

J. Lapetra
Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Seville, Spain

L. Serra-Majem
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

A. Bouzalmate-Hajjaj · N. Cano-Ibáñez
Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain

J. A. Tur
Research Group On Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma, Spain

R. M. M. Pérez
Foundation SEMERGEN (Spanish Society of Primary Care Physicians), Madrid, Spain

M. Fanlo
Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat – Barcelona, Barcelona, Spain

M. Delgado-Rodríguez
Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain

A. B. Bustelo
Endocrinology and Nutrition Department, Hospital Clínico Universitario San Carlos and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

A. B. Bustelo
Facultad de Medicina, Medicina II Department, Universidad Complutense de Madrid, Madrid, Spain

A. B. Bustelo · J. Vidal
CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

J. Vidal
Department of Endocrinology, Institut d'Investigacions Biomédiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain

C. Vázquez
Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz, Instituto de Investigaciones Biomédicas IISFJD, University Autonoma, Madrid, Spain

global cognitive function, general cognitive function, attention, executive function, and language domains. Multivariable-adjusted linear regression models were fitted to examine the association between energy-adjusted cumulative average dietary vitamin D intake over time and 2-year changes in cognitive function. After adjusting for multiple covariates, energy-adjusted cumulative average dietary vitamin D intake as a continuous variable was associated with greater 2-year improvements in global cognitive function (β 1.18×10^{-2}; 95% CI 0.19×10^{-2} to 2.17×10^{-2}), executive function (β 1.12×10^{-2}; 95% CI 0.03×10^{-2} to 2.21×10^{-2}), and language (β 1.61×10^{-2}; 95% CI 0.43×10^{-2} to 2.78×10^{-2}). Additionally, the higher cumulative average dietary vitamin D intake quartile was associated with an increase in global cognitive function (β 7.10×10^{-2}; 95% CI 0.59×10^{-2} to 13.6×10^{-2}), language (β 7.07×10^{-2}; 95% CI -0.52×10^{-2} to 14.7×10^{-2}), and a lower decline in attention (β 9.58×10^{-2}; 95% CI 1.60×10^{-2} to 17.5×10^{-2}). A higher dietary vitamin D intake was associated with modest favorable changes in cognitive function and a reduced cognitive decline over a 2-year period. These findings highlight the need for further research to explore the potential benefits of boosting dietary vitamin D intake for cognitive health in older adults.

L. Daimiel
Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, Madrid, Spain

L. Daimiel
Departamento de Ciencias Farmacéuticas y de La Salud, Faculty de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, Spain

E. Ros
Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain

F. Fernández-Aranda
Psychoneurobiology of Eating and Addictive Behaviors Group, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain

F. Fernández-Aranda
Department of Clinical Psychology, University Hospital of Bellvitge and University of Barcelona, Barcelona, Spain

T. Rognoni
Department of Neurology, Clínica Universidad de Navarra, Madrid, Spain

K.-A. Pérez-Vega · M. Fitó
Unit of Cardiovascular Risk and Nutrition, Hospital del Mar Research Institute (IMIM), Barcelona, Spain

R. Cueto-Galán
Department of Public Health and Psychiatry, School of Medicine, University of Malaga, Malaga, Spain

R. Cueto-Galán
Biomedical Research Institute of Malaga (IBIMA), Malaga, Spain

N. Cano-Ibáñez
Instituto de Investigación Biosanitaria de Granada (IBS-Granada), Granada, Spain

N. Goñi · J. Basterra-Gortari
Navarra Health Service (Osasunbidea), Primary Care, Pamplona, Navarra, Spain

P. Jiménez-Sellés
Primary Health Care Center Santa Pola, Alicante, Spain

Keywords Vitamin D · Cognition · Cognitive decline · Cognitive function · Aging · Older people

Introduction

Cognitive impairment and dementia have become major healthcare and public health concerns [1]. Projections indicate a substantial increase by 2050 in developed countries [2], primarily due to obesity, aging, and unhealthy lifestyles [3]. Effective prevention and control measures are urgently required [4]. Identifying strategies to prevent these conditions by focusing on modifiable risk factors, such as lifestyle behaviors, specifically on diet, could potentially mitigate or delay their onset [5].

Vitamin D metabolites, along with the enzymes involved in its metabolism and its receptors, have been identified in brain regions involved in cognitive processes [6]. Acting as a neurosteroid, vitamin D is involved in behavioral function, neurogenesis, and neuroprotection [7]. It has been reported that individuals with low blood vitamin D concentrations present poorer cognitive function and a higher risk of cognitive decline compared to those with an adequate status [8]. Indeed, individuals with vitamin D deficiency have been shown to have twice the risk of all-cause dementia [9]. Vitamin D is acquired through cutaneous synthesis from sun exposure and dietary intake. Although dietary intake has traditionally been considered a minor source, it becomes crucial for older adults and those with excess weight, as they derive significantly less vitamin D from cutaneous synthesis [10, 11].

Emerging evidence indicates that dietary intake of vitamin D, rather than from supplements, may have a protective association with cognitive function [12]. Inadequate dietary vitamin D intake has been associated with poorer cognitive function and up to 30% increased risk of cognitive impairment [13]. However, epidemiological evidence on this topic remains limited. Cross-sectional studies have suggested a beneficial link between dietary vitamin D intake and cognitive function [14–17], but findings from longitudinal studies have been mixed, showing either slight and modest benefits [18–20] or no clear associations with cognitive function over time [21]. In addition, the impact of vitamin D supplementation on cognition remains unclear, as most intervention studies have not demonstrated significant benefit [22]. Discrepancies among research studies may stem from differences in cognitive assessment tools, supplementation dosage, and duration of the intervention, as well as baseline characteristics of study participants, especially in the initial vitamin D status [23–25].

Therefore, the evidence regarding the beneficial effects of dietary vitamin D intake on cognitive function and/or cognitive decline remains inconclusive. Unraveling a possible connection between dietary vitamin D intake and cognitive function is important for considering healthcare initiatives to prevent or delay cognitive decline [26], particularly among aged and obese individuals, whose vitamin D levels and cognitive health tend to be reduced [27, 28]. Therefore, the aim of this study is to evaluate the association between dietary vitamin D intake and 2-year cognitive changes in older adults with overweight/obesity and metabolic syndrome, who are at risk of cognitive decline. We hypothesize that a higher dietary vitamin D intake may be associated with better cognitive function compared to lower intake over a 2-year follow-up.

Materials and methods

Study design

This study was performed within the framework of the PREDIMED-Plus trial. The trial, ongoing in Spain across 23 centers, aims to assess the impact of an energy-reduced Mediterranean diet (MedDiet), increased physical activity, and behavioral modification on cardiovascular health [29]. More details on the trial protocol are available at https://www.predimedplus.com/ and in published sources [30, 31]. Ethical approval was obtained from all participating centers, and written informed consent was obtained from all participants. The trial was registered in 2014 at the International Standard Randomized Controlled Trial registry [ISRCT; www.isrctn.com/ISRCTN89898870].

Participants

The study enrolled community-dwelling adults aged 55 to 75 years with overweight or obesity (body mass index (BMI) ranging from 27 to 40 kg/m^2) and at least three criteria for metabolic syndrome, as defined by established criteria [32]. Participants enrolled in this study had preserved cognitive function to understand and give consent and were not institutionalized. From October 2013 to December 2016, a total of 6874 eligible participants were randomly assigned in a 1:1 ratio to either the intervention group or the control group receiving usual care (traditional energy-unrestricted MedDiet). Randomization was performed centrally using a computer-generated system, with stratification by center, sex, and age. Couples sharing a household were randomized together. The randomization process was blinded to staff and investigators. For the purpose of the present study, participants not completing dietary questionnaires, reporting energy intakes outside predefined limits ($<$ 800 to $\geq$ 4000 kcal/day for men, $<$ 500 to $\geq$ 3500 kcal/day for women) at baseline, or taking vitamin D medication/supplementation at baseline, 6 months, 1 year, and 2 years of follow-up were excluded [33]. A total of 5454 participants were finally included in the study (Fig. 1).

