TITLE PAGE

Title of the article

Interplay between cognition and weight reduction in individuals following a Mediterranean Diet: three-year follow-up of the PREDIMED-Plus trial

Author's names

Natalia Soldevila-Domenech[†1], Laura Forcano[†2], Cristina Vintro-Alcaraz[3], Aida Cuenca-Royo[4], Xavier Pintó[5], Susana Jiménez-Murcia[6], Jesús F García-Gavilán[7], Stephanie K Nishi[8], Nancy Babio[9], Maria Gomis-González[10], Dolores Corella[11], Jose V. Sorlí[12], Rebeca Fernandez-Carrión[13], Miguel Ángel Martínez-González[14], Amelia Marti[15], Jordi Salas-Salvadó[16], Olga Castañer[17], Fernando Fernandez-Aranda[18]*, Rafael de la Torre[19]*.

Author's affiliations

1. Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), 08003, Barcelona, Spain. Department of Experimental and Health Sciences, Universitat Pompeu Fabra, 08003, Barcelona, Spain. Email: nsoldevila@imim.es. ORCID iD: https://orcid.org/0000-0001-6024-8508
2. Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), 08003, Barcelona, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: lforcano@imim.es. ORCID iD: https://orcid.org/0000-0002-8478-1451
3. Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain. Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: cvintro@bellvitgehospital.cat. ORCID iD: https://orcid.org/0000-0001-9453-8810
4. Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), 08003, Barcelona, Spain. Email: acuenca@imim.es. ORCID iD: https://orcid.org/0000-0001-8551-5457
5. Lipid Unit, Department of Internal Medicine, Bellvitge Biomedical Research Institute (IDIBELL)-Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, 08908, Barcelona, Spain. CIBER

Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: xpinto@bellvitgehospital.cat. ORCID iD: https://orcid.org/0000-0002-2216-2444

6. Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain. Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain. Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: sjimenez@bellvitgehospital.cat. ORCID iD: https://orcid.org/0000-0002-3596-8033
7. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana. Reus, Spain. Institut d'Investigació Sanitària Pere Virgili (IISPV). Hospital Universitari San Joan de Reus. Reus, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: jesusfrancisco.garcia@iispv.cat. ORCID iD: https://orcid.org/0000-0003-2700-7459
8. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana. Reus, Spain. Institut d'Investigació Sanitària Pere Virgili (IISPV). Hospital Universitari San Joan de Reus. Reus, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: stephanie.nishi@urv.cat. ORCID iD: https://orcid.org/0000-0002-7878-5368
9. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana. Reus, Spain. Institut d'Investigació Sanitària Pere Virgili (IISPV). Hospital Universitari San Joan de Reus. Reus, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: nancy.babio@urv.cat. ORCID iD: https://orcid.org/0000-0003-3527-5277
10. Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), 08003, Barcelona, Spain. Email: mgomis@imim.es. ORCID iD: https://orcid.org/0000-0001-9778-4849
11. Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, 46010 Valencia, Spain. CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: dolores.corella@uv.es ORCID iD: https://orcid.org/0000-0002-2366-4104

12. Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, 46010 Valencia, Spain. CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: jose.sorli@uv.es ORCID iD: https://orcid.org/0000-0002-0130-2006
13. Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, 46010 Valencia, Spain. CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: rebeca.fernandez@uv.es
14. University of Navarra, Department of Preventive Medicine and Public Health, Pamplona, Spain. Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition, Instituto de Salud Carlos III, Madrid, Spain. Navarra's Health Research Institute (IdiSNA), Pamplona, Spain. Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA. Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA. Email: mamartinez@unav.es
15. University of Navarra, Department of Nutrition, Food Sciences and Physiology, Pamplona, Spain. Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition, Instituto de Salud Carlos III, Madrid, Spain. Navarra's Health Research Institute (IdiSNA), Pamplona, Spain. Email: amarti@unav.es
16. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana. Reus, Spain. Institut d'Investigació Sanitària Pere Virgili (IISPV). Hospital Universitari San Joan de Reus. Reus, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: jordi.salas@urv.cat. ORCID iD: https://orcid.org/0000-0003-2700-7459
17. Cardiovascular Risk and Nutrition Research Group, Hospital del Mar Medical Research Institute (IMIM), 08003, Barcelona, Spain. Endocrinology Service. Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), 08003, Barcelona, Spain. Consorcio CIBER, M.P. Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain. Email: ocastaner@imim.es. ORCID iD: https://orcid.org/0000-0003-3169-997X
18. Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain. Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain. Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. CIBER Fisiopatología Obesidad

y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: ffernandez@bellvitgehospital.cat. ORCID iD: https://orcid.org/0000-0002-2968-9898

19. Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain. CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain. Email: rtorre@imim.es. ORCID iD: https://orcid.org/0000-0002-6765-1866

†Shared first co-authorship.

*Shared corresponding authorship.

Corresponding authors' name

Rafael de la Torre Fornell, PharmD, PhD

Neurosciences Research Programme, Hospital del Mar Medical Research Institute (IMIM)

Dr Aiguader 88, 08003 Barcelona, Spain

Phone: +34 933 160 484

Email: rtorre@imim.es

ORCID iD: https://orcid.org/0000-0002-6765-1866

Fernando Fernández-Aranda, PhD., FAED

Department of Psychiatry, University Hospital of Bellvitge

Feixa Llarga, 08907 Hospitalet del Llobregat, Barcelona, Spain,

Phone: +34 932 607 227

Email: ffernandez@bellvitgehospital.cat

ORCID iD: http://orcid.org/0000-0002-2968-9898

ABSTRACT

Background & aims: Some cognitive profiles might facilitate successful weight loss and its maintenance. Also, weight reductions may result in cognitive benefits. However, little work to date has examined the interactions between cognition and weight changes in the context of interventions with the Mediterranean diet (MedDiet). We studied the within-subject longitudinal relationships between cognition, body mass index (BMI), physical activity (PA), and quality of life (QoL), in older adults following a MedDiet.

Methods: The PREDIMED-Plus is a primary prevention trial testing the effect of a lifestyle intervention program with an energy-restricted MedDiet (er-MedDiet), weight-loss goals and PA promotion on cardiovascular disease. The PREDIMED-Plus-*Cognition* sub-study included 487 participants (50% women, mean age 65.2 years +/-4.7), with overweight/obesity, metabolic syndrome and normal cognitive performance at baseline. A comprehensive neurocognitive test battery was administered at baseline and after 1 and 3 years.

Results: Baseline higher performance in verbal memory (OR=1.5; 95%CI 1.0, 2.1), visuoconstructive praxis and attention (OR=1.5; 95%CI 0.9, 2.3), and inhibition (OR=1.3; 95%CI 0.9, 1.9) were associated with a higher odd of achieving at least 8% weight loss after 3 years follow-up in participants randomized to the intervention group. There were moderate improvements in specific tests of memory and executive functions during follow-up. Higher adherence to the er-MedDiet was associated with greater improvements in memory. Women exhibited lower rates of change in global cognition, PA and QoL. Moreover, improvements in memory correlated with reductions in BMI after 1 year (β_{STD}=-0.14) and with improvements in PA after 3 years (β_{STD}=0.13). Finally, participants who experienced greater improvements in executive functions and global cognition also experienced greater improvements in their QoL.

Conclusions: This study refines the understanding of the determinants and mutual interrelationships between longitudinally-assessed cognitive performance and weight loss, adding further evidence to the cognitive benefits associated with better adherence to a MedDiet. Our results also suggest that weight loss interventions tailored to the cognitive profile and gender of participants are promising avenues for future studies.

KEYWORDS (max 6):

Mediterranean Diet; Nutrition; Cognition; Metabolic Syndrome; Obesity; Prevention.

INTRODUCTION

According to the World Health Organization, in 2016 39% of worldwide adults had overweight and 13% had obesity (1). This represents a global health concern as overweight and obesity are associated with increased risk of type 2 diabetes, metabolic syndrome, cardiovascular disease and many types of cancer (2). Also, high levels of adiposity negatively influence brain structure and function, increasing the risk of cognitive decline and dementia (3–6).

Conversely, moderate weight reductions have shown to improve multiple metabolic factors such as blood pressure, glucose tolerance, insulin sensitivity, lipid profile, oxidative stress and inflammation, and positively impact mental health and quality of life (QoL) (7,8). Congruently, the treatment of choice for overweight/obesity is weight reduction, commonly through comprehensive lifestyle interventions involving dietary counseling, physical activity (PA) and behavioral change strategies (2). However, although the majority of these interventions show a successful degree of weight loss in the short term (9), a considerable proportion of patients fail to adhere to these treatments and those who achieve optimal weight do not succeed on maintaining it in the long run (10).

The ability to adhere to a healthy lifestyle and achieve weight loss maintenance could be influenced by psychological and cognitive factors (11), including the capacity to self-regulate, the ability to direct one's attention and behavior and the successful achievement of long-term goals. However, individuals with overweight or obesity can present some cognitive alterations that may interfere with the successful follow-up of lifestyle interventions. Accordingly, the most consistent findings are related to measures of executive functions, including impairments in cognitive flexibility, impulsivity/inhibition, attentional bias, decision-making or working memory (12–17), although some authors have also identified alterations in memory, psychomotor speed and complex attention (18,19). As such, cognitive performance could influence the skills required to maintain a healthy lifestyle, but further research is needed to identify key cognitive predictors of weight loss maintenance.

Some lifestyle behaviors such as adherence to specific healthy dietary patterns like the Mediterranean diet (MedDiet) or similar (i.e. DASH or MIND diet) (8,20–24) and PA engagement (25–27) have been associated with slower rates of cognitive decline, reduced risk of dementia and improvements in some cognitive functions. Additionally, weight loss has been associated with improvements in executive/attention functioning and memory (24).

Consequently, interactions between changes in cognition, weight and behavior raise important issues when conducting interventions for weight loss. Some cognitive profiles may influence weight loss and, in turn, weight loss is likely to represent benefits for cognitive performance (14). Nevertheless, evidence on the interplay between cognition and weight reduction is scarce: some studies have focused on the effects of baseline cognitive performance on weight reduction (28,29) and other studies have reported the effects of weight reduction interventions on cognitive performance (24,30). Thus, longitudinal assessments with repeated measurements are needed to better capture the temporal dynamics between cognitive function and weight changes. These kinds of analyses can better test causal hypotheses about the direction of associations, the temporal precedence of their emergence, and the likely consequences of interventions. We postulate that these interactions over time have to be evaluated at the individual level, as there is a wide between-subject variability in responses to any weight loss intervention.

In this context, we present the first prospective results from the *PREDIMED-Plus-Cognition* sub-study (31), focusing on psychological and neuropsychological factors related to intervention adherence and success, considered the achievement of a reduction in baseline body weight of at least 8% as established in the PREDIMED-Plus study protocol. This study had four main objectives: to evaluate which cognitive profiles are associated with the achievement of the 8% body/weight reduction goal and to examine whether MedDiet adherence mediates this relationship, to study the presence of changes in the cognitive performance after 1 and 3 years of exposure to a MedDiet intervention, to identify which individual characteristics may influence the heterogeneity of cognitive changes and to study the presence of within-subject directional associations between cognition and BMI, PA, metabolic syndrome and QoL. Specifically, we were interested in evaluating whether changes in cognition correlate with changes in BMI, PA, metabolic syndrome features and QoL, whether baseline cognitive performance influence changes in these outcomes and vice-versa, whether baseline levels of BMI, PA, metabolic syndrome and QoL predict changes in cognition.

METHODS

Study design and participants

The present study is a longitudinal analysis restricted to a subset of participants of the large PREDIMED-Plus trial included in the PREDIMED-Plus-*Cognition* sub-study (N=487). The study design and procedures of PREDIMED-Plus have been previously described in detail (31–33). Further details on the study inclusion/exclusion criteria as well as the study protocol are available at http://predimedplus.com/.

Briefly, the PREDIMED-Plus is a multi-center randomized parallel-group primary prevention trial (N=6,874) designed to assess and compare the long-term effectiveness of an intensive lifestyle intervention with an energy-restricted Mediterranean diet (er-MedDiet, 30% calorie reduction), PA promotion and behavioral support of weight loss goals (intervention group, IG), with a more common care intervention featuring energy-unrestricted traditional MedDiet recommendations (control group, CG). Participants in both the IG and CG were provided with an allotment of extra-virgin olive oil (1 L/mo) and occasionally almonds (125 g/mo) for free, in order to promote the MedDiet and encourage compliance with the trial. Participants were recruited between October 2013 and December 2016 across 23 Spanish hospitals, universities and research institutes. Participants were randomly assigned, in a 1:1 ratio, to IG or CG. The intervention is scheduled to last for 6 years plus a 2 years follow-up without intervention. Eligible participants were community-dwelling overweight/obese adults (BMI between 27 and 40 kg/m^2) from Primary Care Health Centers of the Spanish National Health System aged between 55 and 75 years in case of men and between 60 and 75 years in women who met at least three criteria for metabolic syndrome (34). The clinical trial is registered at the International Standard Randomized Controlled Trial database (ISRCTN; 89898870).

