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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.

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Conflict of interest

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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

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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.

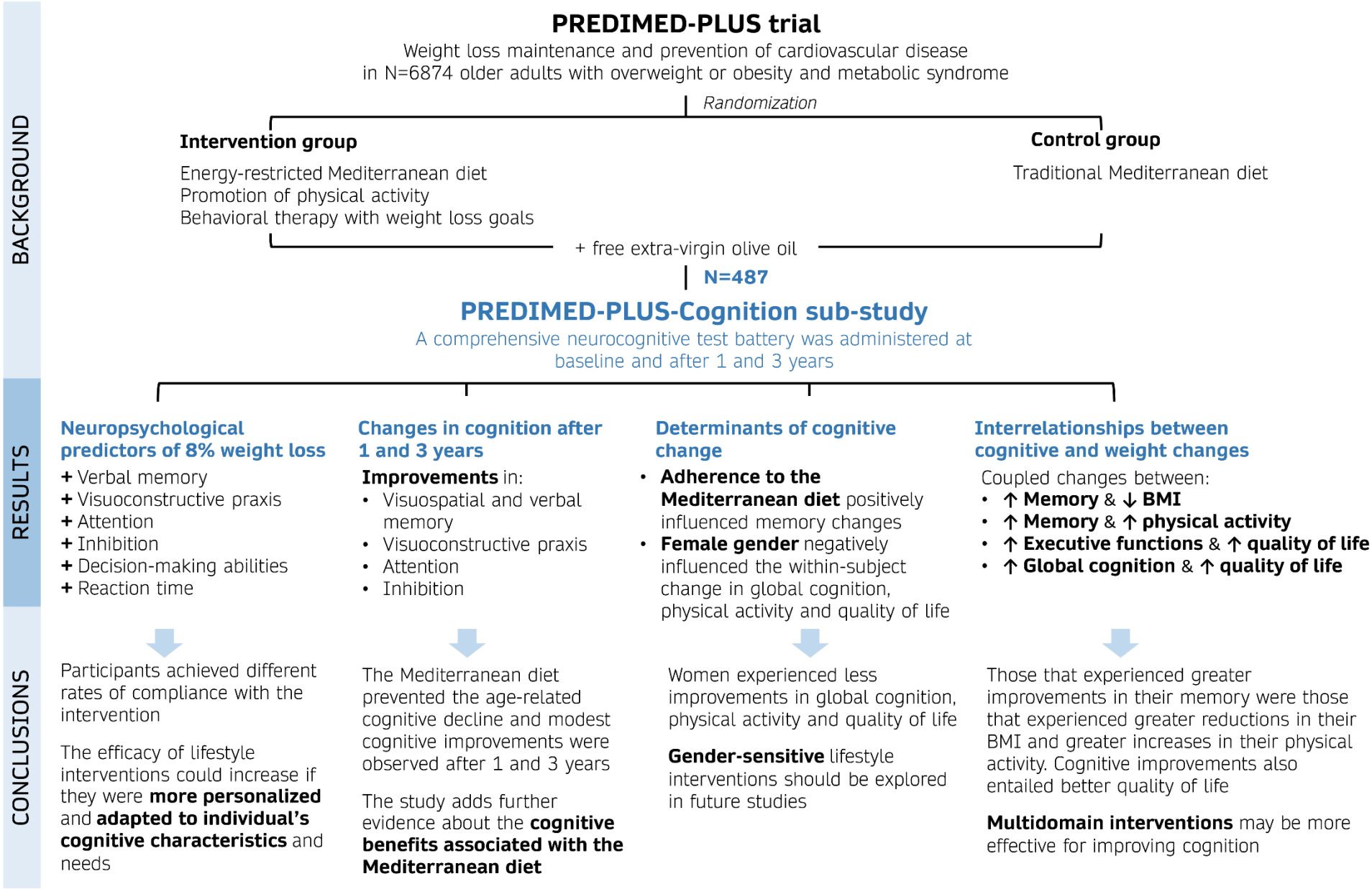

Figure 1. Summary of the main results of the present study.

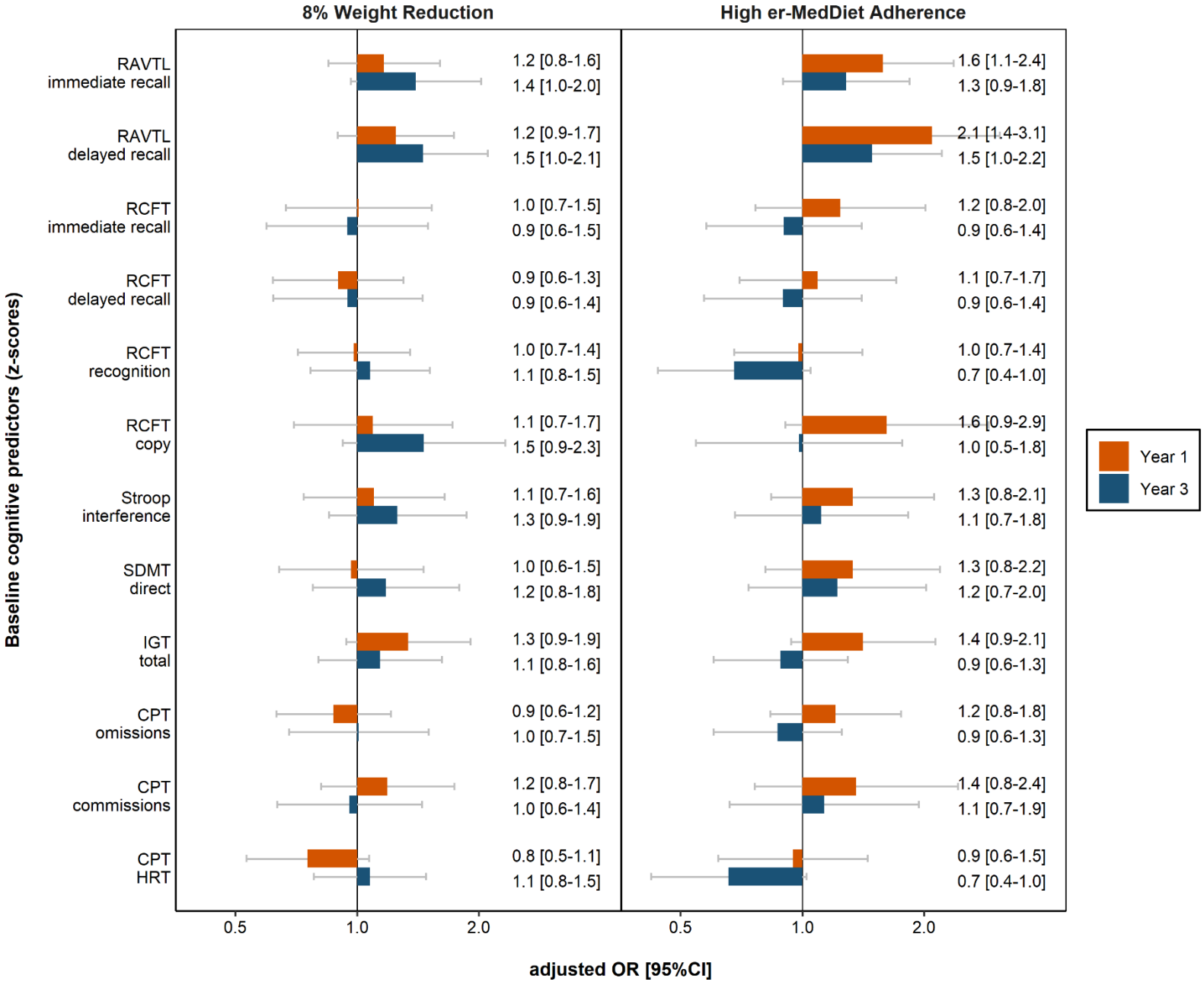

Figure 2. Multivariable-adjusted* odds ratio (OR) and 95% confidence intervals (95%CI) of 8% weight reduction from baseline to year 1 and year 3 (left panel) and high er-MedDiet adherence at 1 and 3 years (right panel) according to baseline cognitive scores (z-scores) in individuals allocated to the 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.