Exposure: vitamin D intake

Trained dietitians conducted face-to-face interviews with participants to assess their dietary habits using a validated 143-item food frequency questionnaire (FFQ) [34]. The FFQ comprised nine response options ranging from “never” to “more than six times per day.” These responses were converted into daily

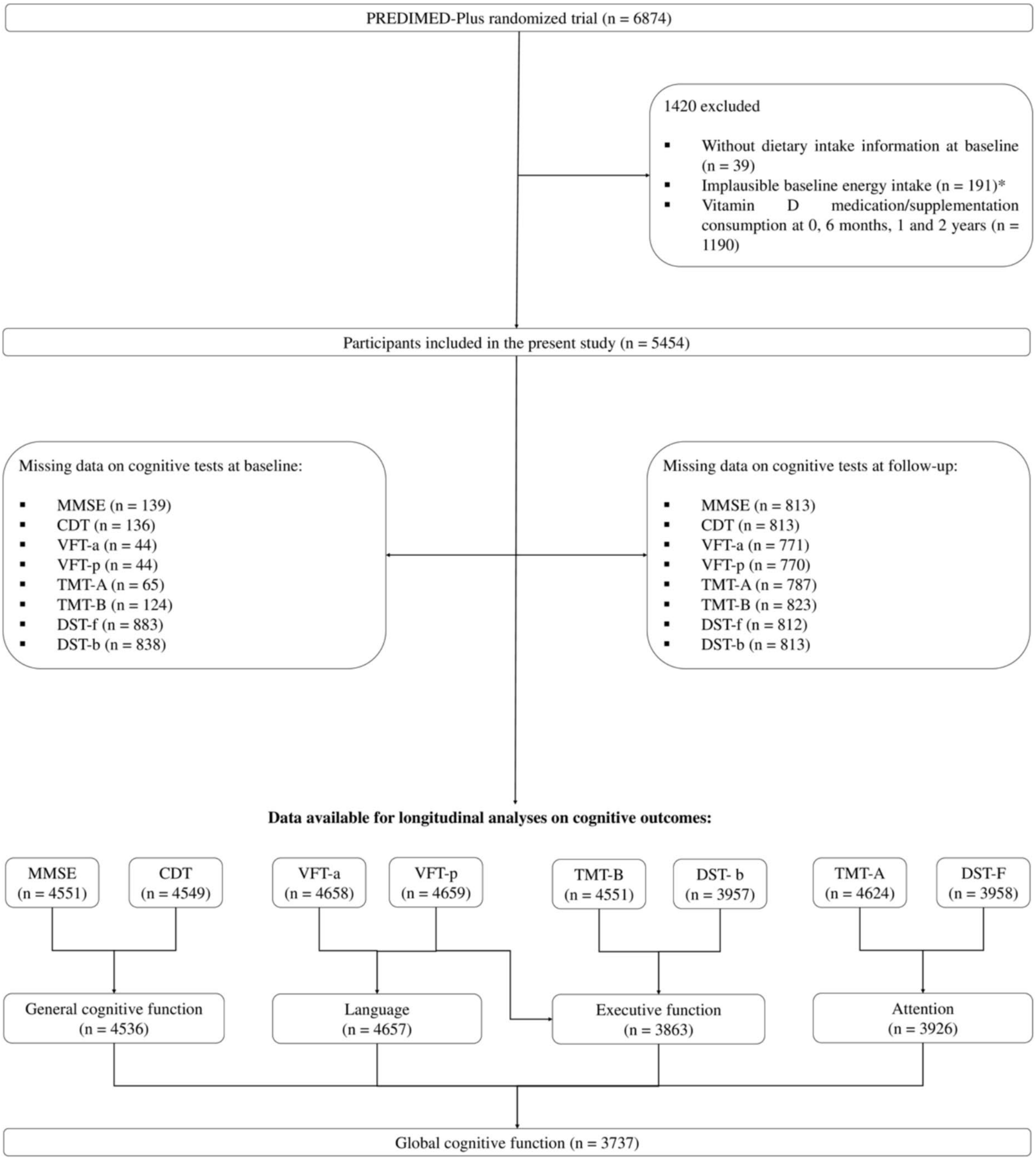


Fig. 1 Flowchart of the study population. CDT, Clock Drawing test; DST-b, Digit Span test backward; DST-f, Digit Span test forward; MMSE, Mini-Mental State Examination; TMT-A, Trail Making test part A; TMT-B, Trail Making test part B; VFT-a, verbal fluency tasks semantical; VFT-p, verbal fluency tasks phonological. Asterisk (*) symbols indicate daily energy intakes for men < 800 kcal or > 4000 kcal and women < 500 kcal or > 3500 kcal

intake values using standard portion sizes for each item. The Spanish food composition database was utilized to estimate the energy and dietary vitamin D intake [35]. Dietary vitamin D intake was assessed at baseline, 6 months, 1 year, and 2 years of follow-up. The energy-adjusted cumulative average of dietary vitamin D intake over these time points was subsequently calculated by summing the reported dietary vitamin D intake from each time point and dividing by the number of assessments available up to that moment, and using the residual method [36] to better represent long-term intake and reduce within-person variation and measurement errors. Participants were additionally categorized into quartiles of energy-adjusted cumulative average dietary vitamin D intake over time.

Outcome: changes in cognitive function

Cognitive function evaluation was conducted by trained personnel both at baseline and at the 2-year follow-up assessment. A battery of eight neuropsychological tests, validated specifically for the Spanish population, was administered via individual interviews. These tests comprised the Mini-Mental State Examination (MMSE), the Clock Drawing test (CDT), the Verbal Fluency tests (VFTs), the forward and backward versions of the Digit Span test (DST-f and DST-b, respectively) from the Wechsler Adult Intelligence Scale-III (WAIS-III), and the Trail Making test parts A (TMT-A) and B (TMT-B). Detailed descriptions of these neuropsychological assessments can be found elsewhere [37]. Each cognitive test administered at baseline and during the 2-year follow-up period was standardized for every participant to a *z*-score, utilizing the mean and standard deviation (SD) derived from the baseline data. Subsequently, the difference between the standardized scores at the two time points was calculated to assess changes in cognitive function over time [38, 39].

Composite measures for four cognitive composite scores (general cognitive function, executive function, attention, and language), as well as a global assessment of cognitive function (GCF), were computed for each participant. The composite cognitive assessments were determined by aggregating or deducting individual test *z*-scores based on whether a higher score indicates superior or inferior cognitive function, respectively, as detailed in Table S1. Following this procedure, the resulting five composite scores were further standardized to *z*-scores using the mean and standard deviation (SD) values from baseline composite score data. The changes observed in these five composite scores over the 2-year period constituted the primary outcome of interest in this study.

Covariate assessments

Sociodemographic and lifestyle information encompassing age, sex, education level, civil status, and smoking habits were gathered by administered questionnaires. Physical activity was estimated utilizing a validated Spanish short version of the Minnesota Leisure Time Physical Activity Questionnaire (the REGICOR questionnaire) [40]. Personal medical history, encompassing conditions such as type 2 diabetes, hypertension, and hypercholesterolemia, and medication usage were either self-reported or extracted from medical records. Depressive symptomatology was evaluated using the Beck Depression Inventory-II (BDI-II), where depression risk was established as a score ≥ 14 [41, 42]. Anthropometric variables, such as weight and height, were assessed using calibrated scales and wall-mounted stadiometers, respectively. BMI was calculated as weight (kg)/height (m)^2. Food group information, including variables related to vegetables, fruits, legumes, cereals, meat, fish, dairy, nuts, oils and fats, olive oils, biscuits, coffee, tea, and alcohol consumption, was collected using the same FFQ used to assess dietary vitamin D intake. Subsequently, energy and nutrient intake estimations were derived utilizing the Spanish Food Composition Tables [35]. Energy-adjusted cumulative averages for dietary variables were obtained using the residual method [36].

Statistical analyses

Baseline characteristics of the study cohort were presented both in overall and categorized by quartiles of energy-adjusted cumulative average dietary vitamin D intake over time as means ± SDs for continuous variables and numbers (percentages) for categorical variables. One-way analysis of variance (ANOVA) was employed for continuous variables, while chi-square tests were utilized for categorical variables.