Within the PREDIMED-Plus-*Cognition* sub-study, an in-depth assessment of the cognitive performance was performed in a sample of 487 individuals from 4 study sites (Cardiovascular Risk and Nutrition Research Group, Endocrinology Service, Hospital del Mar Medical Research Institute, Barcelona, Spain; Rovira i Virgili University, Department of Biochemistry and Biotechnology, Human Nutrition Unit, Sant Joan University Hospital, Pere Virgili Institute for Health Research, Reus, Spain; Department of Preventive Medicine, University of Valencia, University Jaume I, Conselleria de Sanitat de la Generalitat Valenciana, Valencia, Spain; Department of Psychiatry, Bellvitge University Hospital, Barcelona, Spain). Individuals willing to participate in this sub-study underwent an additional neuropsychological assessment at baseline, 1 and 3 years after the initiation of the assigned PREDIMED-Plus intervention. Exclusion criteria for the present study are included in **Supplementary Table 1**. The data were analyzed using the PREDIMED-Plus-*Cognition* database dated 14th January 2021. All participants gave written informed consent. The study protocol was approved by the local Research Ethics Committees from the participating centers and adheres to the standards of the WAMA Declaration of Helsinki.

Outcomes and assessments

Cognitive performance

Cognitive performance was evaluated by trained neuropsychologists and included the following cognitive domains: (i) *Short-term and long-term auditory memory*, using the Rey's Auditory-Verbal Learning Test (RAVLT) (35,36). Participants are given a list of 15 unrelated words (A), each followed by an attempted recall, followed by a second 15-word interference list (B), and again by list A (immediate recall). After 30 minutes, delayed recall is tested. (ii) *Visuoconstructive praxis, short- and long-term visuospatial memory and visual perception*, evaluated with the Rey–Osterrieth complex figure Test (RCFT) (37). The RCTF consists of four test conditions: copy, immediate recall, delayed recall and recognition. First, subjects are given the stimulus card and asked to draw the same figure (copy) and subsequently instructed to draw from memory (immediate recall). After a delay of 30 min, they are required to draw the same figure once again (delayed recall). Finally, subjects have to recognize the pieces of the figure between other distractor pieces (recognition). (iii) *Processing speed* (attention, visual scanning, motor speed, and memory), evaluated with the Symbol Digit Modalities Test (SDMT) (38,39). A coding key is presented, consisting of nine meaningless geometric designs, each paired with a number. The subject must scan the key and write down the number corresponding to each design as rapidly as possible in 90 seconds. The number of correct responses is recorded. The maximum score is 110. (iv) *Inhibition and attention* (mental flexibility and interference resistance), evaluated with the Stroop Color-Word Interference Test (40). This test consists of three printed sheets with 100 words in each, distributed in 5 columns. Participants are allowed to read each sheet for 45 seconds and the total number of words read is recorded. Errors are discounted for the total of words in each part. Three scores are obtained: Stroop-W (word reading), Stroop-C (name of the color) and Stroop-WC (word-color interference). The Stroop-WC score is considered in our analyses. (v) *Decision-making abilities* (risk and reward and punishment values), evaluated with the Iowa Gambling Task (IGT) (41). The subject has to select 100 cards from four decks (A, B, C and D). Following the selection of a card, the subject either gains or loses money. The final objective of the task is to gain as much money as possible. This test is scored by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. Higher results point to better performance while negative results point to preference for the not advantageous decks. This test was not administered to participants recruited in the University of Valencia (N=70). (vi) *Inattentiveness, impulsivity, sustained attention and vigilance*, evaluated with the Conners' Continuous Auditory Test of Attention (CPT) (42). Respondents are required to push the spacebar when any letter, except "X", appears in the screen for 14 minutes. Omission and commission errors and hit reaction time (HRT) scores were

used for the analyses. This test was not administered to participants recruited in the University of Valencia (N=70).

Premorbid intelligence quotient (IQ) was estimated (only at baseline) with The Vocabulary test (43), a verbal test that measures word knowledge and the ability to express definitions of words verbally. Finally, a cognitive screening was also included at baseline using the Folstein Mini-Mental State Examination (MMSE) (44) which assesses attention and orientation, memory, registration, recall, calculation, language and ability to draw a complex polygon. It has 11 items and scores can range from 1 to 30. Scores over 24 define 'normal' cognitive function.

Anthropometry and cardiovascular biomarkers

Weight, height, hip and waist circumference were measured by nurses with standardized procedures. For descriptive purposes, BMI (kg/m^2) was also categorized using general population cut-off values based on morbidity and mortality studies of Caucasian population (45): normo-weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obesity I (BMI 30.0-34.9 kg/m^2) and obesity II (BMI 35.0-39.9 kg/m^2).

Blood pressure was measured in triplicate using a validated semiautomatic oscillometer (Omron HEM 297 705C). Blood samples were collected after an overnight fast to determine levels of fasting blood glucose, glycosylated hemoglobin (HbA1c), and lipid levels: triglycerides, total cholesterol and HDL cholesterol using standard methodology. LDL cholesterol concentrations were calculated with the Friedewald formula whenever triglycerides were inferior to 300 mg/dL.

Finally, baseline type 2 diabetes was defined by previous clinical diagnosis of diabetes or HbA1c $\geq$ 6.5% or use of anti-diabetic medication or use of insulin or fasting plasma glucose >126 mg/dL. Those without a diagnosis of diabetes were diagnosed with prediabetes if their fasting plasma glucose levels were between 100-125 mg/dL at both the screening visit and baseline visit, and their HbA1c levels were between 5.7-6.4%.

Intervention adherence

Adherence to the er-MedDiet was evaluated with a 17-item er-MEDAS questionnaire, an adapted version of the validated 14-item PREDIMED questionnaire (46). Values ranged 0-17 and were categorized using the cut-off values from previous studies based on approximate tertiles in the overall baseline PREDIMED-Plus sample (47), as low (0-7 points), moderate (8-10 points) and high (11-17 points) adherence. On the other hand, leisure-time PA levels (measured as metabolic equivalent tasks –METs-

minute/week) were evaluated with the Minnesota REGICOR Short PA questionnaire (VREM) (48). PA categories were obtained from the Rapid Assessment of PA (RAPA) questionnaire (49).

Mental health and QoL

The Beck's Depression Inventory-II (BDI-II) (50,51) was used to assess the severity of depressive symptoms and was categorized according to general guidelines as no or minimal depression (0-9 points), mild-to-moderate depression (10-18 points), moderate-to-severe depression (19-29 points) and severe depression (≥30 points). Health-related QoL was measured with the Spanish version of the SF-36 questionnaire (52).

Statistical analyses

All analyses were performed in the overall population (N=487) except for the analyses of cognitive predictors of at least 8% weight reduction and high er-MedDiet adherence, which were performed only in participants randomized to the IG (N=240). Descriptive statistics of study variables in each time point (hereafter in this section, baseline=T0, 1 year=T1 and 3 years=T3) were obtained as mean and standard deviation (SD) or 95% confidence intervals (95%CI) for continuous variables and percentages for categorical variables. Multivariable-adjusted logistic regression models with robust standard errors were used to study the associations between baseline cognitive scores and the probability of achieving the goal of at least 8% weight reduction and high er-MedDiet adherence at T1 and T3 among individuals randomized to the IG. Such models were adjusted by gender, age, years of education, baseline weight, IQ, use of treatment for high cholesterol, use of tranquilizers or sedatives, prediabetes, diabetes and current smoking status. Causal mediation analyses (53) were used to determine whether er-MedDiet adherence at T1 (mediator) explained the association between baseline cognitive scores (exposure) and 8% weight reduction at T1 and T3 (outcome). Total effects were decomposed into direct and indirect effects transmitted via the mediator. Average direct effects (ADE), average causal mediation effects (ACME) and proportion of mediation effects (ratio between ACME and total effects) were reported. The latter parameter indicates how much the total effect of baseline cognition on 8% weight reduction operates through high er-MedDiet adherence and vice-versa, the proportion of total effect that remains unexplained by high er-MedDiet adherence. 95%CI in mediation analyses were computed using a quasi-Bayesian approximation with 1000 Monte-Carlo simulations.

To study overall changes in cardiovascular biomarkers, PA, QoL and cognition, T1 and T3 mean changes from baseline were analyzed using linear mixed effects models, with participant and study site included

as random effects, and adjusting for the following covariates: intervention group, gender, age, years of education, IQ, use of treatment for high cholesterol, use of tranquilizers or sedatives, prediabetes, diabetes, current smoking status and baseline weight (only for cognitive outcomes). Additionally, standardized mean differences for changes at T1 and T3 were computed as Cohen's d with cut-offs for effect size interpretation as of 0.2 (small), 0.5 (medium), 0.8 (large) and 1.2 (very large) (54,55).

Within-subject directional associations between cognition and BMI, PA, metabolic syndrome (METSYN) and QoL were estimated using bivariate latent change score models (BLCSM), a class of structural equation modeling (SEM) that can be used to test a wide range of developmental processes (56,57). **Supplementary Table 2** includes a detailed description of BLCSM analyses and the treatment of missing data. Briefly, changes in cognition (global cognition, memory and executive functions and attention), QoL and METSYN were modeled in latent scores rather than in observed scores. The latent variable 'memory' included the following 5 scores (standardized on baseline mean and SD and normalized if necessary): RAVTL immediate recall; RAVTL delayed recall; RCFT immediate recall; RCFT delayed recall; RCFT recognition. The latent variable 'executive functions' included the following 7 scores: RCFT copy; SDMT; Stroop interference; CPT-omission errors; CPT-commission errors; CPT-HRT; and IGT. Finally, the latent variable 'global cognition' included all the 12 scores from memory and executive functions. This multivariate latent variable approach is preferable to computing composite score because it is more robust and powerful in the presence of intermittently missing completing at random (MCAR) scenarios (58). BLCSM were used to test evidence for 4 possible relationships that, exemplified with T0-T1 bivariate changes in BMI and global cognition such relationships were: i) baseline covariance (labeled as δ_1) (*are scores on global cognition at T0 correlated with BMI at T0?),* ii) global cognition as leading variable of BMI changes (labeled as Υ_1) (*do global cognition scores at T0 predict degree of change in BMI between T0 and T1?*); iii) BMI as leading variable (labeled as Υ_2) (*do BMI at T0 predict degree of change in global cognition between T0 and T1?*); iv) correlated change (labeled as δ_2) (*is the degree of improvement in global cognition correlated with the degree of BMI change in individuals?*). Estimates were presented as standardized coefficients (STD) and p-values.

The rates of missing data were higher for cognitive variables (collected in the additional neuropsychological visit of the present sub-study) than for all the other variables (collected in the follow-up cardiovascular visits of the main PREDIMED-Plus study). There were only 3 participants (0.6%) that did not undergo to the T1 follow-up cardiovascular visit, and this number was 17 (3.5%) for the T3

follow-up cardiovascular visit. Missing in variables collected in these visits was assumed to be MCAR. However, for the neuropsychological visits, attrition was present in 65 (13.3%) participants at T1 and 109 (22.4%) participants at T3 (**Supplementary Table 2**). To address potential selection bias due to attrition in neuropsychological visits, all T1 and T3 analyses of cognitive variables were adjusted using inverse probability weights (IPW). In SEM missing data was handled using full-information maximum likelihood (FIML) estimation with robust standard errors. See **Supplementary Table 3** for more details about the treatment of missing data.

Analyses were performed using R statistical software, version 3.6.0. Statistical significance was set at $p<0.05$. The 'nlme' package (version 3.1-149) was used for computing linear mixed effects models. The 'mediation' package (version 4.5.0) (59) was used for causal mediation analyses. The 'lavaan' package (version 0.6.7) (60) was used for SEM.

RESULTS

The main results of the present study are summarized in **Figure 1**.

Description of the study population

A total of 487 individuals participated in the PREDIMED-Plus-*Cognition* sub-study, of which 240 belonged to the IG and 247 to the CG arms of the RCT. Baseline characteristics of study participants are included in **Table 1**. Briefly, 50.5% were women, the mean (SD) age was 65.2 (4.7) years, 53.4% had received primary education, 29.2% had secondary education, and 62.1% were retired. Also, 12% were current smokers, 30.4% had diabetes, 50.3% were taking medications for cholesterol and 23.0% used tranquilizers or sedatives. Finally, participants scored 28.6 (1.7) points in the MMSE at baseline, so they performed within the normal range.

As shown in **Table 2**, at baseline most participants had a low (45.4%) or medium (41.5%) adherence to the er-MedDiet, but after 1 and 3 years over half of all participants were highly adhered to the er-MedDiet (65.3% after 1 year and 64.4% after 3 years). On the other hand, at baseline most participants were under-active (66.9%) or sedentary (15.6%), while after 1 and 3 years the prevalence of physically active participants increased from 8.4% to 15.2% and 14.0%, respectively.

As part of the inclusion criteria, at baseline all study participants presented overweight (27.3%) or obesity (72.7% in total; 48.5% type I obesity and 24.2% type II obesity). However, after 1 year the prevalence of obesity decreased to 57.8% (41.9% type I; 15.3% type II and 0.6% type III), and after 3 years it slightly increased to 62%. Finally, mild-to-moderate depressive symptomatology was detected in 28.7% of

participants at baseline, and it decreased to 21.4% after 1 year of intervention and to 19.6% after 3 years of intervention.