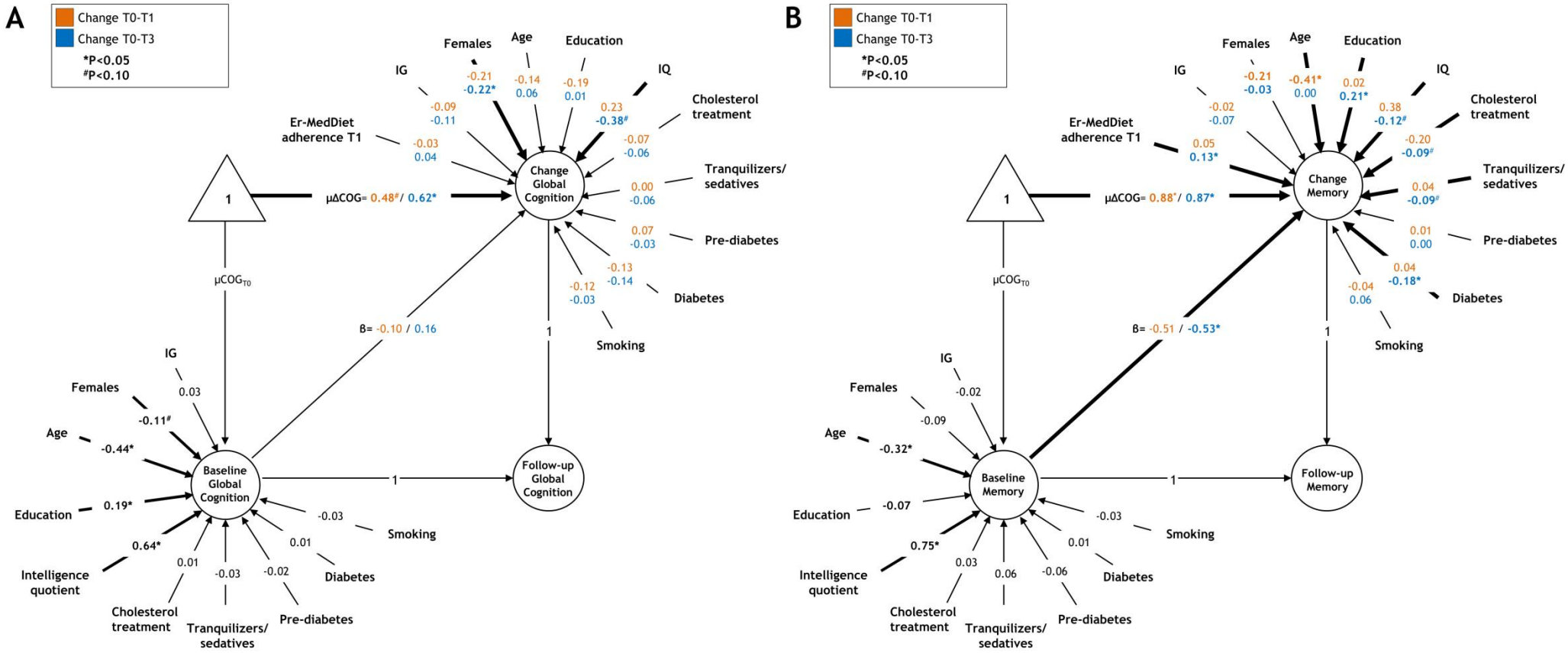

Figure 3. Structural Equation Model (SEM) representations of the univariate part of bivariate latent change score models (BLCSM) of global cognition and memory, showing (A) the effect of baseline characteristics on baseline global cognition and the mean rate of change in global cognition (ΔCOG); and (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.

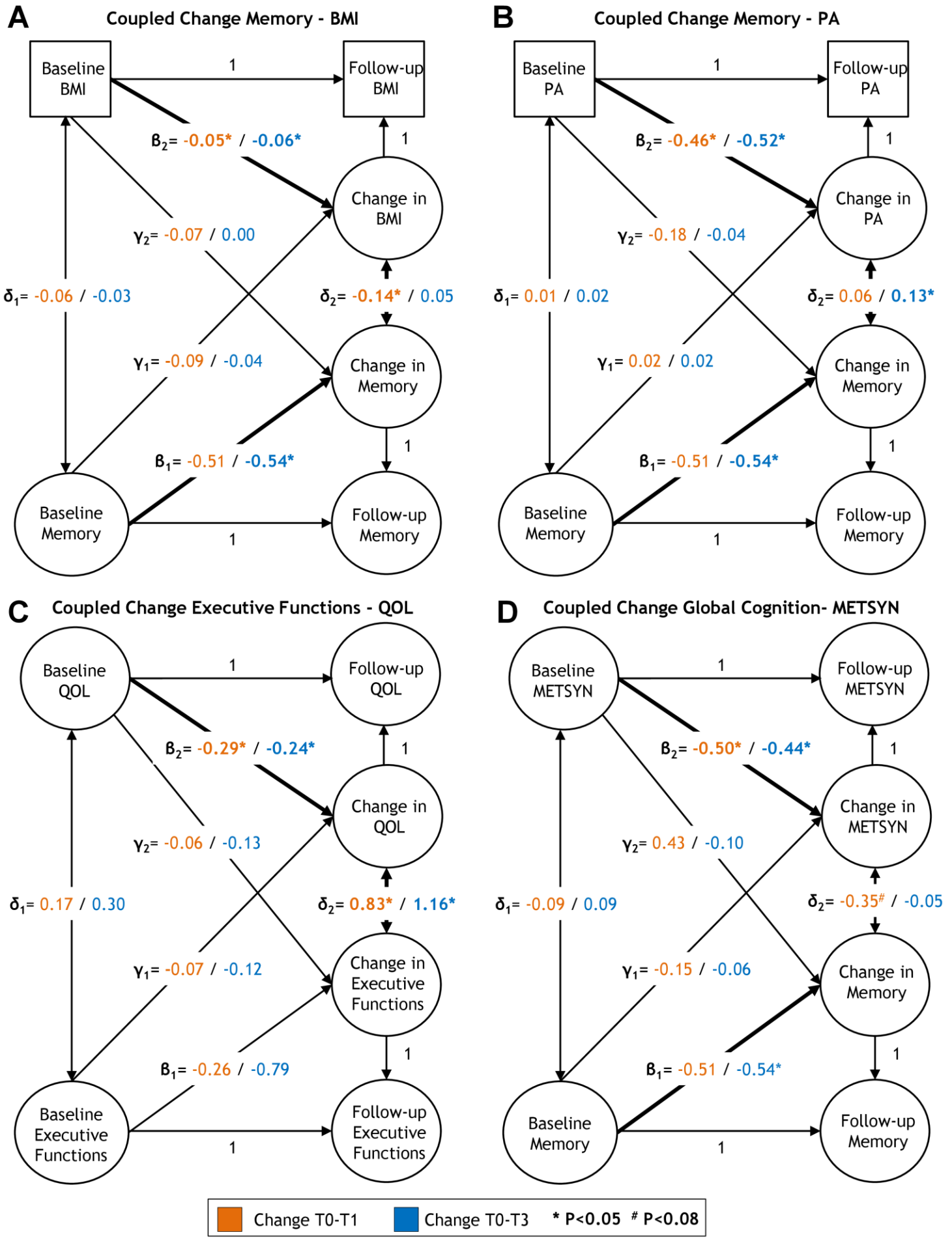

Figure 4. Structural Equation Model (SEM) representations of bivariate latent change score models (BLCSM) from Supplementary Tables 7-10. (A) Coupled change between memory and body mass index (BMI). (B) Coupled change between memory and physical activity (PA). (C) Coupled change between executive functions 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.

SUPPORTING MATERIAL

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Supplementary Table 1. Exclusion criteria from the present study

Number	Criteria
1	History of chronic medical illness or neurological condition that may affect cognitive function
2	Current psychiatric diagnosis or in the year prior to inclusion
3	Traumatic brain injury with loss of consciousness more than 2 minutes, learning disorder, mental retardation or psychotic disorder
4	Psychoactive substance abuse or dependence (either currently or in the past 6 months)
5	Comorbid Eating Disorder (DSM -IV-TR criteria; APA, 2000)

Supplementary Table 2. Comparison of subjects with and without complete follow-up in the third-year neuropsychological visit.

Variable	Category	Complete Follow-up N (%)	No Complete Follow-up N (%)	P-value
N		**378 (100)**	**109 (100)**	
Study group	IG	184 (48.7)	56 (51.4)	0.698
Gender	Women	187 (49.5)	59 (54.1)	0.454
Age	*Mean (SD)*	65.4 (4.76)	64.8 (4.56)	0.268
Education (years)	*Mean (SD)*	11.7 (5.35)	11.4 (5.29)	0.567
Employment status	Employed	70 (18.6)	21 (19.3)	0.210
	Unemployed	27 (7.16)	9 (8.26)	
	Housework	37 (9.81)	13 (11.9)	
	Retired	240 (63.7)	62 (56.9)	
	Other	3 (0.80)	4 (3.67)	
Smoking status	Current smoker	41 (10.8)	18 (16.5)	0.152
Use of treatment for high cholesterol		197 (52.1)	48 (44.0)	0.168
Use of tranquilizers/Sedatives		85 (22.5)	27 (24.8)	0.711
MMSE total score		28.6 (1.58)	28.4 (2.04)	0.259
Er-MedDiet adherence	Low	175 (46.3)	46 (42.2)	0.313
	Medium	158 (41.8)	44 (40.4)	
	High	45 (11.9)	19 (17.4)	
BMI category	Over-weight	105 (27.8)	28 (25.7)	0.353
	Obesity I	188 (49.7)	48 (44.0)	
	Obesity II	85 (22.5)	33 (30.3)	
Diabetes status	Prediabetes	51 (13.5)	24 (22.0)	0.078
	Diabetes	120 (31.7)	28 (25.7)	
Physical activity	Sedentary	49 (13.0)	27 (24.8)	**0.006**
	Under-active	257 (68.0)	69 (63.3)	
	Moderately active	40 (10.6)	4 (3.67)	
	Active	32 (8.47)	9 (8.26)	
Depressive symptomatology	No or Minimal	241 (63.8)	63 (57.8)	0.466
	Mild-to-moderate	106 (28.0)	34 (31.2)	
	Moderate-to-severe	31 (8.20)	12 (11.0)	

BMI: body mass index. IG= intervention group. MMSE: mini-mental state examination.