The associations between energy-adjusted cumulative average dietary vitamin D intake (exposure) and changes observed in cognitive function measurements

Table 1 Baseline characteristics of the PREDIMED-Plus participants both in overall and by quartiles of energy-adjusted cumulative averages of dietary vitamin D intake

	Total population	Categories of dietary vitamin D intake				*P*-value[1]
		1 st quartile	2nd quartile	3rd quartile	4 th quartile	
Vitamin D (µg/day)	6.0 ± 3.4	3.4 ± 1.5	5.0 ± 2.2	6.5 ± 3.0	9.3 ± 3.3	**0.001**
Sociodemographic variables						
Age (years)	64.8 ± 4.9	64.6 ± 5.1	64.6 ± 5.0	64.9 ± 4.9	64.9 ± 4.8	0.279
Women (*n*/%)	2285 (41.9)	492 (36.1)	565 (41.5)	593 (43.5)	635 (46.6)	**0.001**
Education level (*n*/%)						
Primary or less	2627 (48.2)	692 (50.7)	682 (50.0)	673 (49.3)	580 (42.6)	
Secondary	1613 (29.6)	377 (27.6)	411 (30.2)	404 (29.6)	421 (30.9)	**0.001**
College	1214 (22.3)	295 (21.6)	270 (19.8)	287 (21.0)	362 (26.6)	
Civil status (*n*/%)						
Single, divorced, or separated	670 (12.3)	171 (12.5)	166 (12.2)	147 (10.8)	186 (13.6)	
Married	4258 (78.0)	1066 (78.2)	1071 (78.6)	1065 (78.1)	1056 (77.5)	0.164
Widower	526 (9.6)	127 (9.3)	126 (9.2)	152 (11.1)	121 (8.9)	
Disease presence or medication usage at recruitment						
Type 2 diabetes (*n*/%)	1746 (32.0)	441 (32.3)	457 (33.5)	446 (32.7)	402 (29.5)	0.123
Hypertension (*n*/%)	4576 (83.9)	1134 (83.1)	1160 (85.1)	1165 (85.4)	1117 (82.0)	**0.042**
Hypercholesterolemia (*n*/%)	3821 (70.1)	940 (68.9)	980 (71.9)	955 (70.0)	946 (69.4)	0.343
Depressive symptomatology, (*n*/%)	1039 (19.1)	260 (19.1)	263 (19.3)	259 (19.0)	257 (18.9)	0.993
Medication use (*n*/%)						
Insulin or other antidiabetic drugs	1487 (27.3)	380 (27.9)	390 (28.6)	385 (28.2)	332 (24.4)	**0.047**
Antihypertensive agents	4269 (78.3)	1062 (77.9)	1079 (79.2)	1078 (79.0)	1050 (77.0)	0.482
Statins or other hypolipidemic drugs	2818 (51.7)	687 (50.4)	730 (53.6)	689 (50.5)	712 (52.2)	0.286
Anthropometric variables						
BMI (kg/m^2)	32.5 ± 3.4	32.6 ± 3.4	32.5 ± 3.5	32.5 ± 3.4	32.3 ± 3.5	0.231
Waist circumference (cm)						
Women	103.6 ± 9.1	103.8 ± 8.6	103.3 ± 9.3	104.0 ± 9.4	103.5 ± 9.1	0.542
Men	110.7 ± 8.7	110.9 ± 9.0	110.9 ± 8.8	110.7 ± 8.5	110.4 ± 8.5	0.631
Lifestyle variables						
Physical exercise (METs/min/day)	364.3 ± 335.0	344.3 ± 335.2	346.2 ± 316.4	363.7 ± 338.8	403.0 ± 346.0	**0.001**
Smoking status, (*n*/%)						
Current smoker	717 (13.2)	222 (16.3)	182 (13.4)	152 (11.1)	161 (11.8)	**0.001**
Former smoker	2452 (45.0)	610 (44.7)	621 (45.6)	600 (44.0)	621 (45.6)	
Never smoker	2285 (41.9)	532 (39.0)	560 (41.1)	612 (44.9)	581 (42.6)	
Cognitive function assessment						
Global cognitive function (*n* = 3737)[2]	4.1 ± 1.0	2.1 ± 1.0	6.0 ± 1.0	2.6 ± 1.0	11.8 ± 1.0	**0.001**
General cognitive function (*n* = 4536)[2]	− 0.8 ± 1.0	0.6 ± 1.0	− 5.4 ± 1.0	− 1.8 ± 1.0	6.6 ± 1.0	**0.033**
Executive function (*n* = 3863)[2]	− 0.9 ± 1.0	− 4.2 ± 1.0	− 4.1 ± 1.0	− 4.2 ± 1.0	12.6 ± 1.0	**0.001**
Attention (*n* = 3926)[2]	− 0.3 ± 1.0	− 0.5 ± 1.0	− 5.6 ± 1.0	0.0 ± 1.0	6.1 ± 1.0	0.080
Language (*n* = 4657)[2]	− 0.7 ± 1.0	− 3.5 ± 1.0	− 2.5 ± 1.0	− 7.1 ± 1.0	13.1 ± 1.0	**0.001**

Data are presented as *n* (%) or mean ± SD for categorical and continuous variables, respectively. Significant values ($P < 0.05$) were highlighted in bold type

BMI body mass index, *CI* confidence interval, *METs* metabolic equivalents

[1] The *p*-value for differences between categories of energy-adjusted cumulative average dietary vitamin D intake was calculated by Pearson's chi-square test or one-way ANOVA, as appropriate

[2] Values are presented as multiples of 10^{-2} ($\times 10^{-2}$)

Table 2 Longitudinal association between energy-adjusted cumulative average dietary vitamin D intake and changes in cognitive function over 2 years of follow-up in the PREDIMED-Plus cohort

	Continuous		Categories of dietary vitamin D intake				*P*-trend
	Dietary vitamin D intake (μg/day)		1 st quartile	2nd quartile	3rd quartile	4 th quartile	
	β [95% CI][1]	*P*-value	β [95% CI][1]	β [95% CI][1]	β [95% CI][1]	β [95% CI][1]	
Global cognitive function (*n*)	(*n* = 3737)	–	(*n* = 935)	(*n* = 934)	(*n* = 934)	(*n* = 934)	–
Mean ± SD dietary vitamin D intake	6.54 ± 2.42	–	3.61 ± 0.82	5.48 ± 0.50	7.28 ± 0.56	9.79 ± 1.21	–
Basic model	**1.08 [0.39, 1.58]**	**0.002**	Reference	1.49 [− 3.52, 6.49]	3.94 [− 1.03, 8.91]	**6.88 [2.03, 11.7]**	**0.003**
Multivariable-adjusted model	**1.18 [0.19, 2.17]**	**0.019**	Reference	1.74 [− 3.37, 6.86]	4.47 [− 1.13, 10.1]	**7.10 [0.59, 13.6]**	**0.025**
General cognitive function (*n*)	(*n* = 4536)	–	(*n* = 1134)	(*n* = 1134)	(*n* = 1134)	(*n* = 1134)	–
Mean ± SD dietary vitamin D intake	6.56 ± 2.42	–	3.63 ± 0.82	5.51 ± 0.49	7.31 ± 0.64	9.81 ± 1.23	–
Basic model	0.30 [− 0.65, 1.26]	0.534	Reference	− 0.91 [− 7.65, 5.83]	− 1.30 [− 7.90, 5.30]	1.89 [− 4.72, 8.50]	0.579
Multivariable-adjusted model	− 0.17 [− 1.55, 1.20]	0.805	Reference	− 2.00 [− 8.98, 4.97]	− 2.65 [− 10.0, 4.75]	− 1.69 [− 10.5, 0.71]	0.722
Executive function (*n*)	(*n* = 3863)	–	(*n* = 966)	(*n* = 966)	(*n* = 966)	(*n* = 965)	–
Mean ± SD dietary vitamin D intake	6.55 ± 2.42	–	3.63 ± 0.82	5.50 ± 0.49	7.28 ± 0.56	9.79 ± 1.21	–
Basic model	**1.42 [0.67, 2.15]**	**0.001**	Reference	− 1.17 [− 6.36, 4.02]	4.27 [− 0.93, 9.47]	**7.67 [2.54, 12.8]**	**0.001**
Multivariable-adjusted model	**1.12 [0.03, 2.21]**	**0.044**	Reference	− 1.43 [− 6.71, 3.85]	3.10 [− 2.83, 9.05]	4.98 [− 2.00, 12.0]	0.084
Attention (*n*)	(*n* = 3926)	–	(*n* = 982)	(*n* = 981)	(*n* = 982)	(*n* = 981)	–
Mean ± SD dietary vitamin D intake	6.56 ± 2.43	–	3.63 ± 0.82	5.51 ± 0.49	7.30 ± 0.56	9.81 ± 1.22	–
Basic model	**1.28 [0.39, 2.16]**	**0.005**	Reference	5.70 [− 0.39, 11.8]	3.13 [− 3.34, 9.59]	**10.5 [− 3.33, 16.6]**	**0.003**
Multivariable-adjusted model	1.12 [0.10, 2.35]	0.073	Reference	5.26 [− 0.93, 11.4]	3.56 [− 3.60, 10.7]	**9.58 [1.60, 17.5]**	**0.039**
Language (*n*)	(*n* = 4657)	–	(*n* = 1165)	(*n* = 1164)	(*n* = 1164)	(*n* = 1164)	–
Mean ± SD dietary vitamin D intake	6.58 ± 2.43	–	3.64 ± 0.83	5.53 ± 0.49	7.31 ± 0.56	9.82 ± 1.23	–
Basic model	**2.12 [1.31, 2.93]**	**0.001**	Reference	1.70 [− 4.01, 7.41]	7.60 [19.7, 13.2]	**12.1 [6.57, 17.8]**	**0.001**
Multivariable-adjusted model	**1.61 [0.43, 2.78]**	**0.007**	Reference	0.54 [− 5.27, 6.36]	4.95 [− 1.42, 11.3]	**7.07 [− 0.52, 14.7]**	**0.039**

Basic models were adjusted for the respective cognitive test score at baseline, age (years), and sex. Multivariable-adjusted models were further adjusted for the intervention group, geographic area of the participating centers (south/north), 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), energy-adjusted cumulative average of alcohol consumption in g/day (and adding the quadratic term), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), and energy-adjusted cumulative average consumption of food groups (vegetables, fruits, legumes, cereals, oils and fats, olive oils, biscuits, meat, fish, dairy, nuts [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 quartile of energy-adjusted cumulative average dietary vitamin D intake 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

CI confidence interval

[1] β [95% CI] values are expressed as multiples of 10^{-2} ($\times 10^{-2}$)

over a 2-year period (outcome) were investigated through multivariable linear regression models. These models were adjusted for potential confounders pertinent to cognitive function and were presented as β-coefficients along with their corresponding 95% confidence intervals (CIs).