Prevalence of at least 8% weight reduction in the IG and associated cognitive factors

The specific weight loss objective of the IG was to achieve an average weight reduction of at least 8%. As shown in **Table 2**, 37.4% (95%CI 31.5, 43.7) and 33.2% (95%CI 27.4, 39.5) of participants from the IG reduced their weight at least in 8% of their baseline weight after 1 and 3 years of follow-up, respectively (hereafter, 'responders'). Among 1-year responders, 62 out of 89 (69.7%) maintained this weight reduction at the third year of follow-up. Responders were characterized by a high adherence to the er-MedDiet (about 80-90% of them were highly adherent). However, in terms of PA, most presented an under-active lifestyle. The prevalence of obesity type II greatly decreased from 24.7% to 3.4% among 1-year responders and from 23.4% to 2.6% among 3-years responders. Moreover, the prevalence of mild-to-moderate or moderate-to-severe depressive symptomatology decreased by half among these group of participants who responded to the intervention; specifically, from 39.3% to 17.6% among 1-year responders and from 32.5% to 17.6% among 3 years 'responders'.

We evaluated whether baseline cognitive profiles were associated with the response to the intervention, that is, the achievement of at least 8% body-weight reduction. Multivariate associations of baseline cognition (z-scores) with the goal of at least 8% weight reduction are represented in **Figure 2** (left panel). Although most 95%CI reach the null effect cut-off (OR=1), higher scores in short- and long-term verbal memory were associated with increased odds of 8% weight reduction after 1 year and markedly after 3 years of follow-up, with OR estimates of 1.4 (95%CI 1.0, 2.0) for RAVTL immediate recall and OR of 1.5 (95%CI 1.0, 2.1) for RAVTL delayed recall. Moreover, after 1-year slower reaction time measured with CPT-HRT predicted a lower odds of 8% weight reduction (OR= 0.8, 95%CI 0.5, 1.1), while higher decision-making abilities measured with the IGT increased the odds (OR= 1.3, 95%CI 0.9, 1.9). On the other hand, after 3 years, in addition to verbal memory, higher performance on visuoconstructive praxis and attention measured with RCFT (figure copying task score) (OR=1.5, 95%CI 0.9, 2.3) and higher scores in inhibition from Stroop interference (OR= 1.3, 95%CI 0.9, 1.9) predicted higher odds of 8% weight loss.

We then examined the association between baseline cognitive profiles and high er-MedDiet adherence (see details in **Figure 2**, right panel). Better performance in short- and long-term verbal memory was associated with increased probability of high er-MedDiet adherence after 1 year (OR=1.6; 95%CI 1.1,

2.4; and OR=2.1, 95%CI 1.4, 3.1, respectively). This was also observed for visuoconstructive praxis (OR=1.6, 95%CI 0.9, 2.9) and decision-making abilities (OR=1.4, 95%CI 0.9, 2.1). Moreover, those with high adherence to er-MedDiet at 1 year were 8.5 times more likely to achieve the 8% weight loss goal after 1 year (OR=8.5; 95%CI 3.1, 23.5), and 4.8 times more likely to achieve it after 3 years (OR=4.8; 95%CI 1.9, 12.2).

Finally, we tested whether er-MedDiet adherence at 1 year mediated the association between baseline cognitive profiles and the achievement of the 8% weight reduction after 1 and 3 years (**Supplementary Table 4**). Except for long-term verbal memory, the mediation effects of er-MedDiet adherence were not statistically significant. However, as represented in **Supplementary Figure 1**, er-MedDiet adherence explained the 31% and the 46% of the effects of short- and long-term verbal memory on 8% weight reduction in the first year, as well as the 21% of the effects of decision-making abilities. The respective values for 8% weight reduction after 3 years were 13% and 20% for short- and long-term verbal memory, 17% for decision-making abilities, 16% for visuoconstructive praxis and attention and 11% for inhibition.

Mean changes in cardiovascular biomarkers and intervention adherence

As presented in **Supplementary Table 5**, cardiovascular biomarkers improved after 1 and 3 years of follow-up in the overall population (P<0.001). According to effect size estimates (Cohen's d), large mean reductions after 1 year were found for body weight (mean change of -3.7 kg; 95%CI -4.1, -3.3), BMI (-1.4 kg/m^2; 95%CI -1.5, -1.2), waist (-4.0 cm; 95%CI -4.5, -3.5), hip (-2.2 cm; 95%CI -2.6, -1.8), blood pressure (-2.6 mmHg; 95%CI -3.5, -1.8 for diastolic; and -5.5 mmHg; 95%CI -7.0, -4.1 for systolic blood pressure), fasting plasma glucose (-5.5 mg/dL; 95%CI -7.4, -3.7), total cholesterol (-5.2 mg/dL, 95%CI -8.3, -2.0) and triglycerides (-18.6 mg/dL; 95%CI -24.6, -12.5). Compared to baseline values, after 3 years these reductions in body weight, waist, systolic blood pressure, LDL-cholesterol, total cholesterol and triglycerides were maintained, but for hip, diastolic blood pressure, fasting plasma glucose, HbA1c and HDL-cholesterol mean changes were smaller.

Mean levels of PA largely increased after 1 year (mean change of 830.6 METs-minute/week, 95%CI 618.1, 1043.1) and after 3 years (mean change of 820.1 METs-minute/week, 95%CI 605.9, 1034.4) in the overall sample. Daily energy intake decreased a mean of -161.1 Kcal (95%CI -210.1, -112.0) in the first year of follow-up but it increased a mean of 1119.5 Kcal (95%CI 677.2, 1561.9) in the third year of follow-up in the overall population.

Mean changes in specific neuropsychological tests, mental health and QoL

Table 3 includes baseline cognitive scores, mental health and QoL, and changes after 1 and 3 years of follow-up in all participants. Performance in some neuropsychological tests presented small mean improvements after 1 year. That was the case of RCFT immediate recall, RCFT delayed recall, RCFT recognition, and CPT-commission errors. Marginal improvements after 1 year were also observed in RAVTL immediate recall, RAVTL delayed recall, RCFT copy and CPT-omission errors. All these tests significantly improved after 3 years of intervention, with moderate changes for RCFT immediate recall (Cohen's d of 0.53; 95%CI 0.39, 0.67), RCFT delayed recall (Cohen's d of 0.68; 95%CI 0.54, 0.82) and RCFT recognition (Cohen's d of 0.48; 95%CI 0.34, 0.62), and small changes for RAVTL immediate recall (Cohen's d of 0.38 points; 95%CI 0.24, 0.52), RAVTL delayed recall (Cohen's d of 0.44; 95%CI 0.30, 0.58), RCFT copy (Cohen's d of 0.37; 95%CI 0.23, 0.50), and CPT-commission errors (Cohen's d of -0.38; 95%CI -0.55, -0.22). However, performance on SMDT and IGT tests worsened after 3 years, although changes were small.

Finally, mental health generally improved during the follow-up. On the one hand, BDI-II total score decreased -2.0 points after 1 and 3 years in the overall population. On the other hand, several SF-36 scores (energy, health and physical functioning scores) greatly improved after 1 and 3 years in the overall population, and other SF-36 scores (emotional and physical role scores) only improved after 3 years.

Measurement invariance of latent variables

Latent constructs (global cognition, memory, executive functions, QoL and METSYN) were tested for measurement invariance and was confirmed for all constructs as shown in **Supplementary Table 6** and **Supplementary Table 7.**

Interplay between BMI and cognition

As shown in **Supplementary Table 8**, global cognition increased after 3 years of follow-up ($\beta_{STD[\mu\Delta COG]}$ = 0.62, P=0.027). The improvement of global cognition after 1 year of follow-up did not reach the statistical significance ($\beta_{STD[\mu\Delta COG]}$ = 0.48, P=0.073). This increase was mainly due to an improvement in memory at 1 year ($\beta_{STD[\mu\Delta COG]}$ =0.88, P=0.002) and at 3 years ($\beta_{STD[\mu\Delta COG]}$ = 0.87, P<0.001), since executive functions did not present a significant mean change, neither at 1 year ($\beta_{STD[\mu\Delta COG]}$ = 0.07, P=0.793) nor at 3 years ($\beta_{STD[\mu\Delta COG]}$ = 0.17, P=0.684).

The effect of baseline characteristics and er-MedDiet adherence at 1 year on baseline global cognition and memory and on their change after 1 and 3 years is represented in **Figure 3**. Age (β_{STD}=-0.44, P<0.001) and female gender (β_{STD}=-0.11, P=0.07) were negatively associated with baseline global cognition, while

more years of education (β_{STD}=0.19, P=0.002) and higher IQ (β_{STD}=0.64, P<0.001) were associated with better cognitive function. Moreover, women presented lower increases in global cognition than men after 3 years (β_{STD}=-0.22, P=0.052).

Baseline memory performance was age (β_{STD}=-0.32, P<0.001) and IQ (β_{STD}=0.75, P<0.001) dependent. Higher adherence to the er-MedDiet at 1 year was associated with greater improvements in memory after 3 years (β_{STD}=0.13, P=0.013). Moreover, higher age was negatively associated with the mean rate of change in memory after 1 year (β_{STD}=-0.41, P=0.021) but did not affect memory change after 3 years. Memory change after 3 years was also dependent on baseline memory performance ($\beta_{STD[\beta 1]}$=-0.53, P<0.001). Moreover, memory chabge was also positively influenced by years of education (β_{STD}=0.21, P<0.001) and negatively influenced by the use of treatment for high cholesterol (β_{STD}=-0.09, P=0.059) and by a positive diagnosis of diabetes (β_{STD}=-0.18, P<0.001). As for global cognition, predictors of baseline performance in executive functions were age, education and IQ. In addition, women presented marginally lower baseline performance in executive functions than men (β_{STD}=-0.10, P=0.076).

As expected, individuals with higher baseline BMI experienced greater reductions in their BMI after 1 year ($\beta_{STD[\beta 2]}$=-0.07, P=0.002) and after 3 years ($\beta_{STD[\beta 2]}$=0.06, P=0.020) (**Supplementary Figure 2A**). The allocation to the IG, higher adherence to the er-MedDiet at 1 year and higher age predicted greater reductions in BMI after 1 and 3 years. Higher levels of education predicted less reductions in BMI after 1 year (β_{STD}=0.09, P=0.010), as well as the use of medication for the treatment of high cholesterol, which also negatively influenced the decrease in BMI after 1 and 3 years.

As shown in **Figure 4A**, there was evidence for correlated or coupled changes between BMI and memory at 1 year ($\beta_{STD[\delta 2]}$= -0.14, P=0.006), indicating that those with greater improvements in memory were, on average, those with greater reductions in BMI.

A sub-analysis of the interplay between global cognition and BMI stratified by gender was performed and is available upon request. There were no differences between men and women in the predictors of the heterogeneity of changes in global cognition after 1 or 3 years. However, after 1 year the inverse coupled relationship between global cognition and BMI changes was observed in men ($\beta_{STD[\delta 2]}$=-0.160, P=0.032) but not in women ($\beta_{STD[\delta 2]}$=0.095, P=0.294).

Interplay between PA and cognition

As shown in **Supplementary Figure 2B** and **Supplementary Table 9**, baseline levels of PA (PA_{T0}) were negatively associated with female gender (β_{STD}=-0.16, P<0.001) and positively influenced by age

(β_{STD}=0.18, P<0.001). In addition to IG allocation, increases in PA (ΔPA) at 1 and 3 years were negatively influenced by baseline levels of PA so, as expected, those that were more active at baseline experienced less improvements in PA. After 3 years, women also experienced less increases in PA than men (β_{STD}=-0.09, P=0.031). As shown in **Figure 4B**, there was evidence for coupled change between memory and PA after 3 years of follow-up ($\beta_{STD[\delta 2]}$= 0.13, P=0.036), so those that presented greater improvements in memory were those that experienced greater increases in PA.

Interplay between QoL and cognition

As shown in **Supplementary Figure 2C** and **Supplementary Table 10**, baseline QoL (QOL_{T0}) was negatively influenced by being women (β_{STD}=-0.34, P<0.001) and by the use of tranquilizers or sedatives (β_{STD}=-0.37, P<0.001), and it was positively influenced by age (β_{STD}=0.13, P=0.039) and by years of education (β_{STD}=0.12, P=0.027). The mean rate of change in QoL after 1 and 3 years did not reach statistical significance ($\beta_{STD[\mu\Delta COG]}$ = 0.16, P=0.198 at 1 year; and $\beta_{STD[\mu\Delta COG]}$ = 0.13, P=0.304). Change in QoL at both 1 and 3 years was dependent on baseline levels (P<0.001), and enhanced by the study intervention (β_{STD}=0.22, P<0.001 at 1 year and β_{STD}=0.14, P=0.012 at 3 years). Women experienced less improvements in QoL than men at 1 year (β_{STD}=-0.15, P=0.009) and at 3 years (β_{STD}=-0.15, P=0.016). There was evidence for correlated change between executive functions and QoL (**Figure 4C**) at both 1 year ($\beta_{STD[\delta 2]}$= 0.83, P=0.007) and 3 years ($\beta_{STD[\delta 2]}$= 1.16, P=0.011), which was also translated in correlated change between global cognition and QoL at 1 year ($\beta_{STD[\delta 2]}$= 0.73, P=0.008) and 3 years ($\beta_{STD[\delta 2]}$= 0.88, P=0.003).