Supplementary Table 3. Detailed description of the statistical analysis section regarding the bivariate latent change score models (BLCSM) and the treatment of missing data

STEP 1	**Latent Variables**	**Memory**	5 scores (standardized on baseline mean and SD and normalized if necessary) of verbal and visual memory tests: RAVTL immediate recall; RAVTL delayed recall; RCFT immediate recall; RCFT delayed recall; RCFT recognition
		Executive functions and attention	7 scores (standardized on baseline mean and SD and normalized if necessary): RCFT copy; SDMT; Stroop interference; CPT-omission errors*; CPT-commission errors*; CPT-HRT*; IGT As higher CPT scores indicate worse performance, CPT scores were reversed. CPT and IGT tests were not administered to participants recruited in the University of Valencia (N=70)
		Global cognition	Included all the tests from memory and executive functions
		Quality of Life (QoL)	6 scores from the SF-36 questionnaire: Physical functioning; Energy; Wellbeing; Social functioning; Pain; Health scores
		Metabolic syndrome (METSYN)	5 features: Body waist (cm); Triglycerides (mg/dL); HDL-cholesterol (mg/dL, reversed); Systolic blood pressure (mmHg); Glucose (mg/dL).
STEP 2	**Confirmatory Factor Analysis (CFA)**		As a prerequisite of longitudinal analysis of latent variables, confirmatory factor analysis (CFA) was used to test the latent constructs of memory, executive functions, global cognition, metabolic syndrome and quality of life for measurement invariance over time, which means to ensure that the measured constructs are indeed equivalent between time points. Accordingly, a series of increasingly strict parsimonious models were devised and compared. More parsimonious or strict models allow a lesser number of parameters to vary over time for the same latent construct. Such parameters are factor loadings (representativeness of each item, labeled as λ), intercepts (mean levels of each item, labeled as t) and residual variances (unexplained influences predicting item responses, labeled as ε). Levels of invariance range from configural that allows λ, t and ε to vary across time, followed by metric invariance that constraints λ, scalar invariance that also constraints t and residual invariance that additionally constraints ε.
STEP3	**Bivariate Latent Change Score Models (BLCSM)**		All the BLCSM were performed separately for global cognition, memory and executive functions (hereafter in the methods section the three constructs are referred to "cognition") and for T0 to T1 change and T0 to T3 change. Then, BLCSM were fitted to examine within-person change in cognition and BMI, PA, QoL and metabolic syndrome and to identify between-person differences in the within-person change. They were also used to study longitudinal within-subject directional associations between cognition and BMI, PA, QoL and metabolic syndrome that change over time. Specifically, 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: 1) Baseline covariance (labeled as δ1): "*Are scores on global cognition at T0 correlated with BMI at T0*?" 2) Global cognition as leading variable of BMI changes (labeled as ϒ1): "*Do global cognition scores at T0 predict degree of change in BMI between T0 and T1?"* 3) BMI as leading variable (labeled as ϒ2): "*Do BMI at T0 predict degree of change in global cognition between T0 and T1?*" 4) Correlated change (labeled as δ2): "*Is the degree of improvement in global cognition correlated with the degree of BMI change in individuals?"* Estimates were presented as standardized coefficients and p-values.
Determination of model quality in structural equation models (SEM)			Fit indexes in SEM consisted of comparative fit index (CFI) and Tucker Lewis index (TLI), from which values between 0.90-0.95 are considered marginally acceptable whereas values above 0.95 are considered good, as well as, root-mean-square error of approximation (RMSEA) and standardized root-mean-square residual (SRMR), from which values between 0.06-0.08 or lower generally indicate an acceptable level of fit (Hu & Bentler, 1999). To compare change in model fit indexes when testing for measurement invariance from the unconstrained to constrained in CFA, ΔCFI of <-0.010, ΔTLI of <-0.015, ΔRMSEA of >0.015 and ΔSRMR >0.030 suggest that the less parsimonious model should be chosen (Chen, 2007; Cheung & Rensvold, 2009; Meade et al.,

		2008). Regarding the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the lower the value, the better the fit, with differences of 6 or greater suggesting evidence of model difference (Raftery, 1995).
MISSING DATA	**Missing data in the present 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 values in variables collected in these visits were assumed to be completely at random (MCAR). However, for the neuropsychological visits, attrition was present in 65 (13.3%) participants at T1 and 109 (22.4%) participants at T3.
	Treatment of missing data in the neuropsychological visits	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) (Seaman & White, 2013). Attrition (r=1, yes; r=0, no) was defined as the presence of a missing value for the neuropsychological visit T1 (r1) or T3 (r3). Moreover, given that CPT and IGT tests were not performed in participants recruited in the University of Valencia (N=70), additional IPW were calculated for T1 and T3 analyses of such variables, including the remaining N=417 participants. Therefore, 4 different IPW were computed (labelled as "r1.all", "r3.all", "r1.12", "r3.12"). First, variables that were significantly associated with attrition (P<0.05 in chi-squared test) were selected to be included in the missingness model. Then, IPW were calculated using a logistic regression model as the inverse of the estimated probability of completing the follow-up based on observed related covariates. Model selection was based on Hosmer and Lemeshow goodness of fit (GOF) test (P>0.05) and the area under the ROC curve (AUC), with values of AUC=0.73 for "r1.all" (adjusted by study center, family history of hypercholesterolemia, use of metformin, intelligence quotient, BMI, family history of stroke and use of treatment for cholesterol); AUC=0.84 for "r3.all" (adjusted by family history of diabetes mellitus, PA, family history of hypercholesterolemia, use of metformin, intervention group, BMI and treatment for cholesterol); AUC=0.72 for "r1.12" (adjusted by study site, inclusion date, BMI, family history of cholesterol, use of metformin, intelligence quotient, er-MedDiet adherence and intervention group); and finally AUC=0.73 for "r3.12" (adjusted by study site, family history of diabetes mellitus, PA, gender, depression, family history of hypercholesterolemia, family history of diabetes, use of medication for cholesterol, intelligence quotient, presence of cataracts, family history of stroke, BMI, use of metformin and er-MedDiet adherence). Finally, weight stability was revised and weight trimming was applied when necessary to avoid extreme weights. Finally, weights were normalized to the sample size so that the sum of weights was equivalent to the total sample size.
	Missing data in SEM	In SEM missing data was handled using full-information maximum likelihood (FIML) estimation with robust standard errors. FIML estimates the likelihood function for each individual based on the variables that are present, and the FIML fit function is computed for each set of cases with the same unique pattern of missing values (casewise likelihood).

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Supplementary Table 4. Estimates from causal mediation analysis testing the association between baseline cognitive scores and the achievement of the 8% weight loss goal after 1 and 3 years, mediated by high er-MedDiet adherence (yes/no) at 1 year in individuals allocated to the intervention group [N=240]

Baseline cognitive scores (z-score)	Effect	1 Year		3 Years	
		Estimate (95%CI)	p-value	Estimate (95%CI)	p-value
RAVTL: immediate recall	Total Effect	0.03 (-0.04, 0.10)	0.41	0.06 (-0.01, 0.13)	0.14
	ADE	0.01 (-0.05, 0.08)	0.71	0.05 (-0.02, 0.12)	0.20
	ACME	0.02 (-0.01, 0.05)	0.24	0.01 (-0.01, 0.03)	0.31
	Prop. Mediated	0.31 (-2.74, 5.76)	0.44	0.13 (-0.89, 1.40)	0.37
RAVTL: delayed recall	Total Effect	0.04 (-0.03, 0.12)	0.25	0.07 (0.00, 0.15)	0.08
	ADE	0.02 (-0.05, 0.09)	0.63	0.06 (-0.02, 0.13)	0.16
	ACME	0.02 (0.00, 0.05)	**0.04**	0.02 (0.00, 0.04)	0.06
	Prop. Mediated	0.46 (-3.78, 3.83)	0.27	0.20 (-0.85, 1.35)	0.14
RCFT: immediate recall	Total Effect	-0.01 (-0.09, 0.08)	0.88	0.00 (-0.08, 0.09)	0.97
	ADE	-0.02 (-0.10, 0.07)	0.72	-0.01 (-0.08, 0.08)	0.85
	ACME	0.01 (-0.02, 0.04)	0.55	0.01 (-0.02, 0.03)	0.55
	Prop. Mediated	0.07 (-3.85, 4.28)	0.88	0.06 (-3.08, 4.04)	0.87
RCFT: delayed recall	Total Effect	-0.03 (-0.10, 0.05)	0.50	0.00 (-0.08, 0.08)	0.89
	ADE	-0.03 (-0.10, 0.04)	0.41	-0.01 (-0.07, 0.07)	0.85
	ACME	0.00 (-0.03, 0.03)	0.83	0.00 (-0.02, 0.02)	0.86
	Prop. Mediated	0.05 (-3.53, 3.29)	0.89	0.05 (-3.15, 2.38)	0.87
RCFT: recognition	Total Effect	0.00 (-0.07, 0.06)	0.88	0.01 (-0.06, 0.09)	0.74
	ADE	0.00 (-0.07, 0.06)	0.90	0.01 (-0.05, 0.08)	0.69
	ACME	0.00 (-0.03, 0.03)	1.00	0.00 (-0.02, 0.02)	0.90
	Prop. Mediated	0.19 (-4.34, 4.07)	0.72	0.06 (-3.62, 4.44)	0.88
RCFT: copy	Total Effect	0.00 (-0.09, 0.10)	0.93	0.06 (-0.02, 0.16)	0.17
	ADE	-0.01 (-0.10, 0.08)	0.76	0.05 (-0.03, 0.14)	0.22
	ACME	0.02 (-0.01, 0.05)	0.31	0.01 (-0.01, 0.04)	0.34
	Prop. Mediated	0.13 (-4.14, 6.46)	0.85	0.16 (-1.34, 1.68)	0.39
SDMT: direct	Total Effect	-0.02 (-0.11, 0.07)	0.59	0.01 (-0.07, 0.09)	0.76
	ADE	-0.03 (-0.11, 0.05)	0.39	0.01 (-0.07, 0.08)	0.85
	ACME	0.01 (-0.02, 0.05)	0.49	0.00 (-0.02, 0.03)	0.66
	Prop. Mediated	-0.01 (-4.34, 5.79)	0.97	0.10 (-2.47, 2.38)	0.76
Stroop: interference	Total Effect	0.01 (-0.07, 0.10)	0.80	0.04 (-0.04, 0.13)	0.31
	ADE	0.00 (-0.07, 0.08)	0.99	0.04 (-0.04, 0.12)	0.37
	ACME	0.01 (-0.02, 0.04)	0.47	0.01 (-0.02, 0.03)	0.52
	Prop. Mediated	0.17 (-5.03, 5.95)	0.74	0.11 (-1.66, 2.33)	0.57
IGT: total	Total Effect	0.05 (-0.03, 0.14)	0.29	0.02 (-0.06, 0.09)	0.71
	ADE	0.04 (-0.04, 0.12)	0.38	0.01 (-0.06, 0.08)	0.90
	ACME	0.01 (-0.02, 0.05)	0.42	0.01 (-0.02, 0.04)	0.47
	Prop. Mediated	0.21 (-2.83, 2.62)	0.49	0.17 (-4.15, 4.37)	0.7
CPT: omissions	Total Effect	-0.03 (-0.12, 0.07)	0.60	0.00 (-0.10, 0.10)	0.97
	ADE	-0.04 (-0.12, 0.06)	0.44	-0.01 (-0.10, 0.09)	0.88