A basic model was adjusted for respective baseline cognitive function scores, age (years), and sex (men/women). The intervention group (control or intervention), geographic area of the participating centers (south/north), education level (primary or less, secondary, college), civil status (single, divorced or separated, married, widower), BMI (kg/m^2), physical activity (METs/min/day), smoking status (never, former, current), energy-adjusted cumulative average alcohol consumption in g/day (and adding the quadratic term), baseline presence of depressive symptomatology (yes/no), type 2 diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), and energy-adjusted cumulative average consumption of food groups (i.e., vegetables, fruits, legumes, cereals, dairy, meat, fish, nuts, oils and fats, olive oils, biscuits (in g/day), coffee, and tea (in mL/day)) were additionally included as covariates in the multivariable model. Penalized splines were used to explore the potential nonlinearity association using the continuous variable of cumulative average dietary vitamin D intake [43].

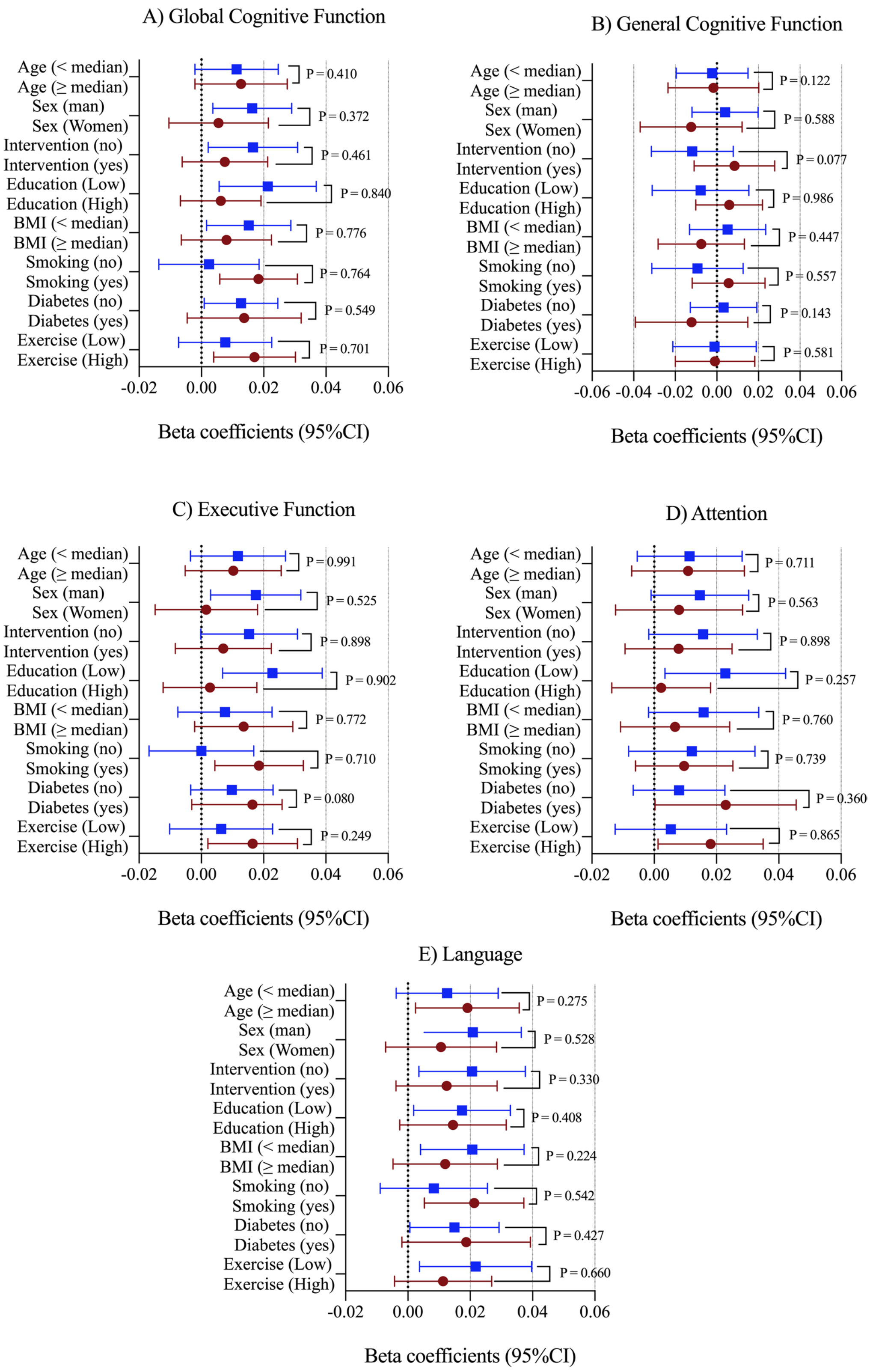
Robust variance estimators were utilized in all models to accommodate intra-cluster correlations, as couples from the same household were randomized together. To explore potential effect modification by age, sex, intervention group, educational level, BMI, smoking, type 2 diabetes status, and physical activity, we used the likelihood ratio test by comparing models with and without the multiplicative interaction term between these factors and energy-adjusted cumulative average dietary vitamin D intake within fully adjusted models. Sensitivity analyses were conducted to assess the robustness of the results, including the exclusion of individuals who met the following criteria at baseline: (1) MMSE <24 and (2) extreme percentiles of GCF z-scores ($<2.5\%$, $>97.5\%$).

All statistical analyses were conducted with Stata/SE version 14.2 (StataCorp LLC, College Station, TX, USA) using the PREDIMED-Plus study dataset updated to December 19, 2023. All graphs were plotted using GraphPad Prism software v.9.0 (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as a two-tailed P-value <0.05.

Results

Table 1 presents the baseline characteristics of the overall study population and by quartiles of energy-adjusted cumulative average dietary vitamin D intake over time. The energy-adjusted cumulative average daily dietary vitamin D intake ranged from 3.4 ± 1.5 µg/day in the lowest quartile to 9.3 ± 3.3 µg/day in the highest quartile (overall mean: 6.0 ± 3.4 µg/day). Participants in the highest quartile had a lower prevalence of hypertension, tended to take fewer anti-diabetic drugs, had a higher educational level, and engaged in more physical activity. Additionally, they exhibited higher baseline z-scores in global cognitive function, general cognitive function, executive function, and language (all $P \leq 0.047$; Table 1). In terms of dietary intake, participants in the highest quartile of energy-adjusted cumulative average dietary vitamin D intake consumed lower quantities of carbohydrates and higher amounts of protein, fat, fiber, vegetables, fruits, legumes, cereals, fish, nuts, oils and fats, olive oils, and alcohol compared to those in the lowest quartile (all $P \leq 0.014$; Table S2). Over a 2-year follow-up period, improvements in global cognitive function, general cognitive function, executive function, and language were observed, while a decline in the attention domain was noted over this time period across categories of dietary vitamin D intake (Table S3). However, this decline in attention was less pronounced in participants with the highest average dietary vitamin D intake (Table S3).