Interplay between METSYN and cognition

As shown in **Supplementary Figure 2D** and **Supplementary Table 11**, according to the BLCSM of memory and METSYN, the negative rate of change in METSYN did not reach statistical significance (β_{STD}=-0.11, P=0.515) after 1 year of follow-up. At baseline, women presented a worse METSYN profile than men (β_{STD}=-0.77, P<0.001). Change in METSYN was proportional to the baseline profile and any improvement (decrease) was enhanced by the er-MedDiet intervention (β_{STD}=-0.57, P<0.001). Finally, there was marginal evidence for correlated changes between memory and METSYN ($\beta_{STD[\delta 2]}$=-0.35, P=0.088), so those that experienced greater improvements in their METSYN were those that experienced greater improvements in memory performance after 1 year of follow-up (**Figure 4D**).

DISCUSSION

Main findings

In the *PREDIMED-Plus-Cognition* sub-study we were interested in evaluating which cognitive profiles are associated with the goal of achieving at least 8% weight loss and studying the impact of weight reduction on participant's cognition. We observed that only one third of participants from the IG achieved the weight reduction goal after 1 and 3 years of follow-up. An increased odds of reaching the 8% weight reduction goal was found among individuals with better performance in verbal memory, reaction time and decision-making abilities at baseline. A higher visuoconstructive praxis and attention and lower impulsivity further contributed to the sustainability of intervention effects. Moreover, several cognitive abilities improved after 1 and 3 years of follow-up in the overall population, including short- and long-term visuospatial and verbal memory, selective and sustained attention, inhibition, and visuoconstructive praxis. Cognitive improvements presented inter-individual differences and adherence to the MedDiet, gender, age and diabetes are contributing factors to this heterogeneity in cognition. We also found evidence for correlated changes between cognition and some intervention outcomes; specifically, the associations of higher improvements in cognition with greater reductions in BMI, and higher improvements in PA and QoL.

Neuropsychological predictors of 8% weight loss in participants allocated to the IG

Our results are in agreement with previous studies proposing that the executive functions profile predicts weight loss outcome, as limiting the calorie intake requires strong planning and inhibitory control skills (61,62). Moreover, higher verbal memory skills may help consolidating the knowledge about the benefits of MedDiet and exercise, which may facilitate adherence to the proposed intervention, and consequently the achievement of the weight reduction goal (63). Accordingly, high adherence to the MedDiet mediated almost half of the association between baseline long-term verbal memory and the achievement of the 8% weight reduction goal in the first year. However, in the third year of follow-up MedDiet adherence mediated a lower proportion of such association, so other factors might better explain this relationship. Overall, these findings support that participants achieved different rates of compliance with the intervention and, consequently, the efficacy of lifestyle interventions could increase if they are more personalized and adapted to individual's cognitive characteristics and needs. There is a need to develop effective behavioral change techniques that can reduce the demands on executive functions among individuals with obesity exhibiting a dysexecutive profile (64).

Changes in cognition after 1 and 3 years in the overall population

At baseline participants displayed a normal cognitive function. Although mean cognitive changes after 1 and 3 years were small, several neuropsychological tests presented improvements in the overall population, in agreement with previous studies with MedDiet (65,66). At the 1st year, small and marginal improvements were detected for short- and long-term visuospatial and verbal memory, as well as for selective and sustained attention and inhibition. At the 3rd year, greater (but still moderated) changes in cognitive performance were found for all these domains, as well as, for visuoconstructive praxis. Our results are consistent with evidences from observational studies about the direct beneficial associations of the MedDiet with brain structure and function, specifically increased cortical thickness (67,68), greater brain volumes (69), slower rate of brain atrophy (70,71), improved structural connectivity and reduced amyloid accumulation at midlife and older age (72,73). Our results also align with existing evidence showing a moderate association between the traditional MedDiet and improved cognitive performance, reduced risk of MCI and dementia, delayed Alzheimer's disease (AD) onset and lower mortality in patients with AD (22,74–80).

When studying cognitive changes using latent variables, we observed a mean improvement in memory after 1 year but especially after 3 years, which is relevant as memory decline is considered a predictor of cognitive impairment (81). Although improvements in executive functions did not reach statistical significance, we did observe significant improvements in global cognition (comprising all the tests from memory and executive functions) at 3 years.

Determinants of the heterogeneity in cognitive change

Importantly, we show that individual changes in cognition were not uniform among participants despite belonging to the same intervention group. Unraveling this heterogeneity is crucial for understanding the impact of preventive interventions for cognitive decline (82). The allocation to IG *vs* CG was not a predictor of cognitive change, probably because both groups received recommendations to follow a MedDiet to prevent cardiovascular diseases and only differed in the provision of advice for calorie restriction, weight loss and physical activity, as well as, in the frequency of the follow-up (31). Indeed, higher adherence to the er-MedDiet was associated with greater improvements in memory after 3 years, independent of intervention group allocation. This finding contrasts with previous studies that have demonstrated benefits of the MedDiet adherence on global cognition, but not on memory nor on

executive functions (83,84). The overall composition of the MedDiet may be the responsible of the modest cognitive improvements observed in the overall population.

Gender also appeared as a main determinant of the within-subject change in cognition. Specifically, women experienced less improvement than men in global cognition after 3 years. On the other hand, as expected, changes in QoL and PA were higher among individuals with lower baseline scores of QoL and PA because their scope for improvement was higher. But paradoxically, although women presented lower baseline levels of QoL and PA than men, the within-subject change in QoL and PA was also lower in women than in men. Finally, gender did not influence the reduction in BMI experienced by our participants. Although gender is known to be an important aspect when considering cognition, there is a lack of studies investigating gender-specific effects on the response to lifestyle interventions (85).

Finally, older age and diabetes negatively influenced memory changes after 1 and 3 years, respectively. Our results align with existing evidence on diabetes as a risk factor for dementia (86,87), and on lower cognitive performance of individuals with type 2 diabetes (6). Future studies should explore the effect of different diabetic medications on cognition, as it is a growing topic of discussion (88,89).

Interrelationships between cognitive and weight changes

We observed a coupled change relationship between memory and BMI and PA, whereby a reduction in BMI during the 1st year of follow-up was associated with improvements in memory; and an increase in PA at the 3rd year of follow-up was positively related with an increase in memory. Participants were more intensively followed during the first year and this could explain why changes in cognition correlated with changes in BMI only at the first year. Therefore, reductions in BMI were more pronounced in the first year than in the third, which is in accordance with evidence from behavioral interventions suggesting that weight loss typically peaks at 6 months into the weight loss attempt, followed by gradual regain of weight in most individuals (61). Results suggest that cognitive benefits accumulated with time, so that greater improvements were observed at the third year of follow-up than in the first one. On the other hand, in a sub-analysis stratified by gender we observed that reductions in BMI only correlated with improvements in global cognition in men, but not in women. Further research in needed to better understand these differences.

Our results also suggest that weight loss could directly affect cognition. Although there were improvements in the metabolic profile of study participants, the correlation between 1-year reductions in the latent variable of METSYN (comprised by waist, triglycerides, HDL-cholesterol (reversed), systolic

blood pressure and glucose) and improvements in memory and global cognition did not reach statistical significance. A possible explanation would be that different mechanisms explain the interrelationships between cognition and the variables that compose the METSYN. Some studies have reported that the direct effect of weight reduction on cognition is plausible (24). However, in contrast to previous studies showing cognitive benefits in individuals with obesity but not in those with overweight (24), we did not find that baseline BMI affected cognitive change. Moreover, although benefits related to weight loss seem to be strongly associated with increased physical activity (90,91), in our study cognitive function correlated with BMI and PA changes at different time points, suggesting that different predictors and mechanisms could operate for BMI and PA. In fact, BMI changes were affected by the study intervention, age (older participants exhibited greater reductions in BMI at 1 and 3 years), education (higher years of education were related with lower reductions in BMI at 1 year) and cholesterol treatment (which was also associated with less BMI reductions at 1 and 3 years). In turn, PA changes were only affected by the study intervention and by the gender of participants. Gender differences in the adherence to the MedDiet or PA programs, as well as, in well-being and QoL have already been reported in previous studies (92–94), and could be partially explained by the lower scoring of women in self-efficacy, coping resources and control over life (95).

Finally, an increase in global cognition and executive functions correlated with an increase in the QoL of individuals. This is important given that cognitive changes may not be perceptible to individuals but they may become more relevant if they are coupled with improvements in the QoL. Moreover, depressive symptomatology decreased in the overall population, suggesting the benefits of the MedDiet in both positive and negative aspects of mental health. Ultimately, dynamic coupling between QoL, PA, BMI and cognition could be crucial for the maintenance of cognitive abilities in later life and may explain why declines are often strongly correlated and why multidomain interventions targeting multiple lifestyle risk factors simultaneously might be more effective.

Strengths and limitations

The strengths of this study include the wide range of cognitive abilities that were evaluated, which provide detailed evidence about the interplay between specific cognitive domains, weight reduction and the impact of a MedDiet intervention. Another strength is the use of latent variables represented by several indicators of memory, executive functions, global cognition, QoL and metabolic syndrome. Using multiple indicators for each latent variable has the advantage of removing measurement error and

establishing measurement invariance over time, thus improving inferences (56). Moreover, the use of latent change score models is a novel approach for testing the effects of the MedDiet on cognition. With these models we assumed intraindividual trajectories, established temporal precedence and drew inferences derived from causal hypotheses.

However, some limitations must be mentioned. First, there were losses in the follow-up of the evaluation of the cognitive function after 1 year (13.3%) and, especially, after 3 years (22.4%). They were not unexpected given the burden of such visits and the fact that the neuropsychological visits were performed in different days than the "cardiovascular" visits. To deal with this missing data problem, all the analyses of 1-year and 3-years change in each cognitive test were computed using inverse probability weights. Weights were applied to the subjects with no missing outcome data, so it was assumed that those who were unsuccessfully followed presented cognitive scores that could be accurately estimated from those successfully followed. Also, missing data in BLCSM was handled with FIML, which maximizes the utility of all existing data, decreases bias and increases statistical power compared to complete case analysis (96). Compared to multiple imputation, FIML performs better and produces stable estimations across uses (97,98). Second, we did not have information regarding genetic risk factors of cognitive impairment, including the *APOE* genotype of participants, which could influence the results (99). However, we found modest improvements in the cognitive performance of the overall population, suggesting that in the study period considered the genetic status of participants had little impact and/or was compensated by the lifestyle intervention. Third, it is important to note that in the analysis of cognitive predictors of 8% weight reduction we obtained wide confidence intervals reaching the null effect cut-off (OR=1). However, our results are interpreted under the premise that the OR point estimate is the most compatible result, and values near it are more compatible than those near the limits (100).

CONCLUSION

To conclude, this is the first study to examine the within-subject dynamic relations between the naturalistic trajectories of cognition, QoL, BMI, PA and metabolic syndrome in older adults at risk of cardiovascular disease following a MedDiet intervention. Altogether results from this study suggest that initial performance in some cognitive functions (i.e. better performance on executive functions and visuoconstructive skills) are related to the success on the weight loss goal. Additionally, following an eating pattern based on the MedDiet, either with or without energy restriction, has shown to slow-down age-related cognitive decline and promote improvements in some cognitive functions (i.e. inhibition, attention, visuoconstructive praxis, visuospatial and verbal memory). Larger improvements in memory are related to a higher adherence to MedDiet. However, relevant gender differences were observed mainly related to the impact of weight reduction on the cognitive performance and perceived QoL. This issue should be explored in future studies to better understand the underlaying mechanism of action and design gender-specific interventions.

In summary, findings from this study can help to identify people who have less probability of responding to a lifestyle-based preventive intervention for cognitive decline, giving the opportunity to improve the preventive strategy by applying more personalized and intensive interventions. Taken together, our findings refine the understanding of the determinants and interrelationships of cognitive change and add to existing evidence about the cognitive benefits associated with the MedDiet.

Acknowledgements

The authors thank the participants for their enthusiastic collaboration and the PREDIMED-Plus personnel for their invaluable support, as well as all affiliated primary care centers, for their excellent work.

Funding statement

Study resulting from the following grants: SLT006/17/00246, SLT002/16/00045 and SLT006/17/00077 funded by the Department of Health of the Generalitat de Catalunya by the calls “Acció instrumental de programes de recerca orientats en l'àmbit de la recerca i la innovació en salut” and "Pla estratègic de recerca i innovació en salut (PERIS)". We thank CERCA Programme / Generalitat de Catalunya for institutional support. This project was funded by Instituto de Salud Carlos III (ISCIII), the Spanish Government Official Agency for funding biomedical research - with competitive grants leaded by Jordi Salas-Salvadó and Josep Vidal for the periods 2014-2016, 2015-2017, 2017-2019 and 2018-2020, through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional

Development Fund, ERDF, a way to build Europe) [grants: PI13/00233, PI13/00728, PI13/01123, PI13/00462, PI16/00533, PI16/00366, PI16/01094, PI16/00501, PI17/01167, PI19/00017, PI19/00781, PI19/01032, PI19/00576]; the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to Jordi Salas-Salvadó; the European Research Council [Advanced Research Grant 2014-2019; agreement #340918] granted to Miguel Ángel Martínez-González; the Recercaixa (number 2013ACUP00194) grant to Jordi Salas-Salvadó. This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2; Ref 728018; and PRIME/ H2020-SC1-BHC-2018-2020; Ref: 847879), Grant PROMETEO/2017/017 (Generalitat Valenciana) and Grant FEA/SEA 2017 for Primary Care Research. This work is also partially supported by ICREA under the ICREA Academia programme. This work was supported by grants from DIUE de la Generalitat de Catalunya 2017 SGR 138 from the Departament d'Economia i Coneixement de la Generalitat de Catalunya (Spain). CVA are supported by a predoctoral Grant of the Ministerio de Educación, Cultura y Deporte (FPU16/01453). JFG-G has received the Contratos Predoctorales de Formación en Investigación en Salud (PFIS FI17/00255) of the Acción Estratégica en Salud program (AES) from the Carlos III Health Institute (ISCIII), Spanish Ministry of Health. The Physiopathology of Obesity and Nutrition Networking Biomedical Research Center (CIBEROBN) is an initiative of ISCIII.