	ACME	0.01 (-0.03, 0.05)	0.61	0.01 (-0.02, 0.03)	0.67
	Prop. Mediated	0.00 (-4.47, 4.91)	0.99	0.05 (-2.79, 2.90)	0.86
CPT: commissions	Total Effect	0.03 (-0.05, 0.13)	0.46	-0.02 (-0.10, 0.07)	0.63
	ADE	0.02 (-0.06, 0.10)	0.55	-0.03 (-0.10, 0.06)	0.52
	ACME	0.01 (-0.02, 0.04)	0.51	0.01 (-0.02, 0.03)	0.61
	Prop. Mediated	0.22 (-3.19, 3.48)	0.56	0.00 (-3.24, 3.06)	0.98
CPT: HRT	Total Effect	-0.05 (-0.13, 0.03)	0.23	0.03 (-0.05, 0.10)	0.51
	ADE	-0.05 (-0.13, 0.03)	0.22	0.02 (-0.05, 0.10)	0.5
	ACME	0.00 (-0.04, 0.03)	0.94	0.00 (-0.02, 0.03)	0.95
	Prop. Mediated	0.06 (-3.33, 1.76)	0.86	0.05 (-2.90, 2.42)	0.87

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.
ADE= average direct effects. ACME= average causal mediation effects. 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.

Supplementary Table 5. Baseline cardiovascular biomarkers and indicators of intervention adherence; and changes after 1 and 3 years of follow-up in all population [N=487]

	Time	Missing N (%)	Mean (95%CI)	Cohen's d	E. size	P-value*
Cardiovascular Biomarkers						
Weight (kg)	Baseline	0 (0.0)	86.1 (84.9, 87.3)	Ref		
	1y change	3 (0.6)	-3.7 (-4.1, -3.3)	-1.23 (-1.38, -1.08)	VL	**<0.001**
	3y change	18 (3.7)	-3.3 (-3.8, -2.8)	-1.07 (-1.21, -0.93)	L	**<0.001**
BMI (kg/m^2)	Baseline	0 (0.0)	32.5 (32.2, 32.8)	Ref		
	1y change	3 (0.6)	-1.4 (-1.5, -1.2)	-0.86 (-1.00, -0.73)	L	**<0.001**
	3y change	18 (3.7)	-1.1 (-1.2, -0.9)	-0.64 (-0.77, -0.51)	M	**<0.001**
Waist (cm)	Baseline	0 (0.0)	107.7 (106.9, 108.6)	Ref		
	1y change	23 (4.7)	-4.0 (-4.5, -3.5)	-1.43 (-1.58, -1.27)	VL	**<0.001**
	3y change	54 (11.1)	-3.1 (-3.7, -2.5)	-1.07 (-1.21, -0.92)	L	**<0.001**
Hip (cm)	Baseline	0 (0.0)	109.4 (108.6, 110.2)	Ref		
	1y change	24 (4.9)	-2.2 (-2.6, -1.8)	-0.87 (-1.01, -0.73)	L	**<0.001**
	3y change	54 (11.1)	-1.6 (-2.1, -1.2)	-0.63 (-0.76, -0.49)	M	**<0.001**
Diastolic blood pressure (mmHg)	Baseline	1 (0.2)	80.6 (79.7, 81.5)	Ref		
	1y change	14 (2.9)	-2.6 (-3.5, -1.8)	-0.84 (-0.98, -0.70)	L	**<0.001**
	3y change	27 (5.5)	-1.7 (-2.7, -0.7)	-0.53 (-0.66, -0.40)	M	**0.001**
Systolic blood pressure (mmHg)	Baseline	2 (0.4)	142.9 (141.5, 144.4)	Ref		
	1y change	15 (3.1)	-5.5 (-7, -4.1)	-1.38 (-1.54, -1.23)	VL	**<0.001**
	3y change	28 (5.7)	-3.9 (-5.4, -2.4)	-0.97 (-1.11, -0.83)	L	**<0.001**
Fasting plasma glucose (mg/dL)	Baseline	1 (0.2)	116.2 (113.5, 119)	Ref		
	1y change	34 (7)	-5.5 (-7.4, -3.7)	-1.09 (-1.24, -0.95)	L	**<0.001**
	3y change	59 (12.1)	-2.0 (-4.4, 0.3)	-0.38 (-0.51, -0.25)	S	0.084
HbA1c (%)	Baseline	17 (3.5)	6.1 (6.1, 6.2)	Ref		
	1y change	47 (9.7)	-0.2 (-0.3, -0.2)	-0.25 (-0.38, -0.12)	S	**<0.001**
	3y change	80 (16.4)	-0.1 (-0.1, 0)	-0.08 (-0.21, 0.06)	VS	**0.033**
HDL-cholesterol (mg/dL)	Baseline	0 (0.0)	51.3 (50.2, 52.4)	Ref		
	1y change	33 (6.8)	2.2 (1.5, 3)	0.70 (0.56, 0.83)	M	**<0.001**
	3y change	58 (11.9)	0.9 (0.2, 1.6)	0.28 (0.15, 0.41)	S	**0.018**
LDL-cholesterol (mg/dL)	Baseline	34 (7)	125.3 (122.1, 128.5)	Ref		
	1y change	70 (14.4)	-4.2 (-7, -1.4)	-0.75 (-0.89, -0.60)	M	**0.001**
	3y change	184 (37.8)	-10.6 (-14.6, -6.6)	-1.79 (-1.97, -1.60)	VL	**<0.001**
Total cholesterol (mg/dL)	Baseline	0 (0.0)	207.9 (204.3, 211.5)	Ref		
	1y change	33 (6.8)	-5.2 (-8.3, -2)	-0.85 (-0.98, -0.71)	L	**0.001**
	3y change	58 (11.9)	-13.5 (-17.2, -9.8)	-2.14 (-2.33, -1.95)	VL	**<0.001**
Triglycerides (mg/dL)	Baseline	0 (0.0)	165.6 (156.9, 174.3)	Ref		
	1y change	34 (7)	-18.6 (-24.6, -12.5)	-2.05 (-2.23, -1.87)	VL	**<0.001**
	3y change	59 (12.1)	-23.8 (-31.9, -15.7)	-2.48 (-2.68, -2.28)	VL	**<0.001**

Intervention adherence						
er-MedDiet adherence (0-17 points)	Baseline	0 (0.0)	7.8 (7.6, 8.0)	Ref		
	1y change	17 (3.5)	3.9 (3.6, 4.2)	2.33 (2.13, 2.52)	VL	**<0.001**
	3y change	46 (9.4)	3.8 (3.5, 4.1)	2.27 (2.07, 2.46)	VL	**<0.001**
PA (MET x min/week)[3]	Baseline	0 (0.0)	2360.8 (2179.5, 2542.1)	Ref		
	1y change	14 (2.9)	830.6 (618.1, 1043.1)	17.74 (16.61, 18.86)	VL	**<0.001**
	3y change	45 (9.2)	820.1 (605.9, 1034.4)	17.65 (16.53, 18.76)	VL	**<0.001**
Total Energy intake (Kcal)	Baseline	0 (0.0)	2406.1 (2354.1, 2458.2)	Ref		
	1y change	23 (4.7)	-161.1 (-210.1, -112)	-6.80 (-7.24, -6.35)	VL	**<0.001**
	3y change	123 (25.3)	1119.5 (677.2, 1561.9)	24.04 (22.51, 25.54)	VL	**<0.001**

95%CI= 95% confidence interval.. HbA1c= glycosylated hemoglobin. MET= metabolic equivalent task. HDL = High-density lipoprotein. LDL = Low-density lipoprotein. [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]From the Short Version of the Minnesota Leisure Time PA Questionnaire (VREM).