Table 2 displays the longitudinal associations (β coefficients and 95% CI) between energy-adjusted cumulative average dietary vitamin D intake and changes in cognitive function over the 2-year follow-up period. Results from multivariable adjusted models show significant positive associations between energy-adjusted cumulative average dietary vitamin D intake and 2-year beneficial changes in cognitive function. In particular, 1 µg/day higher energy-adjusted cumulative average dietary vitamin D intake was associated with more beneficial changes in global cognitive function (β 1.18×10^{-2}; 95% CI 0.19×10^{-2} to 2.17×10^{-2}; P 0.019), executive function (β 1.12×10^{-2}; 95% CI 0.03×10^{-2} to 2.21×10^{-2}; P 0.044), and language (β 1.61×10^{-2}; 95% CI 0.43×10^{-2} to 2.78×10^{-2}; P 0.007). Results from the potential nonlinearity exploration did not show any clear departure from the linearity of the associations (data



A) Global Cognitive Function

B) General Cognitive Function

C) Executive Function

D) Attention

E) Language

◂**Fig. 2** Interaction between energy-adjusted cumulative average dietary vitamin D intake and different baseline variables of the study potentially related to cognitive function. Abbreviations: BMI, body mass index; CI, confidence interval. Multivariable-adjusted models were adjusted for the respective cognitive test score at baseline, age (years), sex, intervention PREDIMED-Plus randomized groups, and participating center (south/north), 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), energy-adjusted cumulative average alcohol consumption in g/day (and adding the quadratic term), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), and energy-adjusted cumulative average consumption of food groups (vegetables, fruits, legumes, cereals, oils and fats, olive oils, biscuits, meat, fish, dairy, nuts [g/day], coffee and tea [mL/day]). Significant values ($P < 0.05$) were highlighted in bold type

not shown). Additionally, participants in the highest quartile of energy-adjusted cumulative average dietary vitamin D intake showed better cognitive function evolution after 2 years of follow-up than those in the lowest quartile, specifically, in global cognitive function (β 7.10 $\times 10^{-2}$; 95% CI 0.59 $\times 10^{-2}$ to 13.6 $\times 10^{-2}$; P-trend 0.025), attention (β 9.58 $\times 10^{-2}$; 95% CI 1.60 $\times 10^{-2}$ to 17.5 $\times 10^{-2}$; P-trend 0.039), and language (β 7.07 $\times 10^{-2}$; 95% CI – 0.52$\times$ 10^{-2} to 14.7 $\times 10^{-2}$; P-trend 0.039). However, no significant association between energy-adjusted cumulative average dietary vitamin D intake and general cognitive function was shown.

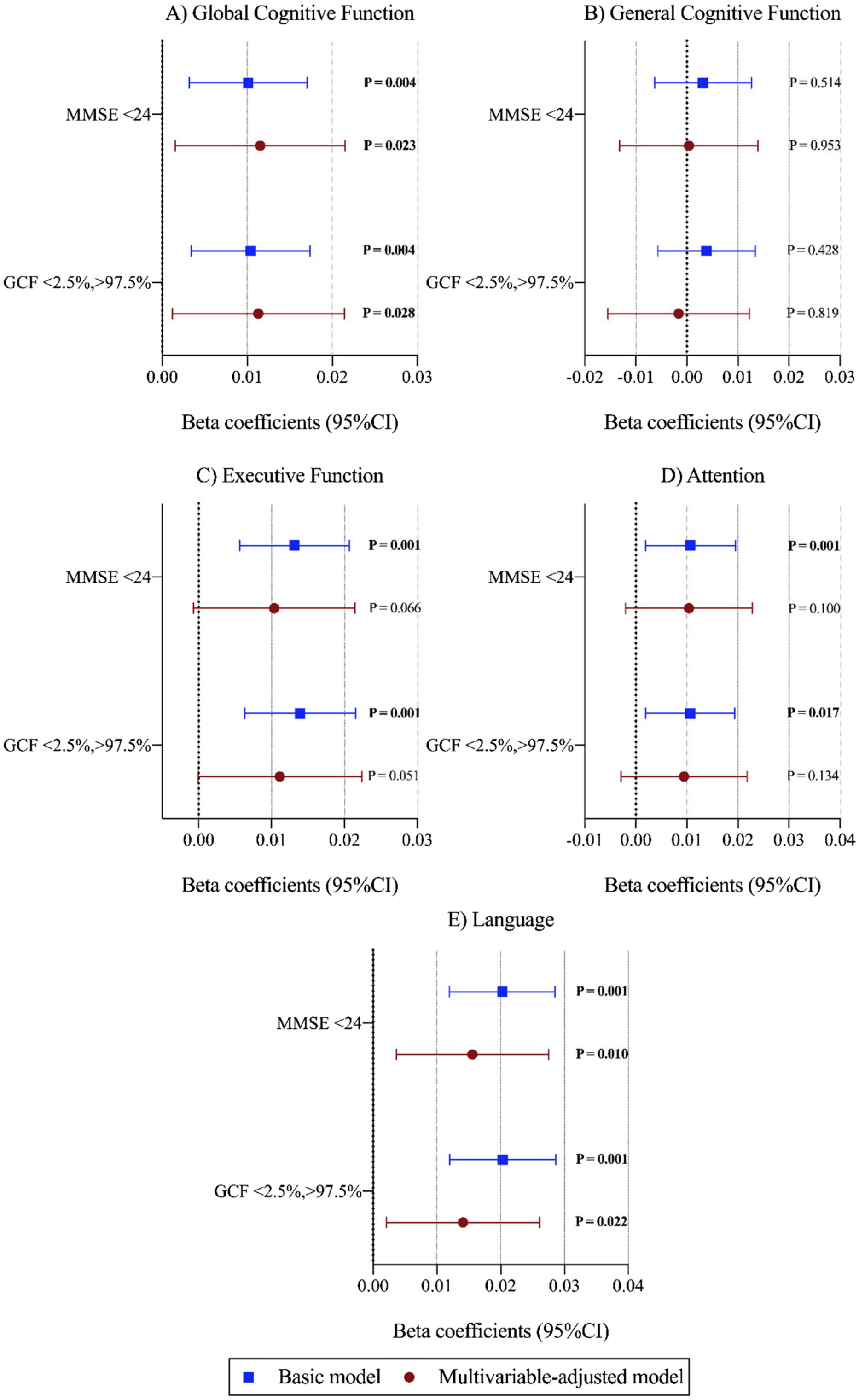
Figure 2 illustrates the results of the interaction analyses between energy-adjusted cumulative average dietary vitamin D intake and various baseline variables potentially related to cognitive function. No significant interactions were found between energy-adjusted cumulative average dietary vitamin D intake and categories of age, sex, intervention group, educational level, BMI, smoking status, type 2 diabetes, and physical activity across all assessed cognitive function domains (all $P \geq 0.080$; Fig. 2A–E).

Figure 3 shows the sensitivity analyses conducted to check the robustness of the associations explored between energy-adjusted cumulative average dietary vitamin D intake and changes in cognitive function over the 2-year period after excluding individuals with baseline MMSE < 24 and extreme percentiles ($< 2.5\%$, $> 97.5\%$) of GCF z-score. After adjusting for potential confounders and treating energy-adjusted cumulative average dietary vitamin D intake as a continuous variable, the results remained consistent with the main analyses shown in Table 2 for global, general cognitive, and executive function and language when removing individuals with baseline MMSE < 24 and extreme percentiles ($< 2.5\%$, $> 97.5\%$) of GCF z-score (Fig. 3A, B and D, E; Table S4). Regarding executive function, the significant associations observed in Table 2 were lost in both analyses (Fig. 3C; Table S4). Comprehensive details regarding sensitivity analyses, particularly those treating energy-adjusted cumulative average dietary vitamin D intake as a categorical variable, are provided in Table S4.

Discussion

The present study contributes to the limited body of longitudinal research investigating the prospective relationship between dietary vitamin D intake and cognitive function. It uniquely provides significant and novel findings over time in a population at high risk for cognitive decline, demonstrating positive associations with global cognitive function, executive function, and language domains, as well as a mitigated decline in the attention domain, even after adjusting for several potential confounders. Taken together, these findings underscore the importance of conducting clinical trials aimed at testing the effect of dietary vitamin D consumption on cognitive decline in older individuals vulnerable to cardiovascular diseases and cognitive impairment.

Cross-sectional studies examining the association between dietary vitamin D intake and cognitive function generally support a direct association, particularly in older individuals [14–17]. Conversely, in a cohort of women aged 80 years divided on the basis of inadequate or recommended weekly dietary vitamin D intake, a positive association between dietary vitamin D intake and cognitive function was observed only in those participants who met the recommendations [15]. Similarly, older adults over 60 years, grouped by inadequate or adequate daily dietary vitamin D intake, showed better cognitive function when their dietary vitamin D intake was adequate [14]. Additionally, in another study conducted in older individuals aged over 65 years with heart failure—a condition directly related to cognitive decline—each 1 µg/day increase in dietary vitamin D intake was reported to be cross-sectionally associated with


A) Global Cognitive Function
MMSE <24
GCF <2.5%,>97.5%
P = 0.004
P = 0.023
P = 0.004
P = 0.028
0.00
0.01
0.02
0.03
Beta coefficients (95%CI)
B) General Cognitive Function
MMSE <24
GCF <2.5%,>97.5%
P = 0.514
P = 0.953
P = 0.428
P = 0.819
-0.02
-0.01
0.00
0.01
0.02
0.03
Beta coefficients (95%CI)
C) Executive Function
MMSE <24
GCF <2.5%,>97.5%
P = 0.001
P = 0.066
P = 0.001
P = 0.051
0.00
0.01
0.02
0.03
Beta coefficients (95%CI)
D) Attention
MMSE <24
GCF <2.5%,>97.5%
P = 0.001
P = 0.100
P = 0.017
P = 0.134
-0.01
0.00
0.01
0.02
0.03
0.04
Beta coefficients (95%CI)
E) Language
MMSE <24
GCF <2.5%,>97.5%
P = 0.001
P = 0.010
P = 0.001
P = 0.022
0.00
0.01
0.02
0.03
0.04
Beta coefficients (95%CI)
■ Basic model
● Multivariable-adjusted model