None of these funding sources plays any role in the design, collection, analysis, or interpretation of the data or in the decision to submit manuscripts for publication. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest

Dr. Salas-Salvadó reports non-financial support from Nut and Dried Fruit Foundation, personal fees from Danone Institute Spain, other from Danone S.A., other from Font Vella Lanjaron, other from Nuts for Life, other from Eroski Distributors, grants from Nut and Dried Fruit Foundation, grants from Eroski Distributors, other from Nut and Dried Fruit Foundation, outside the submitted work. All these relationships did not influence study design, data collection, data analysis, data interpretation, or writing of the report.

Author contribution

RT, NS-D, LF and AC-R contributed to the conception and design of the study, wrote the manuscript, and reviewed/edited the manuscript. NS-D performed the statistical analyses and interpreted the data. AC-R, LF, DC, JVS, RF-C, MG-G, CV-A, XP, SJ-M, JFG-G, SKN, NB, AM, OC contributed to data

acquisition. DC, JVS, MAM, OC, MG-G, JS-S, FF-A contributed to critical revision of the manuscript for key intellectual content. All authors have read and approved the final manuscript. RT, JSS, FFA, MAM obtained funding for the study.

REFERENCES

1. World Health Organization. WHO | Obesity and overweight [Internet]. WHO. World Health Organization; 2016. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of cardiology/American Heart Association task force on practice guidelines and the obesity society. Circulation. 2014;129(25 Suppl 2):S102-38.

3. Gustafson DR. Adiposity and cognitive decline: underlying mechanisms. J Alzheimers Dis. 2012 Jan;30 Suppl 2:S97-112.

4. Boots EA, Zhan L, Dion C, Karstens AJ, Peven JC, Ajilore O, et al. Cardiovascular disease risk factors, tract-based structural connectomics, and cognition in older adults. Neuroimage. 2019 Aug;196:152–60.

5. Dake MD, De Marco M, Blackburn DJ, Wilkinson ID, Remes A, Liu Y, et al. Obesity and Brain Vulnerability in Normal and Abnormal Aging: A Multimodal MRI Study. J Alzheimer's Dis Reports. 2021 Jan;5(1):65–77.

6. Mallorquí-Bagué N, Lozano-Madrid M, Toledo E, Corella D, Salas-Salvadó J, Cuenca-Royo A, et al. Type 2 diabetes and cognitive impairment in an older population with overweight or obesity and metabolic syndrome: baseline cross-sectional analysis of the PREDIMED-plus study. Sci Rep. 2018;8(1):1–9.

7. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Vol. 6, Current obesity reports. NIH Public Access; 2017. p. 187–94.

8. Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2017 Jan;72:87–94.

9. Gómez Puente JM, Martínez-Marcos M. Overweight and obesity: Effectiveness of interventions in adults. Enfermería Clínica (English Ed. 2018 Jan;28(1):65–74.

10. Barte JCM, Ter Bogt NCW, Bogers RP, Teixeira PJ, Blissmer B, Mori TA, et al. Maintenance of weight loss after lifestyle interventions for overweight and obesity, a systematic review. Obes Rev. 2010 Dec;11(12):899–906.

11. Varkevisser RDM, van Stralen MM, Kroeze W, Ket JCF, Steenhuis IHM. Determinants of weight loss maintenance: a systematic review. Obes Rev. 2019;20(2):171–211.

12. Fagundo AB, de la Torre R, Jiménez-Murcia S, Agüera Z, Granero R, Tárrega S, et al. Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. PLoS One. 2012 Jan;7(8):e43382.

13. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: A systematic literature review. Obes Res Clin Pract. 2015 Mar;9(2):93–113.

14. Favieri F, Forte G, Casagrande M. The executive functions in overweight and obesity: A systematic review of neuropsychological cross-sectional and longitudinal studies. Front Psychol. 2019 Sep;10:2126.

15. Jansen A, Houben K, Roefs A. A cognitive profile of obesity and its translation into new interventions. Front Psychol. 2015;6.

16. Fitzpatrick S, Gilbert S, Serpell L. Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? Neuropsychol Rev. 2013 Jun;23(2):138–56.

17. Valls-Pedret C Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, Martínez-Lapiscina EH,Fitó M, Pérez-Heras A, Salas-Salvadó J, Estruch R, Ros E. S-V a. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015;175(7).

18. Cheke LG, Bonnici HM, Clayton NS, Simons JS. Obesity and insulin resistance are associated with reduced activity in core memory regions of the brain. Neuropsychologia. 2017 Feb;96:137–49.

19. Sellbom KS, Gunstad J. Cognitive function and decline in obesity. J Alzheimers Dis. 2012 Jan;30 Suppl 2:S89-95.

20. Okubo H, Inagaki H, Gondo Y, Kamide K, Ikebe K, Masui Y, et al. Association between dietary patterns and cognitive function among 70-year-old Japanese elderly: a cross-sectional analysis of the SONIC study. Nutr J. 2017 Dec;16(1):56.

21. Cadar D, Pikhart H, Mishra G, Stephen A, Kuh D, Richards M. The role of lifestyle behaviors on 20-year cognitive decline. J Aging Res. 2012;2012:304014.

22. Van Den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, Van De Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. Adv Nutr. 2019;10(6):1040–65.

23. Horie NC, Serrao VT, Simon SS, Gascon MRP, Dos Santos AX, Zambone MA, et al. Cognitive effects of intentional weight loss in elderly obese individuals with mild cognitive impairment. J Clin Endocrinol Metab. 2016;101(3):1104–12.

24. Siervo M, Arnold R, Wells JCK, Tagliabue A, Colantuoni A, Albanese E, et al. Intentional weight loss in overweight and obese individuals and cognitive function: A systematic review and meta-analysis. Obes Rev. 2011;12(11):968–83.

25. Daimiel L, Martínez-González MA, Corella D, Salas-Salvadó J, Schröder H, Vioque J, et al. Physical fitness and physical activity association with cognitive function and quality of life: baseline cross-sectional analysis of the PREDIMED-Plus trial. Sci Rep. 2020 Dec;10(1):34.

26. Makizako H, Liu-Ambrose T, Shimada H, Doi T, Park H, Tsutsumimoto K, et al. Moderate-Intensity Physical Activity, Hippocampal Volume, and Memory in Older Adults With Mild Cognitive Impairment. Journals Gerontol Ser A Biol Sci Med Sci. 2015 Apr;70(4):480–6.

27. Xu L, Jiang CQ, Lam TH, Zhang W Sen, Thomas GN, Cheng KK. Dose-Response Relation Between Physical Activity and Cognitive Function: Guangzhou Biobank Cohort Study. Ann Epidemiol. 2011 Nov;21(11):857–63.

28. Cournot M, Marquié JC, Ansiau D, Martinaud C, Fonds H, Ferrières J, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006;67(7):1208–14.

29. Spitznagel MB, Garcia S, Miller LA, Strain G, Devlin M, Wing R, et al. Cognitive function predicts weight loss after bariatric surgery. Surg Obes Relat Dis. 2013 Jan;9(3):453–9.

30. Hayden KM, Baker LD, Bray G, Carvajal R, Demos-McDermott K, Hergenroeder AL, et al. Long-term impact of intensive lifestyle intervention on cognitive function assessed with the National Institutes of Health Toolbox: The Look AHEAD study. Alzheimer's Dement Diagnosis, Assess Dis Monit. 2018 Jan;10:41–8.

31. Martínez-González MA, Buil-Cosiales P, Corella D, Bulló M, Fitó M, Vioque J, et al. Cohort profile: Design and methods of the PREDIMED-Plus randomized trial. Int J Epidemiol. 2019;48(2):387-388o.

32. 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 Oct;322(15):1486–99.

33. 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(5):777–88.

34. 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. Circulation. 2009 Oct;120(16):1640–5.

35. Rey A. L'examen clinique en psychologie. [The clinical examination in psychology]. Paris: Presses Universitaires De France; 1958.

36. Miranda J, Valencia R. English and Spanish versions of a memory test: word length effects versus spoken duration effects. Hisp Jl Behav Sci. 1997;19(171).

37. Osterrieth PA. Test of copying a complex figure; contribution to the study of perception and memory. Arch Psychol (Geneve). 1944;30:206–356.

38. Smith A. Symbol Digit Modalities Test (SDMT). Manual (Revised). Los Angeles: Western Psychological Services.; 1982.

39. Smith A. SDMT. Test de Símbolos y Dígitos [Symbol and Digit Test]. TEA Edicio. Arribas D, editor. Madrid; 2002.

40. Golden C.J. Stroop color and word test. Wood Dale, IL: Stoelting Co.; 1975.

41. Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. Science (80-). 1997;275(5304):1293–5.

42. Conners CK. Conners' CPT II. Continuous Performance Test II. Computer Guide and Software Manual. North Tonawanda, NY: Multi Health Systems; 2000.

43. Wechsler D. Wechsler Adult Intelligence Scale-Third Edition (WAIS). New York: Psychological Corporation; 1997.

44. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.

45. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Heal Organ Tech Rep Ser. 1995;854:1–452.

46. Schröder H, Zomeño MD, Martínez-González MA, Salas-Salvadó J, Corella D, Vioque J, et al. Validity of the energy-restricted Mediterranean Diet Adherence Screener. Clin Nutr. 2021 Jul;0(0).

47. Álvarez-Álvarez I, Martínez-González MÁ, Sánchez-Tainta A, Corella D, Díaz-López A, Fitó M, et al. Adherence to an Energy-restricted Mediterranean Diet Score and Prevalence of Cardiovascular Risk Factors in the PREDIMED-Plus: A Cross-sectional Study. Rev Española Cardiol. 2019 Nov 1;72(11):925–34.

48. Comellas AR, Pera G, Diez JMB, Tuduri XM, Sas TA, Elosua R, et al. Validation of a spanish short version of the minnesota leisure time physical activity questionnaire (vrem). Rev Esp Salud Publica. 2012;86(5):495–508.

49. 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(1):1–14.

50. Beck A, Steer A, Carbin M. Psychometric properties of the Beck depression inventory twenty-five years of evaluation. Clin Psych Rev. 1988;8:77–100.

51. Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiat. 1961;4:561–71.

52. Vilagut G, Ferrer M, Rajmil L, Rebollo P, Permanyer-Miralda G, Quintana JM, et al. El Cuestionario de Salud SF-36 español: una década de experiencia y nuevos desarrollos. Gac Sanit. 2005;19(2):135–50.

53. Imai K, Keele L, Tingley D. A General Approach to Causal Mediation Analysis. Psychol Methods. 2010;15(4):309–34.

54. Cohen J. A power primer. Psychol Bull. 1992;112:155–9.

55. Swilowsky S. New effect size rules of thumb. J Mod Appl Stat Methods. 2009;8:597–9.

56. Kievit RA, Brandmaier AM, Ziegler G, van Harmelen AL, de Mooij SMM, Moutoussis M, et al. Developmental cognitive neuroscience using latent change score models: A tutorial and applications. Dev Cogn Neurosci. 2018;33(February 2017):99–117.

57. McArdle JJ. Latent variable modeling of differences and changes with longitudinal data. Annu Rev Psychol. 2009;60:577–605.

58. Proust-Lima C, Philipps V, Dartigues JF, Bennett DA, Glymour MM, Jacqmin-Gadda H, et al. Are latent variable models preferable to composite score approaches when assessing risk factors of change? Evaluation of type-I error and statistical power in longitudinal cognitive studies. Stat Methods Med Res. 2019;28(7):1942–57.

59. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. J Stat Softw. 2014;59(5):1–38.

60. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. J Stat Softw. 2012;48(2):1–36.

61. Severin R, Sabbahi A, Mahmoud A, Arena R, Phillips S. Precision Medicine in Weight Loss and Healthy Living. Prog Cardiovasc Dis. 2019;62(1):15–20.

62. Butryn ML, Martinelli MK, Remmert JE, Roberts SR, Zhang F, Forman EM, et al. Executive Functioning as a Predictor of Weight Loss and Physical Activity Outcomes. Ann Behav Med. 2019;53(10):909–17.

63. van der Wardt V, Hancox J, Gondek D, Logan P, Nair R das, Pollock K, et al. Adherence support strategies for exercise interventions in people with mild cognitive impairment and dementia: A systematic review. Prev Med Reports. 2017;7:38–45.