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

Supplementary Table 6. Nested models fit indices for testing measurement invariance of cognitive latent variables (COG) [N=487]

COG	Global Cognition				Memory				Executive Functions			
Measurement model	**Configural invariance[1]**	**Metric invariance[2]**	**Scalar invariance[3]**	**Residual invariance[4]**	**Configural invariance[1]**	**Metric invariance[2]**	**Scalar invariance[3]**	**Residual invariance[4]**	**Configural invariance[1]**	**Metric invariance[2]**	**Scalar invariance[3]**	**Residual invariance[4]**
No. of Estimated Parameters	147	123	90	66	65	55	43	33	81	66	48	34
Raw Loglikelihood	-15639.114	-15674.726	-15832.385	-15905.982	-6628.8	-6647.5	-6691.1	-6703.5	-9067.7	-9079.6	-9091.5	-9128.2
Δ $\chi 2$ (df), p-value	**Ref**	73.5 (24), <0.001	315.5 (33), <0.001	113.23 (24), <0.001	**Ref**	34.5 (10), <0.001	88.2 (12), <0.001	24.16 (10), 0.007	Ref	19.7 (15), 0.184	**23.46 (18), 0.174**	49.6 (14), <0.001
Robust CFI	0.895	**0.890**	0.859	0.847	0.977	**0.972**	0.957	0.954	0.926	0.924	**0.922**	0.906
Robust TLI	0.881	**0.880**	0.855	0.848	0.965	0.963	**0.951**	0.953	0.909	0.914	**0.92**	0.91
Raw AIC	31572.228	31595.453	31844.771	31943.964	13387.6	13405	13468.2	13473.1	18297.4	18291.1	18278.9	18324.5
Δ AIC		-23.225	**-249.318**	-99.193	Ref	-17.42	**-63.17**	-4.85	Ref	6.25	12.19	**-45.53**
Raw BIC	32187.903	32110.609	32221.714	32220.389	13659.9	13635.4	13648.3	13611.3	18636.6	18567.5	18480	18466.9
Δ BIC		77.294	**-111.105**	1.325	Ref	24.46	**-12.91**	37.04	**Ref**	69.08	87.58	13.1
Robust RMSEA	0.06	**0.06**	0.066	0.068	0.06	**0.062**	0.071	0.069	0.054	0.053	**0.051**	0.054
SRMR	0.101	**0.108**	0.118	0.118	0.106	**0.106**	0.117	0.122	**0.081**	0.084	0.085	0.087

[1]The same pattern of fixed and free factor loadings across time
[2]Invariant factor loadings across time
[3]Invariant factor loadings and intercepts across time
[4]Invariant factor loadings, intercepts and residual variances across time
Bold font indicates preferred model/s according to index.
Δ values are calculated between the current column model and the preceding column model.
CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.
AIC= Akaike information criterion. BIC= Bayesian information criterion. df=degrees of freedom.

Supplementary Table 7. Nested models fit indices for testing measurement invariance of metabolic syndrome (METSYN) and quality of life (QOL) latent variables [N=487]

Latent variable	**METSYN**				**QOL**			
Measurement model	**Configural invariance[1]**	**Metric invariance[2]**	**Scalar invariance[3]**	**Residual invariance[4]**	**Configural invariance[1]**	**Metric invariance[2]**	**Scalar invariance[3]**	**Residual invariance[4]**
No. of Estimated Parameters	53	43	31	21	69	57	42	30
Raw Loglikelihood	-7400.0	-7416.6	-7530.1	-7560.4	-9107.8	-9115.4	-9151.2	-9158.8
Δ $\chi 2$ (df), p-value	**Ref**	28.09 (10), 0.002	318.3 (12), <0.001	45.8 (10) <0.001	Ref	**14.96 (12), 0.244**	70.37 (15), <0.001	11.21 (12), 0.511
Robust CFI	0.968	**0.963**	0.918	0.909	0.956	**0.955**	0.943	0.943
Robust TLI	0.959	**0.958**	0.918	0.916	0.944	**0.948**	0.941	0.945
Raw AIC	14905.9	14919.2	15122.1	15162.8	18353.6	18344.9	18386.3	18377.6
Δ AIC	Ref	-13.30	**-202.90**	-40.68	Ref	8.69	**-41.42**	8.71
Raw BIC	15127.9	15099.3	15251.9	15250.7	18642.6	18583.6	18562.2	18503.3
Δ BIC	Ref	28.59	**-152.64**	1.20	**Ref**	58.95	21.40	58.97
Robust RMSEA	0.063	**0.063**	0.088	0.089	0.059	**0.057**	0.061	0.058
SRMR	0.09	**0.092**	0.098	0.096	0.060	**0.064**	0.066	0.067

[1]The same pattern of fixed and free factor loadings across time
[2]Invariant factor loadings across time
[3]Invariant factor loadings and intercepts across time
[4]Invariant factor loadings, intercepts and residual variances across time
Bold font indicates preferred model/s according to index.
Δ values are calculated between the current column model and the preceding column model.
CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.
AIC= Akaike information criterion. BIC= Bayesian information criterion. df=degrees of freedom.

Supplementary Table 8. Bivariate latent change score models of body mass index (BMI) (kg/m2) and Cognition (COG)

		Bivariate latent change score models of BMI (kg/m2) and Cognition (COG)																	
		COG= Global Cognition						COG= Memory						COG= Executive functions					
		T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change		
Parameter	**Label**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**
Factor loadings for COG																			
RCFT Copy	λ_1	0.13 (0.02)	0.42	**<0.001**	0.19 (0.03)	0.49	**<0.001**							0.12 (0.03)	0.44	**<0.001**	0.08 (0.04)	0.40	0.058
CPT omissions	λ_2	0.13 (0.02)	0.45	**<0.001**	0.18 (0.02)	0.46	**<0.001**							0.12 (0.02)	0.45	**<0.001**	0.09 (0.05)	0.46	**0.053**