◂**Fig. 3** Sensitivity analyses for the longitudinal association between energy-adjusted cumulative average dietary vitamin D intake and changes in cognitive function over a 2-year follow-up period in the PREDIMED-Plus cohort. Abbreviations: GCF, global cognitive function; MMSE, Mini-Mental State Examination. From the top to the bottom, removal of participants at baseline (1) with MMSE <24, (2) with extreme percentiles of GCF z-score ($<2.5\%$, $>97.5\%$). Basic models were adjusted for the respective cognitive test score at baseline, age (years), and sex. Multivariable-adjusted models were adjusted for the respective cognitive test score at baseline, age (years), sex, intervention PREDIMED-Plus randomized groups, and participating center (south/north), 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), energy-adjusted cumulative average alcohol consumption in g/day (and adding the quadratic term), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), and energy-adjusted cumulative average consumption of food groups (vegetables, fruits, legumes, cereals, oils and fats, olive oils, biscuits, meat, fish, dairy, nuts [g/day], coffee, and tea [mL/day]). Significant values ($P< 0.05$) were highlighted in bold type

an 8% higher cognitive performance, suggesting a dose–response effect [16]. Conversely, although no relationship between dietary vitamin D intake and cognitive function among frail older adults aged over 65 years has been previously reported, the authors attributed their findings to the low dietary vitamin D intake and a narrow range of intake within the study population [44].

Within the framework of our investigation, we observed that dietary vitamin D intake was associated with improvements in global cognitive function, executive function, and language, as well as less decline in the attention domain over a 2-year period. Of note, to help report the observed mean difference in age-equivalents for global cognitive function as a main outcome, the difference in changes in global cognitive function between the highest and the lowest group of cumulative average dietary vitamin D was roughly equivalent to 4.2 years of cognitive aging given consistent dietary vitamin D intake over time [45]. Regarding middle-aged cohorts, baseline dietary vitamin D intake, although positively associated with a limited subset of cognitive function domains both 5 years [19] and 13 years [18] thereafter, did not show a discernible relationship with any of the five cognitive function scores assessed in our study. Conversely, in relation to older populations, no prospective associations were reported between dietary vitamin D intake and cognitive function among men aged 70 years followed for 18 years [21], whereas within a cohort of women aged 80 years, higher baseline dietary vitamin D intake was associated with better cognitive function after 7 years of trajectories [20]. Although both investigations exclusively relied on the MMSE for cognitive assessment and solely measured dietary vitamin D intake at baseline, the cohort of males exhibited lower dietary vitamin D intakes, which may explain the lack of associations. The controversial results of the aforementioned studies may be attributed to methodological issues, including exclusive reliance on baseline dietary vitamin D exposure measurements, disparities between tools used for cognitive assessment [46], demographic heterogeneity of the studied population in relation to age, gender, geographic areas, the sample size, and the background of dietary vitamin D intake [47]. While the magnitude of the associations reported in our study may be considered of limited clinical relevance, it is important to note that our study consisted of older adults. Therefore, if such minimal differences can reveal a significant association, they may serve as a warning of cognitive impairment. Large-scale and well-designed longitudinal studies are warranted in the future to better elucidate a potential relationship between dietary vitamin D intake and cognitive function, especially in older adults at risk of vitamin D deficiency and cognitive decline [48].

The potential mechanisms underlying the correlations between dietary vitamin D intake and cognition have been the subject of proposed hypotheses. It is posited that lower dietary vitamin D intake may induce significant nitrosative stress within the brain, thereby potentially fostering cognitive decline among middle-aged and elderly individuals [49]. Adequate dietary vitamin D intake has also been reported to increase insulin sensitivity and reduce neuroinflammation in the brain, favoring cognitive function [50]. Given that the brain's vitamin D receptor is involved in cognitive function, maintaining a dietary vitamin D intake near recommended levels could enhance bloodstream vitamin D concentrations and, consequently, confer cognitive benefits [51].

However, when assessing these associations, it is imperative to consider the potential for reverse causality, wherein cognitive impairments or diminished autonomy could precipitate suboptimal dietary habits [18]. Furthermore, despite the pervasive issue of insufficient dietary vitamin D intake, attributable in part to the restricted availability of dietary sources rich in vitamin D [52], principally found in fish products and to a lesser extent in eggs, oils, bakery, and dairy products [53], the elderly population confronts an augmented susceptibility to vitamin D deficiency. This scenario may be further compounded by several factors, including lower dietary vitamin D intake and heightened dietary recommendations [54], decreased outdoor activity, diminished synthesis of vitamin D in the skin, and impaired hepatic and renal function, which diminish the activation of vitamin D [44]. In conjunction with the aging process, individuals who are overweight, as observed in our study, may require higher dietary vitamin D intake to potentially preserve cognitive function compared to their younger or normal-weight counterparts [47]. Healthcare practitioners are encouraged to regularly inform elderly patients and their caregivers—particularly those who are overweight—about the possible benefits of maintaining adequate dietary vitamin D intake, conduct assessments for potential vitamin D deficiency in the bloodstream, and offer guidance to ensure sufficient dietary vitamin D consumption [48]. Consequently, intervention studies exploring the effect of increased dietary vitamin D intake could help to clarify its potential physiological benefits on cognitive function [55].

Our study presents notable strengths. First, its longitudinal prospective design facilitated the observation of temporal associations over a 2-year follow-up period, although this design does not establish potential causal relationships. Second, the comprehensive assessment of cognitive function utilized a diverse array of neuropsychological tests, enabling the measurement of composite scores across multiple cognitive domains. Third, the study benefitted from a large sample size, affording the adjustment of statistical models for various potential confounding factors. Lastly, the robustness of the findings was corroborated through the execution of different sensitivity analyses. Nevertheless, our study findings should be interpreted in light of certain limitations. Firstly, the potential for reverse causality and residual confounding persists, particularly from unmeasured factors not accounted for in the analyses. Secondly, the generalizability of the results may be limited to older populations with overweight/obesity and metabolic syndrome, precluding extrapolation to other populations. Thirdly, the absence of data pertaining to blood 25(OH)D levels, kidney function, sun exposure, seasonality, and racial background represents a notable information gap. Fourthly, as PREDIMED-Plus is a randomized controlled trial, though all the analyses were adjusted for the intervention group, the lifestyle advice that participants received could be affecting our findings [31]. Of note, dietary patterns and physical activity have a direct impact on body weight that is also critical, as overweight or obesity are linked to cognitive decline [56]. Furthermore, although we employed the energy-adjusted cumulative average of dietary vitamin D intake using the residual method to better represent long-term intake and reduce within-person variation and measurement error, reliance on a FFQ to estimate dietary vitamin D intake introduces potential sources of measurement error and recall bias, particularly given its dependence on participants' memory and susceptibility to cognitive decline.

Conclusion

In conclusion, our results suggest that a higher dietary vitamin D intake is associated with modest, favorable changes in cognitive function and may help to mitigate cognitive decline in the short term in older adults not following vitamin D supplementation with overweight/obesity and metabolic syndrome. Further research in this area aimed at increasing dietary vitamin D intake is warranted, especially in individuals at risk of vitamin D deficiency and cognitive impairment, given the rapidly expanding elderly population and the absence of curative treatment for cognitive decline.

Acknowledgements The authors especially thank the PREDIMED-Plus participants for the enthusiastic collaboration, the PREDIMED-Plus personnel for outstanding support, and the personnel of all associated primary care centers for the exceptional effort. CIBEROBN, CIBERESP, and CIBERDEM are initiatives of Instituto de Salud Carlos III (ISCIII), Madrid, Spain.

Author contribution Héctor Vázquez-Lorente: writing—original draft, writing—review and editing, methodology, investigation, data curation, conceptualization. Jiaqi Ni: writing—original draft, writing—review and editing, methodology, formal analysis, data curation, conceptualization. Indira Paz-Graniel: writing—review and editing, methodology, formal analysis, data curation, conceptualization. Estefanía Toledo: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Dolores Corella: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Olga Castañer: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. J. Alfredo Martínez: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Ángel M. Alonso-Gómez: writing—review and editing, investigation, data curation, conceptualization. Julia Wärnberg: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Jesús Vioque: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Dora Romaguera: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. José López-Miranda: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Ramon Estruch: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Francisco J. Tinahones: writing—review and editing, investigation, data curation, conceptualization. José Lapetra: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Lluís Serra-Majem: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Amira Bouzalmate-Hajjaj: writing—review and editing, investigation, data curation, conceptualization. Josep A. Tur: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Rafael M. Micó Pérez: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Xavier Pintó: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Miguel Delgado-Rodríguez: writing—review and editing, investigation, data curation, conceptualization, funding acquisition.