64. Forcano L, Mata F, de la Torre R, Verdejo-Garcia A. Cognitive and neuromodulation strategies for unhealthy eating and obesity: Systematic review and discussion of neurocognitive mechanisms. Neurosci Biobehav Rev. 2018;87(2010):161–91.

65. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, De La Torre R, Martínez-González MÁ, et al. Mediterranean diet and age-related cognitive decline: A randomized clinical trial. JAMA Intern Med. 2015;175(7):1094–103.

66. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013 Dec 1;84(12):1318–25.

67. Mosconi L, Murray J, Tsui WH, Li Y, Davies M, Williams S, et al. Mediterranean Diet and Magnetic Resonance Imaging-Assessed Brain Atrophy in Cognitively Normal Individuals at Risk for Alzheimer's Disease. J Prev Alzheimer's Dis. 2014 Jun;1(1):23–32.

68. Staubo SC, Aakre JA, Vemuri P, Syrjanen JA, Mielke MM, Geda YE, et al. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimer's Dement. 2017 Feb 1;13(2):168–77.

69. Pelletier A, Barul C, Féart C, Helmer C, Bernard C, Periot O, et al. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimer's Dement. 2015 Sep 1;11(9):1023–31.

70. Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, et al. Mediterranean

diet and brain structure in a multiethnic elderly cohort. Neurology. 2015 Nov 17;85(20):1744–51.

71. Luciano M, Corley J, Cox SR, Hernández MCV, Craig LCA, Dickie DA, et al. Mediterranean-Type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology. 2017 Jan 31;88(5):449–55.

72. Karstens AJ, Tussing-Humphreys L, Zhan L, Rajendran N, Cohen J, Dion C, et al. Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults. Am J Clin Nutr. 2019 Feb 1;109(2):361–8.

73. Rainey-Smith SR, Gu Y, Gardener SL, Doecke JD, Villemagne VL, Brown BM, et al. Mediterranean diet adherence and rate of cerebral Aβ-amyloid accumulation: Data from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Transl Psychiatry. 2018 Dec 1;8(1):238.

74. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol. 2018 Nov 1;17(11):1006–15.

75. Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME. The impact of the mediterranean diet on the cognitive functioning of healthy older adults: A systematic review and meta-analysis. Adv Nutr. 2017 Jul 1;8(4):571–86.

76. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: An umbrella review of meta-analyses of observational studies and randomised trials. Vol. 72, European Journal of Clinical Nutrition. Nature Publishing Group; 2018. p. 30–43.

77. Aridi YS, Walker JL, Wright ORL. The association between the mediterranean dietary pattern and cognitive health: A systematic review. Nutrients. 2017 Jul 1;9(7).

78. Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. Sci Rep. 2017 Jan 23;7.

79. Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA. Effect of the Mediterranean diet on cognition and brain morphology and function: A systematic review of randomized controlled trials. Am J Clin Nutr. 2018;107(3):389–404.

80. Keenan TD, Agrón E, Mares JA, Clemons TE, van Asten F, Swaroop A, et al. Adherence to a Mediterranean diet and cognitive function in the Age-Related Eye Disease Studies 1 & 2. Alzheimer's Dement. 2020;16(6):831–42.

81. Petersen R, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275(3):214–28.

82. Soldevila-Domenech N, Boronat A, Langohr K, de la Torre R. N-of-1 Clinical Trials in Nutritional Interventions Directed at Improving Cognitive Function. Front Nutr. 2019;6(110).

83. Limongi F, Siviero P, Bozanic A, Noale M, Veronese N, Maggi S. The Effect of Adherence to the Mediterranean Diet on Late-Life Cognitive Disorders: A Systematic Review. J Am Med Dir Assoc. 2020;21(10):1402–9.

84. Knight A, Bryan J, Murphy K. The Mediterranean diet and age-related cognitive functioning: A systematic review of study findings and neuropsychological assessment methodology. Nutr Neurosci. 2017;20(8):449–68.

85. Aronica L, Rigdon J, Offringa LC, Stefanick ML, Gardner CD. Examining differences between overweight women and men in 12-month weight loss study comparing healthy low-carbohydrate vs. low-fat diets. Int J Obes. 2021;45(1):225–34.

86. 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. 2020;396(10248):413–46.

87. Chatterjee S, Peters SAE, Woodward M, Arango SM, Batty GD, Beckett N, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care. 2016;39(2):300–7.

88. McMillan JM, Mele BS, Hogan DB, Leung AA. Impact of pharmacological treatment of diabetes mellitus on dementia risk: Systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2018;6(1):1–12.

89. Areosa Sastre A, Vernooij RWM, González-Colaço Harmand M, Martínez G. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia.

Cochrane Database Syst Rev. 2017;(6):CD003804.

90. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. Journals Gerontol - Ser A Biol Sci Med Sci. 2006;61(11):1166–70.

91. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, et al. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. Neurology. 2010 Oct 19;75(16):1415–22.

92. Carmel S. Health and Well-Being in Late Life: Gender Differences Worldwide. Front Med. 2019;6(October):3–6.

93. Leblanc V, Bégin C, Hudon AM, Royer MM, Corneau L, Dodin S, et al. Gender differences in the long-term effects of a nutritional intervention program promoting the Mediterranean diet: Changes in dietary intakes, eating behaviors, anthropometric and metabolic variables. Nutr J. 2014;13.

94. Raparelli V, Romiti GF, Spugnardi V, Borgi M, Cangemi R, Basili S, et al. Gender-related determinants of adherence to the mediterranean diet in adults with ischemic heart disease. Nutrients. 2020;12(3):1–12.

95. Jonker AAGC, Comijs HC, Knipscheer KCPM, Deeg DJH. The role of coping resources on change in well-being during persistent health decline. J Aging Health. 2009;21(8):1063–82.

96. Baraldi AN, Enders CK. An introduction to modern missing data analyses. J Sch Psychol. 2010 Feb;48(1):5–37.

97. von Hippel PT. New Confidence Intervals and Bias Comparisons Show That Maximum Likelihood Can Beat Multiple Imputation in Small Samples. Struct Equ Model. 2016;23(3):422–37.

98. Larsen R. Missing data imputation versus full information maximum likelihood with second-level dependencies. Struct Equ Model. 2011;18(4):649–62.

99. Solomon A, Turunen H, Ngandu T, Peltonen M, Levälahti E, Helisalmi S, et al. Effect of the

apolipoprotein e genotype on cognitive change during a multidomain lifestyle intervention a subgroup analysis of a randomized clinical trial. JAMA Neurol. 2018;75(4):462–70.

100. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019 Mar 21;567(7748):305–7.

TABLES AND FIGURES

Table 1. Description of study participants

		N	%
N		487	100
Variable	**Category**		
Treatment group	Control	247	50.7
	Intervention	240	49.3
Gender	Men	241	49.5
	Women	246	50.5
Age	*Mean (SD)*	487	65.2 (4.7)
Origin	European	479	98.4
	Latin American	8	1.6
Education (years)	*Mean (SD)*	487	11.7 (5.3)
Education level	Primary	260	53.4
	Secondary	142	29.2
	University (grade)	38	7.8
	University (higher)	47	9.7
Employment status	Employed	91	18.7
	Unemployed	36	7.4
	Housework	50	10.3
	Retired	302	62.1
	Other	7	1.4
	Missing	1	
Civil status	Married	382	78.4
	Single	54	11.1
	Widowed	51	10.5
Smoking status	Never smoker	239	49.1
	Smoker	59	12.1
	Former smoker	189	38.8
Cholesterol treatment		245	50.3
Diabetes status	Normal	264	54.2
	Prediabetes	75	15.4
	Diabetes	148	30.4
Use of tranquilizers or sedatives		112	23
Intelligence Quotient estimation[1]	*Mean (SD)*	487	92.0 (39.5)
MMSE[2]	*Mean (SD)*	482	28.6 (1.7)

[1]Obtained from the WAIS-III Vocabulary Subtest.
[2]MMSE, Mini-Mental State Examination.
N= number. SD= standard deviation.

Table 2. Distribution of intervention adherence, BMI and depressive symptomatology categories at baseline, 1 year and 3 years in all population and in individuals allocated to the intervention group that achieved or not the goal of 8% weight reduction

			All		Intervention group [N=240]							
					8% weight reduction after 1 year				8% weight reduction after 3 years			
					No		Yes		No		Yes	
Variable	**Time**	**Category**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total N[1]			487	100	149	100	89	100	155	100	77	100
8% weight reduction	1 year		104	21.5					27	17.5	62	81.6
		Missing	3									
	3 years		95	20.3	14	9.9	62	69.7				
		Missing	18									
Er-MedDiet adherence	Baseline	Low	221	45.4	72	48.3	39	43.8	71	45.8	38	49.4
		Medium	202	41.5	60	40.3	37	41.6	65	41.9	28	36.4
		High	64	13.1	17	11.4	13	14.6	19	12.3	11	14.3
	1 year	Low	43	9.2	7	4.9	1	1.1	6	4.0	0	0.0
		Medium	120	25.5	28	19.7	7	8.0	25	16.7	9	12.0
		High	307	65.3	107	75.4	80	90.9	119	79.3	66	88.0
		Missing	17				1					
	3 years	Low	36	8.2	5	3.9	1	1.2	5	3.6	1	1.3
		Medium	121	27.4	18	14.1	17	19.5	23	16.4	12	15.8
		High	284	64.4	105	82.0	69	79.3	112	80.0	63	82.9
		Missing	46				2		5			
Physical activity[2]	Baseline	Sedentary	76	15.6	14	9.4	15	16.9	12	7.7	14	18.2
		Under-active	326	66.9	104	69.8	58	65.2	114	73.5	45	58.4
		Moderately active	44	9	15	10.1	11	12.4	13	8.4	13	16.9
		Active	41	8.4	16	10.7	5	5.6	16	10.3	5	6.5
	1 year	Sedentary	27	5.7	7	4.9	4	4.5	6	4.0	3	4.0
		Under-active	312	66.4	84	58.7	55	61.8	94	62.3	43	56.6
		Moderately active	62	13.1	19	13.3	13	14.6	18	11.9	14	18.4
		Active	72	15.2	33	23.1	17	19.1	33	21.9	16	21.1
		Missing	14		6		0		4		1	
	3 years	Sedentary	44	10	9	7.0	9	10.3	11	7.8	7	9.2
		Under-active	274	62	71	55.0	55	63.2	84	59.6	43	56.6
		Moderately active	62	14	21	16.3	9	10.3	20	14.2	10	13.2
		Active	62	14	28	21.7	14	16.1	26	18.4	16	21.1
		Missing	45		20		2		14		1	
BMI category	Baseline	Normal weight	0	0	0	0.0	0	0.0	0	0.0	0	0.0
		Over-weight	133	27.3	50	33.6	23	25.8	48	31.0	23	29.9
		Obesity I	236	48.5	64	43.0	44	49.4	68	43.9	36	46.8
		Obesity II	118	24.2	35	23.5	22	24.7	39	25.2	18	23.4
	1 year	Normal weight	9	1.9	0	0.0	8	9.0	3	2.0	5	6.6
		Over-weight	195	40.3	69	46.3	53	59.6	71	46.1	49	64.5
		Obesity I	203	41.9	57	38.3	25	28.1	60	39.0	18	23.7
		Obesity II	74	15.3	23	15.4	3	3.4	20	13.0	4	5.3
		Obesity III	3	0.6	0	0.0	0	0.0	0	0.0	0	0.0
		Missing	3		0		0		1		1	
	3 years	Normal weight	7	1.5	1	0.7	5	5.6	1	0.7	5	6.5
		Over-weight	171	36.5	59	41.8	50	56.2	62	40.0	47	61.0
		Obesity I	206	43.9	60	42.6	28	31.5	66	42.6	23	29.9
		Obesity II	79	16.8	19	13.5	6	6.7	24	15.5	2	2.6
		Obesity III	6	1.3	2	1.4	0	0.0	2	1.3	0	0.0
		Missing	18		8		0		0		0	

Depressive symptomatology[3]	Baseline	No or Minimal	304	62.4	94	63.1	54	60.7	94	60.6	52	67.5
		Mild-to-moderate	140	28.7	42	28.2	25	28.1	48	31.0	18	23.4
		Moderate-to-severe	43	8.8	13	8.7	10	11.2	13	8.4	7	9.1
	1 year	No or Minimal	329	74.1	102	76.7	70	82.4	110	77.5	60	82.2
		Mild-to-moderate	95	21.4	28	21.1	12	14.1	29	20.4	10	13.7
		Moderate-to-severe	20	4.5	3	2.3	3	3.5	3	2.1	3	4.1
		Missing	43		16		4		13		4	
	3 years	No or Minimal	315	74.5	89	73.0	66	77.6	95	70.9	61	82.4
		Mild-to-moderate	83	19.6	29	23.8	14	16.5	34	25.4	9	12.2
		Moderate-to-severe	25	5.9	4	3.3	5	5.9	5	3.7	4	5.4
		Missing	64		27		4		21		3	

BMI= body mass index; er-MedDiet= energy-restricted Mediterranean Diet.
[1]Comparisions relative to the total sample (N=487) or to the intervention group sample (N=240)
[2]Physical activity categories from the Rapid Assessment of physical activity (RAPA-1) questionnaire.
[3]Depressive symptomatology categories from the Beck's Depression Inventory II (BDI-II)