CPT commissions	λ_3	0.04 (0.02)	0.13	**0.015**	0.05 (0.02)	0.11	**0.033**							0.04 (0.02)	0.14	**0.019**	0.03 (0.02)	0.14	0.146
CPT hit reaction time	λ_4	0.07 (0.02)	0.23	**<0.001**	0.09 (0.02)	0.22	**<0.001**							0.06 (0.02)	0.22	**<0.001**	0.04 (0.02)	0.20	0.102
SMDT	λ_5	0.2 (0.03)	0.69	**<0.001**	0.25 (0.03)	0.69	**<0.001**							0.18 (0.03)	0.68	**<0.001**	0.12 (0.06)	0.68	**0.047**
IGT	λ_6	0.06 (0.01)	0.19	**<0.001**	0.08 (0.02)	0.20	**<0.001**							0.06 (0.01)	0.21	**<0.001**	0.04 (0.02)	0.21	0.059
Stroop interference	λ_7	0.05 (0.01)	0.17	**<0.001**	0.07 (0.02)	0.19	**<0.001**							0.05 (0.01)	0.19	**<0.001**	0.04 (0.02)	0.20	0.099
RAVTL Immediate recall	λ_8	0.09 (0.02)	0.29	**<0.001**	0.1 (0.03)	0.23	**0.002**	0.16 (0.04)	0.31	**<0.001**	0.71 (0.03)	0.86	**<0.001**						
RAVTL delayed recall	λ_9	0.07 (0.02)	0.23	**<0.001**	0.1 (0.03)	0.22	**0.004**	0.14 (0.04)	0.27	**<0.001**	0.72 (0.03)	0.87	**<0.001**						
RCFT immediate recall	λ_{10}	0.14 (0.02)	0.45	**<0.001**	0.21 (0.03)	0.52	**<0.001**	0.26 (0.05)	0.50	**<0.001**	0.26 (0.03)	0.30	**<0.001**						
RCFT delayed recall	λ_{11}	0.14 (0.02)	0.46	**<0.001**	0.21 (0.03)	0.53	**<0.001**	0.27 (0.05)	0.52	**<0.001**	0.34 (0.03)	0.40	**<0.001**						
RCFT recognition	λ_{12}	0.08 (0.02)	0.26	**<0.001**	0.14 (0.02)	0.35	**<0.001**	0.14 (0.03)	0.27	**<0.001**	0.19 (0.04)	0.22	**<0.001**						
Mean rate of change in COG	μΔCOG	0.51 (0.29)	0.48	0.073	0.68 (0.31)	0.62	**0.027**	1 (0.32)	0.88	**0.002**	1.18 (0.16)	0.87	**<0.001**	0.08 (0.3)	0.07	0.793	0.24 (0.58)	0.17	0.684
Mean rate of change in BMI	μΔBMI	-0.28 (0.05)	-0.26	**<0.001**	-0.17 (0.06)	-0.16	**0.005**	-0.28 (0.04)	-0.26	**<0.001**	-0.19 (0.05)	-0.18	**<0.001**	-0.27 (0.06)	-0.26	<0.001	-0.11 (0.15)	-0.11	0.468
Effect of baseline characteristics on the mean rate of change in BMI																			
$BMI_{T0} \rightarrow \Delta BMI$	β2	-0.07 (0.02)	-0.07	**0.002**	-0.07 (0.03)	-0.06	**0.020**	-0.06 (0.02)	-0.06	**0.004**	-0.06 (0.03)	-0.06	**0.023**	-0.08 (0.03)	-0.08	**0.005**	-0.11 (0.08)	-0.10	0.147
$COG_{T0} \rightarrow \Delta BMI$	γ2	-0.09 (0.04)	-0.28	**0.031**	-0.03 (0.04)	-0.07	0.473	-0.05 (0.05)	-0.09	0.322	-0.03 (0.02)	-0.03	0.237	-0.1 (0.06)	-0.35	0.066	-0.13 (0.14)	-0.66	0.351
IG → ΔBMI		-0.46 (0.04)	-0.22	**<0.001**	-0.43 (0.05)	-0.21	**<0.001**	-0.48 (0.04)	-0.23	**<0.001**	-0.44 (0.05)	-0.21	**<0.001**	-0.44 (0.06)	-0.21	**<0.001**	-0.36 (0.14)	-0.17	**0.010**
Gender [women] → ΔBMI		-0.04 (0.05)	-0.02	0.511	0.01 (0.06)	0.00	0.912	0.01 (0.04)	0.00	0.865	0.03 (0.05)	0.02	0.520	-0.05 (0.07)	-0.02	0.487	-0.11 (0.22)	-0.05	0.609
Age → ΔBMI		-0.16 (0.07)	-0.16	**0.018**	-0.08 (0.05)	-0.08	0.073	-0.06 (0.04)	-0.06	0.090	-0.06 (0.02)	-0.06	**0.016**	-0.21 (0.11)	-0.20	**0.064**	-0.38 (0.47)	-0.36	0.416
Education years → ΔBMI		0.1 (0.04)	0.09	**0.010**	-0.01 (0.04)	-0.01	0.839	0.04 (0.02)	0.03	0.085	-0.02 (0.04)	-0.02	0.525	0.11 (0.05)	0.10	**0.042**	0.16 (0.26)	0.15	0.548
IQ → ΔBMI		0.09 (0.1)	0.09	0.335	-0.05 (0.07)	-0.04	0.494	-0.02 (0.08)	-0.02	0.744	-0.08 (0.03)	-0.08	**0.002**	0.14 (0.15)	0.13	0.343	0.33 (0.61)	0.31	0.587
Cholesterol treatment → ΔBMI		0.14 (0.04)	0.07	**<0.001**	0.2 (0.05)	0.09	**<0.001**	0.15 (0.04)	0.07	**<0.001**	0.19 (0.05)	0.09	**<0.001**	0.16 (0.05)	0.08	**0.001**	0.21 (0.08)	0.10	**0.010**
Use of tranquilizers/sedatives → ΔBMI		0 (0.05)	0.00	0.967	-0.05 (0.05)	-0.02	0.312	0.04 (0.04)	0.02	0.385	-0.05 (0.05)	-0.02	0.322	-0.03 (0.07)	-0.01	0.626	-0.14 (0.16)	-0.05	0.376
Prediabetes → ΔBMI		0.04 (0.06)	0.01	0.454	0.09 (0.07)	0.03	0.242	0.04 (0.05)	0.01	0.417	0.09 (0.07)	0.03	0.216	0.06 (0.07)	0.02	0.347	0.05 (0.13)	0.02	0.712
Diabetes → ΔBMI		0.07 (0.05)	0.03	0.172	-0.06 (0.05)	-0.03	0.243	0.06 (0.04)	0.03	0.157	-0.07 (0.05)	-0.03	0.184	0.1 (0.06)	0.04	0.113	-0.02 (0.11)	-0.01	0.833
Smoking → ΔBMI		-0.03 (0.07)	-0.01	0.648	0.07 (0.09)	0.02	0.443	-0.02 (0.07)	-0.01	0.810	0.07 (0.09)	0.02	0.412	-0.05 (0.08)	-0.02	0.533	-0.02 (0.18)	-0.01	0.907
er-MedDiet adherence at 1 year --> ΔBMI		-0.1 (0.02)	-0.09	**<0.001**	-0.08 (0.03)	-0.08	**0.001**	-0.09 (0.02)	-0.09	**<0.001**	-0.08 (0.03)	-0.07	**0.002**	-0.11 (0.03)	-0.11	**<0.001**	-0.11 (0.06)	-0.10	0.073
Effect of baseline characteristics on the mean rate of change in COG																			
$COG_{T0} \rightarrow \Delta COG$	β1	-0.03 (0.17)	-0.10	0.845	0.07 (0.1)	0.16	0.456	-0.31 (0.27)	-0.51	0.247	-0.64 (0.08)	-0.53	**<0.001**	-0.1 (0.22)	-0.32	0.657	-0.3 (0.33)	-1.12	0.376
$BMI_{T0} \rightarrow \Delta COG$	γ1	0.1 (0.12)	0.09	0.382	0.06 (0.1)	0.05	0.563	-0.06 (0.13)	-0.05	0.646	0 (0.07)	0.00	0.963	0.18 (0.14)	0.16	0.219	0.18 (0.25)	0.13	0.463
IG → ΔCOG		-0.19 (0.25)	-0.09	0.451	-0.24 (0.23)	-0.11	0.281	0.04 (0.26)	0.02	0.876	-0.18 (0.14)	-0.07	0.189	-0.23 (0.31)	-0.10	0.458	-0.17 (0.48)	-0.06	0.716