Ana Barabash Bustelo: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Josep Vidal: writing—review and editing, investigation, data curation, conceptualization. Clotilde Vázquez: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Lidia Daimiel: writing—review and editing, investigation, data curation, conceptualization, funding acquisition. Emili Ros: writing—review and editing, investigation, data curation, conceptualization. Fernando Fernández-Aranda: writing—review and editing. Teresa Rognoni: writing—review and editing. Nancy Babio: writing—review and editing, methodology, formal analysis, data curation, conceptualization. Eva M. Asensio: writing—review and editing. Alejandra Pérez-Vega: writing—review and editing. Antonio García-Ríos: writing—review and editing. Laura Compañ-Gabucio: writing—review and editing. Raquel Cueto-Galán: writing—review and editing. M. Angeles Zulet: writing—review and editing. Mar Nafria: writing—review and editing. Rosa Casas: writing—review and editing. Naomi Cano-Ibáñez: writing—review and editing. Luis Tojal-Sierra: writing—review and editing. Ana María Gómez-Pérez: writing—review and editing. Nuria Goñi: writing—review and editing. José V. Sorli: writing—review and editing. María Dolores Zomeño: writing—review and editing. Antonio P. Arenas-Larriva: writing—review and editing. Pedro Jiménez-Sellés: writing—review and editing. Javier Basterra-Gortari: writing—review and editing. Montserrat Fitó: writing—review and editing. Jordi Salas-Salvadó: writing—original draft, writing—review and editing, visualization, validation, methodology, investigation, data curation, conceptualization, funding acquisition.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature. This study was supported by the official Spanish Institutions for Funding Scientific Biomedical Research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects led by JSS and JV, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, and PI20/01158); the Especial Action Project entitled "Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus" grant to JSS; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to MMG; the Recercaixa (number 2013 ACUP00194) grant to JSS; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, and PI0137/2018); the PROMETEO/21/2021 and the AICO/2021/347 grants from the Generalitat Valenciana; and the Horizon 2020 PRIME study (Prevention and Remediation of Insulin Multimorbidity in Europe; grant agreement #847879). HVL was funded by a research grant from the Agència de Gestió d'Ajuts Universitaris de Recerca via Unión Europea, Next Generation EU (AGAUR, record number: 2023POST-INV- 01). JN is supported by a predoctoral grant from Ministerio de Ciencia, Innovación y Universidades (FPU 20/00385). KAPV is granted by the ISCIII (Reference: IFI20/00002).

None of the funding sources took part in the design, collection, analysis, interpretation of the data, or writing the report, or in the decision to submit the manuscript for publication. JSS, senior author, gratefully acknowledges the financial support by ICREA under the ICREA Academia program.

Data availability Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval of the PREDIMED-Plus Steering Committee. There are restrictions on the availability of data for the PREDIMED-Plus trial due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

Declarations

Ethics approval and consent to participate The study protocol was approved by the Research Ethics Committees of all recruiting centers. In addition, all participants signed an informed consent form upon entry into the study.

Competing interests The authors declare no competing interests.

References

1. Ai F, Li E, Dong A, Zhang H. Association between disability and cognitive function in older Chinese people: a moderated mediation of social relationships and depressive symptoms. Front Public Health. 2024;12:1354877. https://doi.org/10.3389/fpubh.2024.1354877.
2. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022;7:e105-25. https://doi.org/10.1016/S2468-2667(21)00249-8.
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet Lond Engl. 2020;396:413–46. https://doi.org/10.1016/S0140-6736(20)30367-6.
4. Chen W, Sun X, Han J, Wu X, Wang Q, Li M, et al. Joint effect of abnormal systemic immune-inflammation index (SII) levels and diabetes on cognitive function and survival rate: a population-based study from the NHANES 2011–2014. PLoS One. 2024;19:e0301300. https://doi.org/10.1371/journal.pone.0301300.
5. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol. 2018;17:1006–15. https://doi.org/10.1016/S1474-4422(18)30338-7.
6. Byrn MA, Sheean PM. Serum 25(OH)D and cognition: a narrative review of current evidence. Nutrients. 2019;11:729. https://doi.org/10.3390/nu11040729.
7. Li D, Xu Y, Wang K, Yang Z, Li H, Lei S, et al. Maternal Vit D supplementation in AMA mice and the role of Vit D/VDR signaling in the offspring's cognition. Am J Transl Res. 2021;13:12650–61.
8. Denniss RJ, Barker LA, Day CJ. Improvement in cognition following double-blind randomized micronutrient interventions in the general population. Front Behav Neurosci. 2019;13:115. https://doi.org/10.3389/fnbeh.2019.00115.
9. Byrn MA, Adams W, Penckofer S, Emanuele MA. Vitamin D supplementation and cognition in people with type 2 diabetes: a randomized control trial. J Diabetes Res. 2019;2019:5696391. https://doi.org/10.1155/2019/5696391.
10. Benedik E. Sources of vitamin D for humans. Int J Vitam Nutr Res. 2022;92:118–25. https://doi.org/10.1024/0300-9831/a000733.
11. McDonnell SL, French CB, Heaney RP. Quantifying the food sources of basal vitamin D input. J Steroid Biochem Mol Biol. 2014;144:149–51. https://doi.org/10.1016/j.jsbmb.2013.10.017.

12 Qualheiro A, d´Orsi E, Moreira JD, Xavier AJ, Peres MA. The association between vitamin D and BDNF on cognition in older adults in Southern Brazil. Rev Saúde Pública. 2022;56:109. https://doi.org/10.11606/s1518-8787.2022056004134.

13. Macpherson H, Brownell S, Duckham RL, Meyer B, Mirzaee S, Daly RM. Multifaceted intervention to enhance cognition in older people at risk of cognitive decline: study protocol for the Protein Omega-3 and Vitamin D Exercise Research (PONDER) study. BMJ Open. 2019;9:e024145. https://doi.org/10.1136/bmjopen-2018-024145.
14. Wang R, Wang W, Hu P, Zhang R, Dong X, Zhang D. Association of dietary Vitamin D intake, serum 25(OH)D3, 25(OH)D2 with cognitive performance in the elderly. Nutrients. 2021;13:3089. https://doi.org/10.3390/nu13093089.
15. Annweiler C, Schott AM, Rolland Y, Blain H, Herrmann FR, Beauchet O. Dietary intake of vitamin D and cognition in older women: a large population-based study. Neurology. 2010;75:1810–6. https://doi.org/10.1212/WNL.0b013e3181fd6352.
16. Song EK, Wu J-R. Associations of vitamin D intake and sleep quality with cognitive dysfunction in older adults with heart failure. J Cardiovasc Nurs. 2018;33:392–9. https://doi.org/10.1097/JCN.0000000000000469.
17. Rondanelli M, Trotti R, Opizzi A, Solerte SB. Relationship among nutritional status, pro/antioxidant balance and cognitive performance in a group of free-living healthy elderly. Minerva Med. 2007;98:639–45.
18. Andreeva VA, Whegang-Youdom S, Touvier M, Assmann KE, Fezeu L, Hercberg S, et al. Midlife dietary vitamin D intake and subsequent performance in different cognitive domains. Ann Nutr Metab. 2014;65:81–9. https://doi.org/10.1159/000365154.
19. Beydoun MA, Hossain S, Fanelli-Kuczmarski MT, Beydoun HA, Canas J-A, Evans MK, et al. Vitamin D status and intakes and their association with cognitive trajectory in a longitudinal study of urban adults. J Clin Endocrinol Metab. 2018;103:1654–68. https://doi.org/10.1210/jc.2017-02462.
20. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Herrmann FR, et al. Higher vitamin D dietary intake

is associated with lower risk of Alzheimer's disease: a 7-year follow-up. J Gerontol Ser A. 2012;67:1205–11. https://doi.org/10.1093/gerona/gls107.