Table 3. Baseline cognitive scores, mental health and quality of life, and changes after 1 and 3 years of follow-up in all population [N=487]

	Time	Missing N (%)	Mean (95%CI)	Cohen's d (95%CI)	E. size	P-value*
Cognitive performance						
RAVTL: immediate recall	Baseline	1 (0.2)	7.5 (7.3, 7.7)	Ref		
	1y change	67 (13.8)	0.3 (0.0, 0.5)	0.14 (0.00, 0.27)	VS	0.064
	3y change	110 (22.6)	1.0 (0.6, 1.3)	0.38 (0.24, 0.52)	S	**<0.001**
RAVTL: delayed recall	Baseline	1 (0.2)	7.3 (7.1, 7.6)	Ref		
	1y change	66 (13.6)	0.3 (0.0, 0.5)	0.12 (-0.02, 0.25)	VS	0.064
	3y change	110 (22.6)	1.2 (0.8, 1.5)	0.44 (0.30, 0.58)	S	**<0.001**
RCFT: immediate recall	Baseline	9 (1.8)	14.6 (14, 15.2)	Ref		
	1y change	73 (15)	1.2 (0.7, 1.8)	0.30 (0.16, 0.43)	S	**<0.001**
	3y change	115 (23.6)	2.4 (1.8, 3)	0.53 (0.39, 0.67)	M	**<0.001**
RCFT: Delayed recall	Baseline	10 (2.1)	14.2 (13.6, 14.8)	Ref		
	1y change	78 (16)	1.3 (0.8, 1.8)	0.33 (0.20, 0.46)	S	**<0.001**
	3y change	117 (24)	3.0 (2.4, 3.6)	0.68 (0.54, 0.82)	M	**<0.001**
RCFT: recognition	Baseline	0 (0)	19.1 (18.9, 19.4)	Ref		
	1y change	65 (13.3)	0.8 (0.6, 1.1)	0.38 (0.24, 0.51)	S	**<0.001**
	3y change	109 (22.4)	1.3 (0.9, 1.7)	0.48 (0.34, 0.62)	M	**<0.001**
RCFT: copy	Baseline	7 (1.4)	27.7 (27.1, 28.4)	Ref		
	1y change	74 (15.2)	0.4 (-0.1, 0.9)	0.10 (-0.04, 0.23)	VS	0.090
	3y change	115 (23.6)	1.7 (1.0, 2.3)	0.37 (0.23, 0.50)	S	**<0.001**
SMDT	Baseline	50 (10.3)	36.7 (35.5, 37.9)	Ref		
	1y change	113 (23.2)	-0.7 (-1.6, 0.1)	-0.11 (-0.25, 0.03)	VS	0.137
	3y change	143 (29.4)	-2.2 (-3.6, -0.8)	-0.25 (-0.39, -0.10)	S	**<0.001**
Stroop: Interference	Baseline	0 (0)	-0.4 (-1.3, 0.5)	Ref		
	1y change	65 (13.3)	-0.2 (-1.1, 0.6)	-0.04 (-0.17, 0.09)	VS	0.991
	3y change	109 (22.4)	-0.8 (-1.9, 0.4)	-0.10 (-0.23, 0.04)	VS	0.086
CPT: Commission errors[3]	Baseline	11 (2.6)	22.3 (20.8, 23.9)	Ref		
	1y change	152 (36.5)	-1.5 (-2.7, -0.2)	-0.18 (-0.32, -0.03)	S	**0.014**
	3y change	269 (64.5)	-2.6 (-3.9, -1.3)	-0.38 (-0.55, -0.22)	S	**<0.001**
CPT: Hit reaction time[3]	Baseline	14 (3.4)	461.1 (453.1, 469.1)	Ref		
	1y change	87 (20.9)	-1.3 (-9.7, 7.2)	-0.02 (-0.17, 0.12)	VS	0.793
	3y change	202 (48.4)	-10.7 (-23.4, 1.9)	-0.19 (-0.36, -0.02)	S	0.274
CPT: Omission errors[3]	Baseline	10 (2.4)	7.3 (5.9, 8.7)	Ref		
	1y change	81 (19.4)	-1.1 (-2.8, 0.5)	-0.10 (-0.25, 0.04)	VS	0.099
	3y change	198 (47.5)	0.8 (-1.8, 3.3)	0.06 (-0.10, 0.23)	VS	0.865
IGT: total[3]	Baseline	18 (4.3)	2.1 (0, 4.2)	Ref		
	1y change	96 (23.0)	0.8 (-2.4, 4)	0.04 (-0.11, 0.19)	VS	0.412
	3y change	192 (46.0)	5.0 (0.8, 9.2)	0.26 (0.09, 0.42)	S	**0.024**
Mental health: Depressive symptomatology (BDI) and QoL (SF-36)						
BDI-II: total score	Baseline	0 (0)	8.5 (7.9, 9.1)	Ref		
	1y change	43 (8.8)	-1.9 (-2.4, -1.4)	-0.75 (-0.89, -0.61)	M	**<0.001**
	3y change	64 (13.1)	-2.0 (-2.6, -1.4)	-0.79 (-0.93, -0.65)	L	**<0.001**
SF-36: Energy score	Baseline	18 (3.7)	61.5 (59.6, 63.5)	Ref		
	1y change	63 (12.9)	3.3 (1.5, 5.0)	0.73 (0.59, 0.87)	M	**<0.001**

	3y change	85 (17.5)	2.6 (0.8, 4.5)	0.59 (0.45, 0.73)	M	**0.004**
SF-36: Health score	Baseline	14 (2.9)	48.6 (47.6, 49.6)	Ref		
	1y change	67 (13.8)	2.0 (1.0, 3.0)	0.61 (0.47, 0.74)	M	**<0.001**
	3y change	79 (16.2)	1.3 (0.2, 2.3)	0.38 (0.25, 0.51)	S	**0.019**
SF-36: Pain score	Baseline	4 (0.8)	67.5 (65.2, 69.8)	Ref		
	1y change	47 (9.7)	0.4 (-2.0, 2.8)	0.08 (-0.05, 0.21)	VS	0.616
	3y change	70 (14.4)	1.6 (-1.0, 4.2)	0.31 (0.18, 0.45)	S	0.198
SF-36: Physical functioning score	Baseline	25 (5.1)	75.1 (73.3, 76.9)	Ref		
	1y change	77 (15.8)	4.0 (2.4, 5.6)	0.94 (0.79, 1.09)	L	**<0.001**
	3y change	91 (18.7)	4.6 (2.9, 6.3)	1.08 (0.92, 1.23)	L	**<0.001**
SF-36: Emotional role score	Baseline	4 (0.8)	86.2 (83.5, 88.9)	Ref		
	1y change	51 (10.5)	1.3 (-1.8, 4.4)	0.24 (0.11, 0.37)	S	0.242
	3y change	70 (14.4)	5.1 (1.9, 8.3)	0.91 (0.77, 1.05)	L	**0.002**
SF-36: Physical role score	Baseline	7 (1.4)	76.1 (73.0, 79.2)	Ref		
	1y change	54 (11.1)	1.9 (-1.5, 5.4)	0.32 (0.19, 0.45)	S	0.389
	3y change	72 (14.8)	3.9 (0.1, 7.7)	0.64 (0.50, 0.78)	M	**0.040**
SF-36: Social score	Baseline	12 (2.5)	77.7 (76.1, 79.3)	Ref		
	1y change	57 (11.7)	-1.5 (-3.2, 0.3)	-0.35 (-0.48, -0.22)	S	0.195
	3y change	78 (16)	-0.2 (-2.1, 1.7)	-0.04 (-0.18, 0.09)	VS	0.985
SF-36: Wellbeing score	Baseline	21 (4.3)	74.5 (72.7, 76.3)	Ref		
	1y change	76 (15.6)	-0.1 (-1.7, 1.6)	-0.01 (-0.14, 0.12)	VS	0.786
	3y change	76 (15.6)	-0.1 (-1.7, 1.6)	-0.01 (-0.14, 0.12)	VS	0.786

95%CI= 95% confidence interval. BDI=Beck's Depression Inventary -II. CPT= Conner's Performance Task. IGT= Iowa Gambling Task. N= number. RAVTL= Rey Auditory Verbal Learning Test. RCFT= Rey-Osterrieth Complex Figure Test. Ref= Reference category. SDMT= Symbol Digit Modalities Test. 1y= 1 year. 3y= 3 years.

[#]Inverse probability weights were applied to compute 1y and 3y mean change and P-values.

[1]Positive/negative values for 1y and 3y change indicate increase and decrease, respectively, compared to the baseline value.

[2]Effect Size: VS= very small (Cohen's d <0.2); S= small (Cohen's d (0.2-0.5)); M= medium (Cohen's d (0.5-0.8)); L= large (Cohen's d (0.8-1.2)); VL= very large (Cohen's d ≥ 1.2).

[3]IGT and CPT tests were not applied to participants recruited in the University of Valencia (N=70), so the sample size is N=417. For CPT, higher scores indicate worse performance.

*1-year and 3-years change from baseline were analyzed using linear mixed effects models, adjusted by intervention group, gender, baseline age, years of education, intelligence quotient, use of lipid-lowering drugs, use of tranquilizers or sedatives, prediabetes and diabetes, smoking status and baseline weight (only for cognitive scores). Participant and study site were included as random effects.

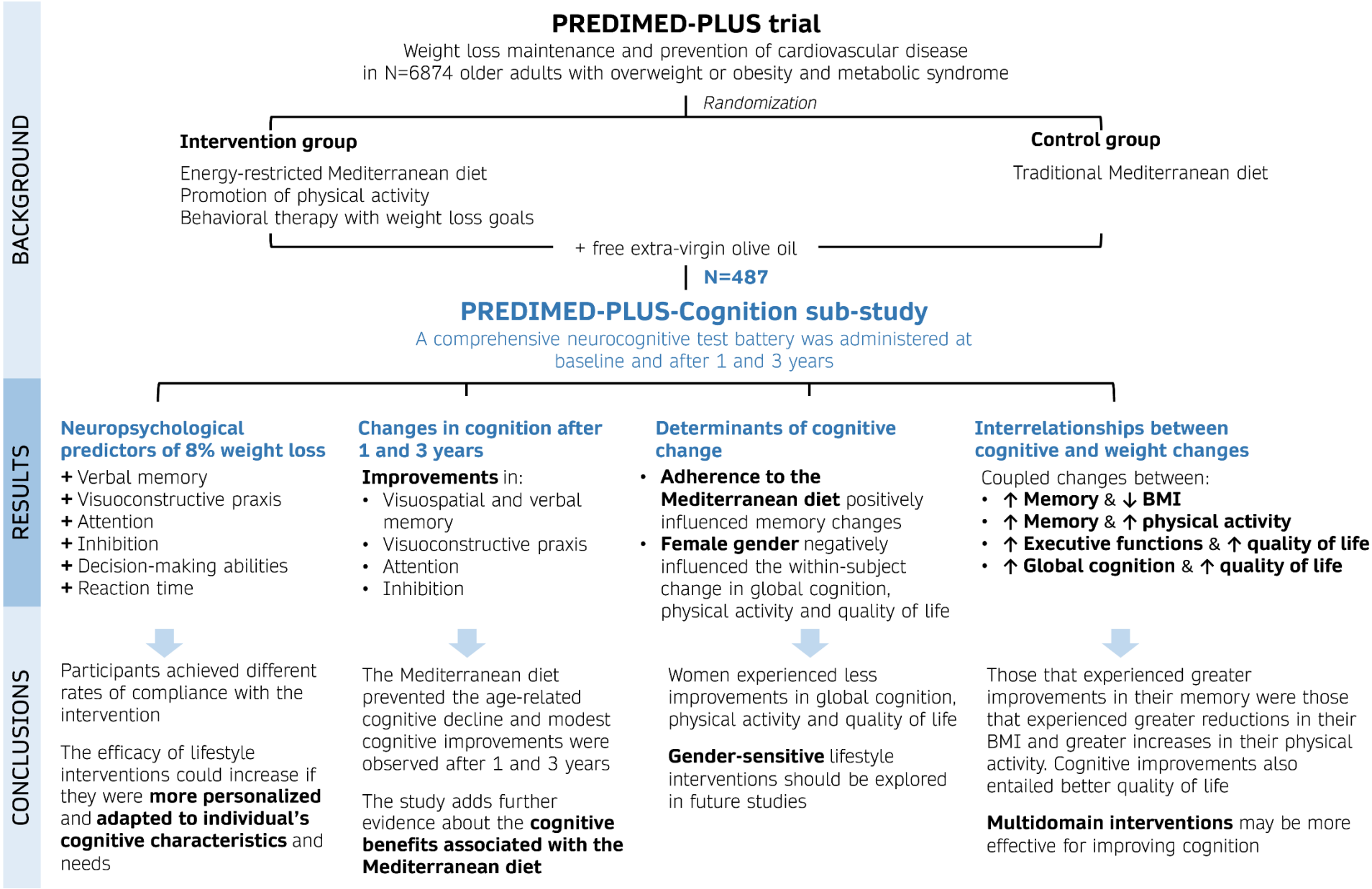

Figure 1. Summary of the main results of the present study.