Gender [women] → ΔCOG	-0.45 (0.29)	-0.21	0.113	-0.48 (0.25)	-0.22	**0.052**	-0.48 (0.31)	-0.21	0.116	-0.09 (0.15)	-0.03	0.536	-0.34 (0.35)	-0.15	0.336	-1.37 (0.95)	-0.50	0.149
Age → ΔCOG	-0.15 (0.25)	-0.14	0.563	0.06 (0.15)	0.06	0.683	-0.46 (0.2)	-0.41	**0.020**	0.01 (0.07)	0.00	0.920	-0.09 (0.37)	-0.08	0.809	-0.63 (0.93)	-0.46	0.496
Education years → ΔCOG	-0.2 (0.17)	-0.19	0.222	0.01 (0.14)	0.01	0.947	0.02 (0.19)	0.02	0.907	0.29 (0.07)	0.21	**<0.001**	-0.17 (0.21)	-0.15	0.416	0.39 (0.6)	0.28	0.522
IQ → ΔCOG	0.24 (0.36)	0.23	0.501	-0.42 (0.22)	-0.38	0.055	0.43 (0.4)	0.38	0.279	-0.16 (0.09)	-0.12	0.062	0.47 (0.49)	0.43	0.343	0.41 (1.11)	0.30	0.709
Cholesterol treatment → ΔCOG	-0.16 (0.23)	-0.07	0.482	-0.13 (0.21)	-0.06	0.542	-0.45 (0.3)	-0.20	0.138	-0.24 (0.13)	-0.09	0.059	0.03 (0.25)	0.01	0.906	-0.32 (0.43)	-0.12	0.464
Use of tranquilizers/sedatives → ΔCOG	-0.01 (0.28)	0.00	0.983	-0.15 (0.26)	-0.06	0.557	0.1 (0.28)	0.04	0.735	-0.28 (0.16)	-0.09	0.084	0 (0.33)	0.00	0.993	-0.31 (0.62)	-0.10	0.615
Pre-diabetes → ΔCOG	0.21 (0.31)	0.07	0.496	-0.09 (0.24)	-0.03	0.707	0.02 (0.34)	0.01	0.948	0 (0.18)	0.00	0.996	0.15 (0.38)	0.05	0.685	-0.37 (0.6)	-0.10	0.541
Diabetes → ΔCOG	-0.31 (0.27)	-0.13	0.253	-0.35 (0.28)	-0.14	0.223	0.1 (0.3)	0.04	0.749	-0.53 (0.14)	-0.18	**<0.001**	-0.32 (0.33)	-0.13	0.338	-0.61 (0.59)	-0.21	0.298
Smoking → ΔCOG	-0.39 (0.36)	-0.12	0.279	-0.1 (0.35)	-0.03	0.765	-0.13 (0.36)	-0.04	0.710	0.23 (0.22)	0.06	0.288	-0.42 (0.42)	-0.12	0.325	-0.43 (0.72)	-0.10	0.555
er-MedDiet adherence at 1 year → ΔCOG	-0.03 (0.12)	-0.03	0.783	0.05 (0.11)	0.04	0.686	0.06 (0.13)	0.05	0.643	0.18 (0.07)	0.13	**0.013**	-0.16 (0.14)	-0.14	0.277	-0.12 (0.26)	-0.08	0.650
Coupled change ΔCOG ↔ ΔBMI δ2	-0.08 (0.05)	-0.08	0.109	0.08 (0.09)	0.08	0.370	-0.14 (0.05)	-0.14	0.006	0.06 (0.04)	0.06	0.157	-0.04 (0.06)	-0.04	0.544	-0.32 (0.24)	-0.33	0.183
Baseline covariance COGT0 ↔ BMIT0 δ1	-0.16 (0.11)	-0.16	0.135	-0.11 (0.07)	-0.11	0.146	-0.06 (0.11)	-0.06	0.606	-0.02 (0.04)	-0.02	0.634	-0.23 (0.13)	-0.23	0.083	1 (0)	0.91	#N/A
Effect of baseline characteristics on baseline COG																		
IG → COG_{T0}	0.21 (0.32)	0.03	0.519	0.15 (0.24)	0.03	0.538	-0.07 (0.31)	-0.02	0.816	-0.2 (0.11)	-0.09	0.086	0.38 (0.37)	0.05	0.310	-1.05 (0.8)	-0.10	0.185
Gender [women] → COG_{T0}	-0.68 (0.38)	-0.11	0.070	-0.58 (0.28)	-0.12	**0.039**	-0.34 (0.4)	-0.09	0.398	0.42 (0.12)	0.18	**<0.001**	-0.74 (0.42)	-0.10	0.076	-2.41 (1.25)	-0.47	**0.054**
Age → COG_{T0}	-1.43 (0.23)	-0.44	**<0.001**	-0.99 (0.17)	-0.40	**<0.001**	-0.62 (0.18)	-0.32	**<0.001**	-0.24 (0.06)	-0.21	**<0.001**	-1.67 (0.34)	-0.46	**<0.001**	1.31 (0.74)	0.25	0.078
Education years → COG_{T0}	0.61 (0.2)	0.19	**0.002**	0.43 (0.16)	0.17	**0.007**	-0.14 (0.16)	-0.07	0.382	-0.08 (0.06)	-0.07	0.149	0.62 (0.26)	0.17	**0.018**	3.11 (1.62)	0.60	0.055
IQ → COG_{T0}	2.07 (0.33)	0.64	**<0.001**	1.56 (0.22)	0.63	**<0.001**	1.43 (0.26)	0.75	**<0.001**	0.46 (0.06)	0.41	**<0.001**	2.26 (0.45)	0.62	**<0.001**	0.14 (0.5)	0.01	0.771
Cholesterol treatment → COG_{T0}	0.07 (0.3)	0.01	0.806	0.07 (0.23)	0.02	0.744	0.13 (0.29)	0.03	0.651	-0.08 (0.1)	-0.03	0.458	0.21 (0.35)	0.03	0.543	-0.62 (0.7)	-0.05	0.374
Use of tranquilizers/sedatives → COG_{T0}	-0.24 (0.4)	-0.03	0.540	-0.07 (0.31)	-0.01	0.813	0.29 (0.37)	0.06	0.430	-0.02 (0.13)	-0.01	0.896	-0.55 (0.47)	-0.06	0.238	-0.29 (0.7)	-0.02	0.674
Prediabetes → COG_{T0}	-0.17 (0.38)	-0.02	0.649	-0.15 (0.28)	-0.02	0.609	-0.32 (0.37)	-0.06	0.378	-0.06 (0.15)	-0.02	0.674	0.03 (0.46)	0.00	0.942	0.27 (0.6)	0.02	0.649
Diabetes → COG_{T0}	0.06 (0.36)	0.01	0.866	0.16 (0.27)	0.03	0.554	0.02 (0.35)	0.01	0.950	-0.08 (0.12)	-0.03	0.499	0.35 (0.42)	0.04	0.413	-0.64 (0.76)	-0.04	0.400
Smoking → COG_{T0}	-0.25 (0.44)	-0.03	0.567	-0.14 (0.33)	-0.02	0.665	-0.16 (0.44)	-0.03	0.710	0.04 (0.19)	0.01	0.836	-0.38 (0.48)	-0.03	0.420	-0.17 (0.28)	-0.03	0.555
er-MedDiet adherence at 1 year --> COG_T0	-0.03 (0.16)	-0.01	0.854	-0.05 (0.12)	-0.02	0.691	0.04 (0.17)	0.02	0.825	0.11 (0.06)	0.09	0.057	-0.19 (0.19)	-0.05	0.327	0.04 (0.1)	0.02	0.669
Effect of baseline characteristics on baseline BMI																		
IG → BMI_{T0}	0.04 (0.1)	0.02	0.669	0.04 (0.1)	0.02	0.669	0.04 (0.1)	0.02	0.669	0.04 (0.1)	0.02	0.669	0.04 (0.1)	0.02	0.669	0.17 (0.09)	0.08	0.065
Gender [women] → BMI_{T0}	0.17 (0.09)	0.08	0.065	0.17 (0.09)	0.08	0.065	0.17 (0.09)	0.08	0.065	0.17 (0.09)	0.08	0.065	0.17 (0.09)	0.08	0.065	-0.06 (0.05)	-0.06	0.197
Age → BMI_{T0}	-0.06 (0.05)	-0.06	0.197	-0.06 (0.05)	-0.06	0.197	-0.06 (0.05)	-0.06	0.197	-0.06 (0.05)	-0.06	0.197	-0.06 (0.05)	-0.06	0.197	0.01 (0.05)	0.01	0.782
Education years → BMI_{T0}	0.01 (0.05)	0.01	0.782	0.01 (0.05)	0.01	0.782	0.01 (0.05)	0.01	0.782	0.01 (0.05)	0.01	0.782	0.01 (0.05)	0.01	0.782	0.03 (0.05)	0.03	0.573
IQ → BMI_{T0}	0.03 (0.05)	0.03	0.573	0.03 (0.05)	0.03	0.573	0.03 (0.05)	0.03	0.573	0.03 (0.05)	0.03	0.573	0.03 (0.05)	0.03	0.573	-0.14 (0.09)	-0.07	0.119
Cholesterol treatment → BMI_{T0}	-0.14 (0.09)	-0.07	0.119	-0.14 (0.09)	-0.07	0.119	-0.14 (0.09)	-0.07	0.119	-0.14 (0.09)	-0.07	0.119	-0.14 (0.09)	-0.07	0.119	-0.09 (0.11)	-0.04	0.412
Use of tranquilizers/sedatives → BMI_{T0}	-0.09 (0.11)	-0.04	0.412	-0.09 (0.11)	-0.04	0.412	-0.09 (0.11)	-0.04	0.412	-0.09 (0.11)	-0.04	0.412	-0.09 (0.11)	-0.04	0.412	-0.02 (0.13)	-0.01	0.861
Prediabetes → BMI_{T0}	-0.02 (0.13)	-0.01	0.861	-0.02 (0.13)	-0.01	0.861	-0.02 (0.13)	-0.01	0.861	-0.02 (0.13)	-0.01	0.861	-0.02 (0.13)	-0.01	0.861	0.17 (0.11)	0.08	0.103
Diabetes → BMI_{T0}	0.17 (0.11)	0.08	0.103	0.17 (0.11)	0.08	0.103	0.17 (0.11)	0.08	0.103	0.17 (0.11)	0.08	0.103	0.17 (0.11)	0.08	0.103	-0.19 (0.14)	-0.06	0.173
Smoking → BMI_{T0}	-0.19 (0.14)	-0.06	0.173	-0.19 (0.14)	-0.06	0.173	-0.19 (0.14)	-0.06	0.173	-0.19 (0.14)	-0.06	0.173	-0.19 (0.14)	-0.06	0.173	-0.09 (0.05)	-0.09	0.065
er-MedDiet adherence at 1 year → BMI_{T0}	-0.09 (0.05)	-0.09	0.065	-0.09 (0.05)	-0.09	0.065	-0.09 (0.05)	-0.09	0.065	-0.09 (0.05)	-0.09	0.065	-0.09 (0.05)	-0.09	0.065	0.25 (0)	1.00	<0.001
Model Fit Indexes	CFI=0.94; TLI=0.92; RMSEA=0.04; SRMR=0.06			CFI=0.89; TLI=0.85; RMSEA=0.06; SRMR=0.08			CFI=0.97; TLI=0.94; RMSEA=0.05; SRMR=0.05			CFI=0.94; TLI=0.88; RMSEA=0.07; SRMR=0.09			CFI=0.93; TLI=0.9; RMSEA=0.05; SRMR=0.06			CFI=0.9; TLI=0.84; RMSEA=0.05; SRMR=0.06		