21. Olsson E, Byberg L, Karlström B, Cederholm T, Melhus H, Sjögren P, et al. Vitamin D is not associated with incident dementia or cognitive impairment: an 18-y follow-up study in community-living old men1, 2, 3. Am J Clin Nutr. 2017;105:936–43. https://doi.org/10.3945/ajcn.116.141531.
22. Beauchet O, Cooper-Brown LA, Allali G. Vitamin D supplementation and cognition in adults: a systematic review of randomized controlled trials. CNS Drugs. 2021;35:1249–64. https://doi.org/10.1007/s40263-021-00876-z.
23. Pham H, Waterhouse M, Rahman S, Baxter C, Romero BD, McLeod DSA, et al. Vitamin D supplementation and cognition—results from analyses of the D-Health trial. J Am Geriatr Soc. 2023;71:1773–84. https://doi.org/10.1111/jgs.18247.
24. da Silva AD, Oliveira JS, de Castro IC, Paiva WC, Gomes JMG, Pimenta LCJP. Association of vitamin D and cognition in people with type 2 diabetes: a systematic review. Nutr Rev. 2024;82:622–38. https://doi.org/10.1093/nutrit/nuad085.
25. Harse JD, Marriott RJ, Zhu K, Murray K, Bucks RS. Vitamin D status and cognitive performance in community-dwelling adults: a dose-response meta-analysis of observational studies. Front Neuroendocrinol. 2023;70:101080. https://doi.org/10.1016/j.yfrne.2023.101080.
26. Owusu JE, Islam S, Katumuluwa SS, Stolberg AR, Usera GL, Anwarullah AA, et al. Cognition and vitamin D in older African-American women– physical performance and osteoporosis prevention with vitamin D in older African Americans trial and dementia. J Am Geriatr Soc. 2019;67:81–6. https://doi.org/10.1111/jgs.15607.
27. Hoeft B, Weber P, Eggersdorfer M. Micronutrients - a global perspective on intake, health benefits and economics. Int J Vitam Nutr Res Int Z Vitam- Ernahrungsforschung J Int Vitaminol Nutr. 2012;82:316–20. https://doi.org/10.1024/0300-9831/a000125.
28. Zhao W, Zhu D, Li S, Cui S, Jiang P, Wang R, et al. The reduction of vitamin D in females with major depressive disorder is associated with worse cognition mediated by abnormal brain functional connectivity. Prog Neuropsychopharmacol Biol Psychiatry. 2022;118:110577. https://doi.org/10.1016/j.pnpbp.2022.110577.
29. Martínez-González MÁ, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, et al. Cohort profile: design and methods of the PREDIMED study. Int J Epidemiol. 2012;41:377–85. https://doi.org/10.1093/ije/dyq250.
30. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, Basora J, Fitó M, Corella D, et al. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus trial. Diabetes Care. 2019;42:777–88. https://doi.org/10.2337/dc18-0836.
31. Sayón-Orea C, Razquin C, Bulló M, Corella D, Fitó M, Romaguera D, et al. Effect of a nutritional and behavioral intervention on energy-reduced Mediterranean diet adherence among patients with metabolic syndrome: interim analysis of the PREDIMED-Plus randomized clinical trial. JAMA. 2019;322:1486–99. https://doi.org/10.1001/jama.2019.14630.
32. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.
33. Willett W. Nutritional epidemiology. Oxford University Press; 2012. https://doi.org/10.1093/acprof:oso/9780199754038.001.0001.
34. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103:1808–16. https://doi.org/10.1017/S0007114509993837.
35. Moreiras O, Carbajal A, Cabrera L, Cuadrado C. Tablas De Composicion De Alimentos. 10 th ed. Editorial Piramides; 2005. n.d.
36 Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65:1220S-1228S. https://doi.org/10.1093/ajcn/65.4.1220S. (discussion 1229S-1231S).
37. Ni J, Nishi SK, Babio N, Ros E, Basterra-Gortari FJ, Corella D, et al. Higher versus lower nut consumption and changes in cognitive performance over two years in a population at risk of cognitive decline: a cohort study. Am J Clin Nutr. 2023;118:360–8. https://doi.org/10.1016/j.ajcnut.2023.05.032.
38. Nooyens ACJ, Baan CA, Spijkerman AMW, Verschuren WMM. Type 2 diabetes and cognitive decline in middle-aged men and women: the Doetinchem Cohort Study. Diabetes Care. 2010;33:1964–9. https://doi.org/10.2337/dc09-2038.
39. Duff K. Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. Arch Clin Neuropsychol Off J Natl Acad Neuropsychol. 2012;27:248–61. https://doi.org/10.1093/arclin/acr120.
40. Molina L, Sarmiento M, Peñafiel J, Donaire D, Garcia-Aymerich J, Gomez M, et al. Validation of the Regicor Short Physical Activity Questionnaire for the adult population. PLoS One. 2017;12:e0168148. https://doi.org/10.1371/journal.pone.0168148.
41. Sanz Fernández J, Vázquez Valverde C, Perdigón AL. Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): 2. Propiedades psicométricas en población general. Clín Salud Investig Empírica En Psicol. 2003;14:249–80.
42. Wu J. Beck depression inventory-second edition. Natl Child Trauma Stress Netw 2017. https://www.nctsn.org/measures/beck-depression-inventory-second-edition Accessed 8 May 2024
43. Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci. 1996;11:89–121. https://doi.org/10.1214/ss/1038425655.
44. Brouwer-Brolsma EM, van de Rest O, Tieland M, van der Zwaluw NL, Steegenga WT, Adam JJ, et al. Serum 25-hydroxyvitamin D is associated with cognitive executive

function in Dutch prefrail and frail elderly: a cross-sectional study exploring the associations of 25-hydroxyvitamin D with glucose metabolism, cognitive performance and depression. J Am Med Dir Assoc. 2013;14(852):e9-17. https://doi.org/10.1016/j.jamda.2013.06.010.

45 Sala-Vila A, Valls-Pedret C, Rajaram S, Coll-Padrós N, Cofán M, Serra-Mir M, et al. Effect of a 2-year diet intervention with walnuts on cognitive decline. The Walnuts and Healthy Aging (WAHA) study: a randomized controlled trial. Am J Clin Nutr. 2020;111:590–600. https://doi.org/10.1093/ajcn/nqz328.

46. Lewis JE, Poles J, Shaw DP, Karhu E, Khan SA, Lyons AE, et al. The effects of twenty-one nutrients and phytonutrients on cognitive function: a narrative review. J Clin Transl Res. 2021;7:575–620.

47. Lefèvre-Arbogast S, Dhana K, Aggarwal NT, Zhang S, Agarwal P, Liu X, et al. Vitamin D intake and brain cortical thickness in community-dwelling overweight older adults: a cross-sectional study. J Nutr. 2021;151:2760–7. https://doi.org/10.1093/jn/nxab168.

48. Li J. Higher vitamin D intake could improve sleep and cognitive outcomes in older adults with heart failure. Evid Based Nurs. 2018;21:69. https://doi.org/10.1136/eb-2018-102947.

49. Keeney JTR, Förster S, Sultana R, Brewer LD, Latimer CS, Cai J, et al. Dietary vitamin D deficiency in rats from middle to old age leads to elevated tyrosine nitration and proteomics changes in levels of key proteins in brain: implications for low vitamin D-dependent age-related cognitive decline. Free Radic Biol Med. 2013;65:324–34. https://doi.org/10.1016/j.freeradbiomed.2013.07.019.

50. Hardatt D, Devi M, Vyas S, Singh G, Jain J, Gupta S, et al. Effect of vitamin D on retinoblastoma protein in prediabetic individuals. Curr Diabetes Rev. 2024;20:e310323215281. https://doi.org/10.2174/1573399819666230331083715.

51. Rowe K, Bröcker E, Suliman S, Blaauw R, Seedat S, van den Heuvel LL. The relationship between nutrient intake and executive function in adults with post-traumatic stress disorder. J Affect Disord. 2024;349:125–31. https://doi.org/10.1016/j.jad.2024.01.065.

52. Lambrinoudaki I, Ceasu I, Depypere H, Erel T, Rees M, Schenck-Gustafsson K, et al. EMAS position statement: diet and health in midlife and beyond. Maturitas. 2013;74:99–104. https://doi.org/10.1016/j.maturitas.2012.10.019.

53 Buckinx F, Aubertin-Leheudre M. Nutrition to prevent or treat cognitive impairment in older adults: a GRADE recommendation. J Prev Alzheimers Dis. 2021;8:110–6. https://doi.org/10.14283/jpad.2020.40.

54. Rivan NFM, Shahar S, Rajab NF, Singh DKA, Che Din N, Mahadzir H, et al. Incidence and predictors of cognitive frailty among older adults: a community-based longitudinal study. Int J Environ Res Public Health. 2020;17:1547. https://doi.org/10.3390/ijerph17051547.

55. Goodman S, Morrongiello B, Meckling K. A randomized, controlled trial evaluating the efficacy of an online intervention targeting vitamin D intake, knowledge and status among young adults. Int J Behav Nutr Phys Act. 2016;13:116. https://doi.org/10.1186/s12966-016-0443-1.

56. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016;45:14–21. https://doi.org/10.1093/ageing/afv151.