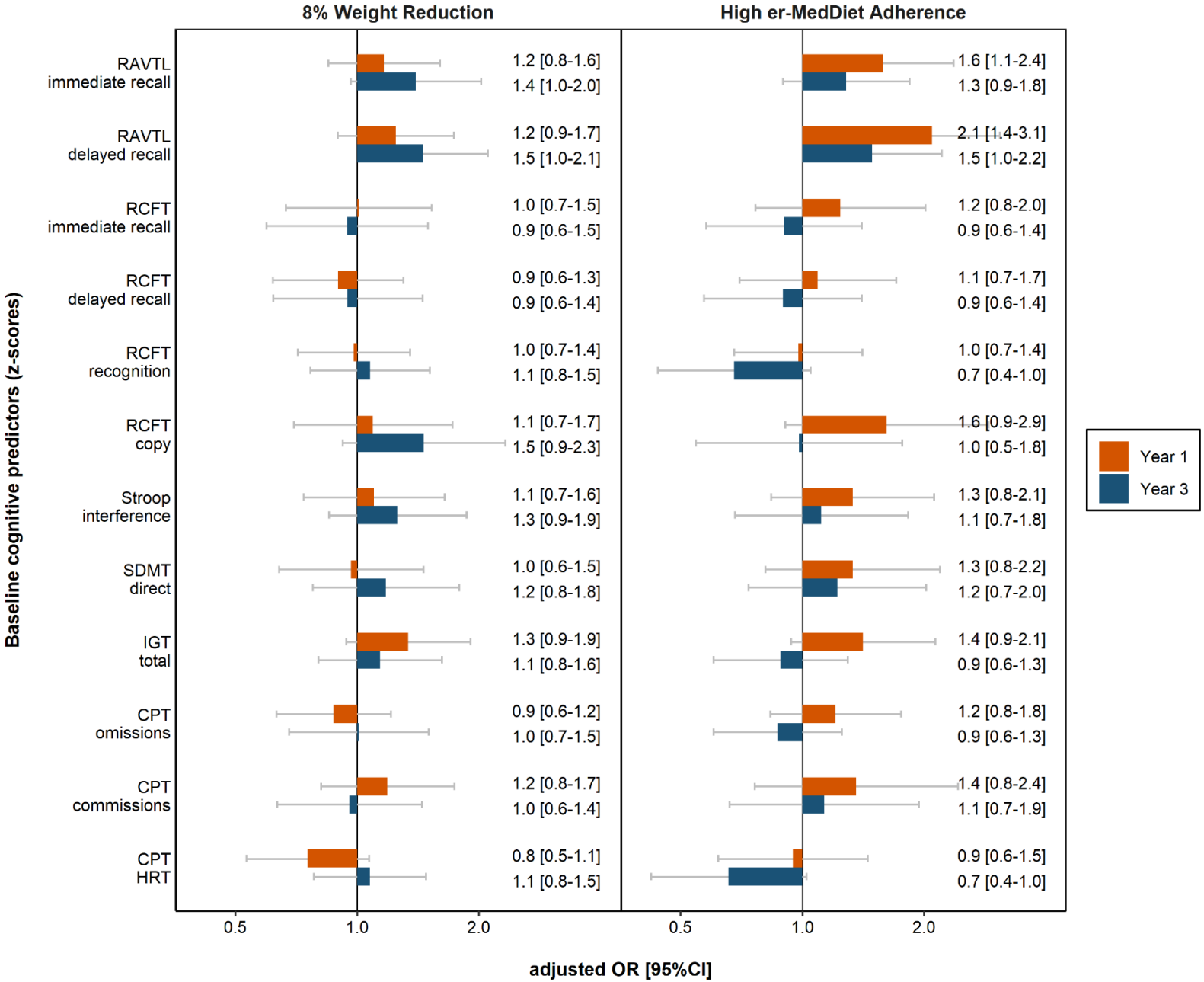

Figure 2. Multivariable-adjusted* odds ratio (OR) and 95% confidence intervals (95%CI) of 8% weight reduction from baseline to year 1 and year 3 (left panel) and high er-MedDiet adherence at 1 and 3 years (right panel) according to baseline cognitive scores (z-scores) in individuals allocated to the intervention group [N=240].*Models were adjusted by gender, age, years of education, intelligence quotient, diabetes, prediabetes, use of treatment for cholesterol, use of tranquilizers or sedatives, smoking status, baseline weight and study center. er-MedDiet= energy-restricted Mediterranean diet. RAVTL= Rey Auditory Verbal Learning Test. RCFT= Rey-Osterrieth Complex Figure Test. SDMT= Symbol Digit Modalities Test. IGT= Iowa Gambling Task. CPT= Conner's Performance Task. HRT= hit reaction time. CPT and IGT scores were not applied to participants to participants recruited in the University of Valencia, so the sample size for these tests is N=215. Higher scores in CPT indicate worse performance.

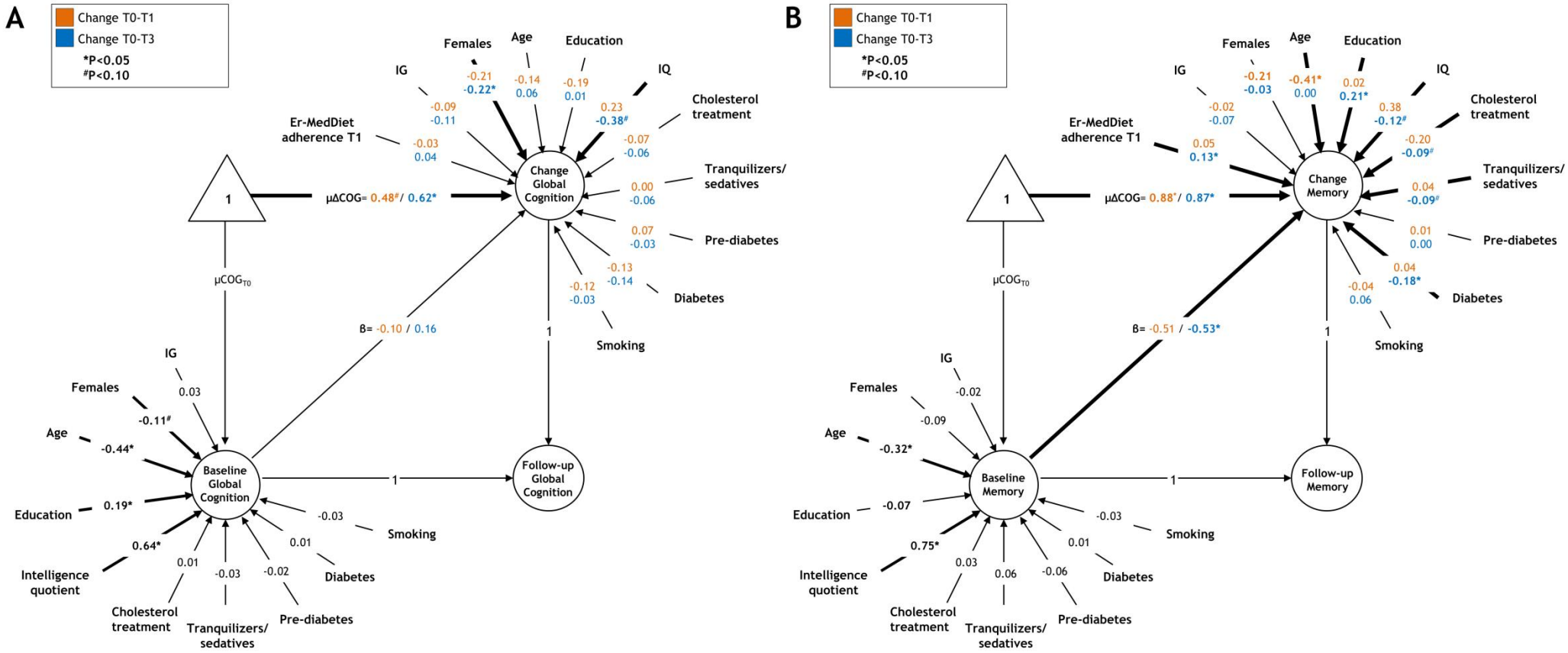

Figure 3. Structural Equation Model (SEM) representations of the univariate part of bivariate latent change score models (BLCSM) of global cognition and memory, showing (A) the effect of baseline characteristics on baseline global cognition and the mean rate of change in global cognition (ΔCOG); and (B) the effect of baseline characteristics on baseline memory and the mean rate of change in memory (ΔCOG). Values represent standardized estimates; orange color indicates change from baseline (T0) to 1 year (T1), while blue color indicates change from T0 to 3 years (T3). *P<0.05. #P<0.10. Bold lines refer to significant coefficients (<0.05 or <0.10 level). Measurement invariance of latent variables and correlated residual errors over time were assumed.

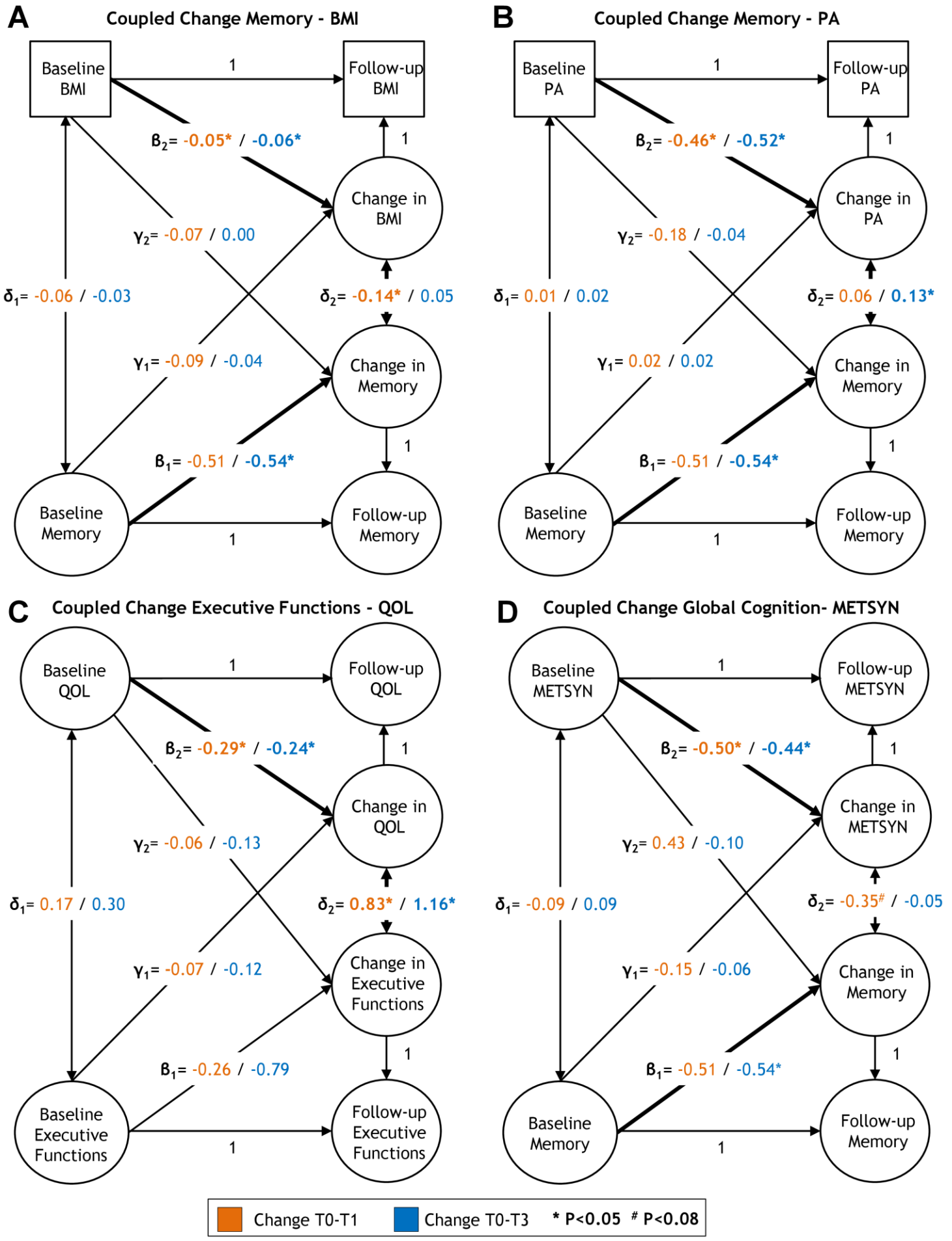

Figure 4. Structural Equation Model (SEM) representations of bivariate latent change score models (BLCSM) from Supplementary Tables 7-10. (A) Coupled change between memory and body mass index (BMI). (B) Coupled change between memory and physical activity (PA). (C) Coupled change between executive functions and quality of life (QoL). (D) Coupled change between cognition and metabolic syndrome (METSYN). Values represent standardized estimates; orange color indicates change from baseline (T0) to 1 year (T1), while blue color indicates change from T0 to 3 years (T3). *P<0.05. #P=0.08. Bold lines refer to significant coefficients (<0.05 level). Measurement invariance of latent variables and correlated residual errors over time were assumed.