IQ = intelligence quotient. IG= Intervention group. Est_{STD}= standardized estimate. → = regression path. ↔ = correlation path. CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.

Supplementary Table 9. Bivariate latent change score models of physical activity (PA) (METs-min/week) and Cognition (COG)*

		COG= Global Cognition						COG= Memory						COG= Executive functions					
		T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change		
Parameter	**Label**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**
Mean rate of change in PA	$\mu\Delta PA$	0.32 (0.1)	0.28	**<0.001**	0.45 (0.12)	0.38	**<0.001**	0.32 (0.09)	0.28	**<0.001**	0.48 (0.09)	0.41	**<0.001**	0.33 (0.1)	0.29	**0.001**	0.4 (0.18)	0.34	**0.028**
Effect of baseline characteristics on the mean rate of change in PA																			
$PA_{T0} \rightarrow \Delta PA$	β_2	-0.53 (0.05)	-0.46	**<0.001**	-0.61 (0.04)	-0.52	**<0.001**	-0.53 (0.05)	-0.46	**<0.001**	-0.62 (0.04)	-0.52	**<0.001**	-0.53 (0.05)	-0.46	**<0.001**	-0.61 (0.05)	-0.51	**<0.001**
$COG_{T0} \rightarrow \Delta PA$	γ_1	0.00 (0.11)	0.00	0.991	0.04 (0.07)	0.08	0.582	0.01 (0.10)	0.02	0.895	0.02 (0.04)	0.02	0.636	-0.04 (0.13)	-0.12	0.76	0.12 (0.18)	0.53	0.478
$IG \rightarrow \Delta PA$		0.41 (0.08)	0.18	**<0.001**	0.39 (0.08)	0.16	**<0.001**	0.41 (0.08)	0.18	**<0.001**	0.4 (0.08)	0.17	**<0.001**	0.42 (0.09)	0.18	**<0.001**	0.34 (0.13)	0.14	**0.006**
Gender [women] $\rightarrow \Delta PA$		-0.09 (0.12)	-0.04	0.444	-0.22 (0.10)	-0.09	**0.031**	-0.09 (0.09)	-0.04	0.351	-0.25 (0.09)	-0.11	**0.005**	-0.12 (0.14)	-0.05	0.384	-0.12 (0.24)	-0.05	0.619
Age $\rightarrow \Delta PA$		0.09 (0.15)	0.08	0.557	0.10 (0.08)	0.09	0.172	0.10 (0.07)	0.08	0.184	0.07 (0.04)	0.06	0.083	0.02 (0.21)	0.02	0.908	0.36 (0.47)	0.3	0.445
Education years $\rightarrow \Delta PA$		0.05 (0.07)	0.05	0.449	-0.01 (0.05)	-0.01	0.871	0.06 (0.06)	0.05	0.328	0.01 (0.05)	0.01	0.818	0.08 (0.08)	0.07	0.343	-0.15 (0.26)	-0.13	0.559
IQ $\rightarrow \Delta PA$		-0.01 (0.23)	-0.01	0.953	-0.10 (0.12)	-0.08	0.415	-0.03 (0.16)	-0.03	0.851	-0.05 (0.05)	-0.04	0.353	0.07 (0.28)	0.06	0.795	-0.41 (0.61)	-0.35	0.495
Cholesterol treatment $\rightarrow \Delta PA$		0.01 (0.08)	0.00	0.945	-0.07 (0.08)	-0.03	0.364	0.00 (0.08)	0	0.964	-0.07 (0.08)	-0.03	0.395	0.01 (0.08)	0.01	0.874	-0.09 (0.1)	-0.04	0.398
Use of tranquilizers/sedatives $\rightarrow \Delta PA$		-0.08 (0.11)	-0.03	0.466	-0.08 (0.10)	-0.03	0.421	-0.09 (0.11)	-0.03	0.418	-0.08 (0.1)	-0.03	0.406	-0.1 (0.14)	-0.04	0.464	-0.01 (0.17)	0	0.962
Prediabetes $\rightarrow \Delta PA$		-0.14 (0.11)	-0.04	0.228	-0.09 (0.11)	-0.03	0.408	-0.13 (0.12)	-0.04	0.268	-0.09 (0.11)	-0.03	0.371	-0.14 (0.11)	-0.04	0.226	-0.06 (0.15)	-0.02	0.701
Diabetes $\rightarrow \Delta PA$		-0.13 (0.09)	-0.05	0.140	-0.16 (0.09)	-0.06	0.090	-0.13 (0.09)	-0.05	0.138	-0.15 (0.09)	-0.06	0.102	-0.12 (0.1)	-0.05	0.24	-0.19 (0.13)	-0.07	0.142
Smoking $\rightarrow \Delta PA$		0.09 (0.14)	0.03	0.504	0.00 (0.13)	0.00	0.971	0.10 (0.14)	0.03	0.491	0.00 (0.14)	0	0.998	0.08 (0.15)	0.02	0.586	0.08 (0.19)	0.02	0.687
Effect of Baseline PA on the mean rate of change in COG	γ_2	0.01 (0.12)	0.01	0.945	-0.02 (0.12)	-0.02	0.841	-0.21 (0.12)	-0.18	0.086	-0.05 (0.07)	-0.04	0.441	0.07 (0.12)	0.07	0.553	-0.05 (0.22)	-0.04	0.831
Coupled change $\Delta COG \leftrightarrow \Delta PA$	δ_2	0.01 (0.11)	0.01	0.894	0.18 (0.12)	0.18	0.118	0.06 (0.11)	0.06	0.547	0.13 (0.06)	0.13	**0.036**	-0.03 (0.13)	-0.03	0.837	0.11 (0.19)	0.11	0.567
Baseline covariance $COG_{T0} \leftrightarrow PA_{T0}$	δ_1	-0.03 (0.12)	-0.03	0.793	-0.06 (0.08)	-0.07	0.446	0.01 (0.12)	0.01	0.912	0.02 (0.04)	0.02	0.709	-0.05 (0.13)	-0.05	0.732	-0.02 (0.19)	-0.02	0.905
Effect of baseline characteristics on baseline PA																			
$IG \rightarrow PA_{T0}$		0.07 (0.09)	0.03	0.438	0.07 (0.09)	0.03	0.438	0.07 (0.09)	0.03	0.438	0.07 (0.09)	0.03	0.438	0.07 (0.09)	0.03	0.438	0.07 (0.09)	0.03	0.438
Gender [women] $\rightarrow PA_{T0}$		-0.33 (0.09)	-0.16	**<0.001**	-0.33 (0.09)	-0.16	**<0.001**	-0.33 (0.09)	-0.16	**<0.001**	-0.33 (0.09)	-0.16	**<0.001**	-0.33 (0.09)	-0.16	**<0.001**	-0.33 (0.09)	-0.16	**<0.001**
Age $\rightarrow PA_{T0}$		0.18 (0.04)	0.18	**<0.001**	0.18 (0.04)	0.18	**<0.001**	0.18 (0.04)	0.18	**<0.001**	0.18 (0.04)	0.18	**<0.001**	0.18 (0.04)	0.18	**<0.001**	0.18 (0.04)	0.18	**<0.001**
Education years $\rightarrow PA_{T0}$		-0.02 (0.05)	-0.02	0.700	-0.02 (0.05)	-0.02	0.700	-0.02 (0.05)	-0.02	0.7	-0.02 (0.05)	-0.02	0.7	-0.02 (0.05)	-0.02	0.7	-0.02 (0.05)	-0.02	0.7
IQ $\rightarrow PA_{T0}$		-0.07 (0.05)	-0.07	0.171	-0.07 (0.05)	-0.07	0.171	-0.07 (0.05)	-0.07	0.171	-0.07 (0.05)	-0.07	0.171	-0.07 (0.05)	-0.07	0.171	-0.07 (0.05)	-0.07	0.171
Cholesterol treatment $\rightarrow PA_{T0}$		0.14 (0.09)	0.07	0.122	0.14 (0.09)	0.07	0.122	0.14 (0.09)	0.07	0.122	0.14 (0.09)	0.07	0.122	0.14 (0.09)	0.07	0.122	0.14 (0.09)	0.07	0.122
Use of tranquilizers/sedatives $\rightarrow PA_{T0}$		-0.17 (0.11)	-0.07	0.113	-0.17 (0.11)	-0.07	0.113	-0.17 (0.11)	-0.07	0.113	-0.17 (0.11)	-0.07	0.113	-0.17 (0.11)	-0.07	0.113	-0.17 (0.11)	-0.07	0.113
Prediabetes $\rightarrow PA_{T0}$		0.02 (0.13)	0.01	0.901	0.02 (0.13)	0.01	0.901	0.02 (0.13)	0.01	0.901	0.02 (0.13)	0.01	0.901	0.02 (0.13)	0.01	0.901	0.02 (0.13)	0.01	0.901
Diabetes $\rightarrow PA_{T0}$		-0.08 (0.10)	-0.04	0.414	-0.08 (0.1)	-0.04	0.414	-0.08 (0.1)	-0.04	0.414	-0.08 (0.10)	-0.04	0.414	-0.08 (0.1)	-0.04	0.414	-0.08 (0.1)	-0.04	0.414
Smoking $\rightarrow PA_{T0}$		-0.24 (0.13)	-0.08	0.063	-0.24 (0.13)	-0.08	0.063	-0.24 (0.13)	-0.08	0.063	-0.24 (0.13)	-0.08	0.063	-0.24 (0.13)	-0.08	0.063	-0.24 (0.13)	-0.08	0.063
Model Fit Indexes		CFI=0.94; TLI=0.92; RMSEA=0.04; SRMR=0.07			CFI=0.89; TLI=0.85; RMSEA=0.06; SRMR=0.08			CFI=0.97; TLI=0.94; RMSEA=0.05; SRMR=0.05			CFI=0.94; TLI=0.87; RMSEA=0.07; SRMR=0.09			CFI=0.91; TLI=0.87; RMSEA=0.05; SRMR=0.06			CFI=0.89; TLI=0.83; RMSEA=0.05; SRMR=0.06		

IQ = intelligence quotient. IG= Intervention group. Est_{STD}= standardized estimate. $\rightarrow$ = regression path. $\leftrightarrow$ = correlation path. CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.

*Those parameters that only refer to cognition (Factor loadings for COG, mean rate of change for COG and the effect of baseline characteristics on baseline COG or on the mean rate of change for COG) are not included since they are equivalent to ones from Supplementary Table 7.

Supplementary Table 10. Bivariate latent change score models of quality of life (QOL) and Cognition (COG)*

		COG= Global Cognition						COG= Memory						COG= Executive functions					
		T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change		
Parameter	**Label**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**	**Est (SE)**	**Est_{STD}**	**P**
Factor loadings for QOL																			
SF36 – Physical functioning score	λ_1	0.41 (0.03)	0.57	**<0.001**	0.42 (0.03)	0.58	**<0.001**	0.41 (0.03)	0.57	**<0.001**	0.42 (0.03)	0.58	**<0.001**	0.41 (0.03)	0.57	**<0.001**	0.42 (0.03)	0.59	**<0.001**
SF36 – Energy score	λ_2	0.52 (0.02)	0.74	**<0.001**	0.54 (0.02)	0.76	**<0.001**	0.53 (0.03)	0.75	**<0.001**	0.54 (0.02)	0.76	**<0.001**	0.53 (0.03)	0.75	**<0.001**	0.51 (0.02)	0.73	**<0.001**
SF36 – Wellbeing score	λ_3	0.48 (0.03)	0.68	**<0.001**	0.47 (0.03)	0.65	**<0.001**	0.47 (0.03)	0.66	**<0.001**	0.47 (0.03)	0.65	**<0.001**	0.47 (0.03)	0.67	**<0.001**	0.45 (0.03)	0.64	**<0.001**
SF36 – Social functioning score	λ_4	0.51 (0.03)	0.67	**<0.001**	0.48 (0.03)	0.63	**<0.001**	0.5 (0.03)	0.66	**<0.001**	0.48 (0.03)	0.63	**<0.001**	0.5 (0.03)	0.66	**<0.001**	0.45 (0.03)	0.6	**<0.001**
SF36 – QOL pain score	λ_5	0.45 (0.02)	0.62	**<0.001**	0.45 (0.02)	0.62	**<0.001**	0.44 (0.02)	0.61	**<0.001**	0.45 (0.02)	0.62	**<0.001**	0.44 (0.02)	0.61	**<0.001**	0.45 (0.02)	0.63	**<0.001**
SF36 – Health score	λ_6	0.38 (0.02)	0.52	**<0.001**	0.39 (0.02)	0.52	**<0.001**	0.39 (0.02)	0.52	**<0.001**	0.39 (0.02)	0.52	**<0.001**	0.39 (0.02)	0.52	**<0.001**	0.37 (0.02)	0.5	**<0.001**
Mean rate of change in QOL	μΔQOL	0.17 (0.13)	0.15	0.198	0.14 (0.14)	0.13	0.304	0.19 (0.13)	0.17	0.161	0.11 (0.13)	0.11	0.393	0.18 (0.13)	0.17	0.162	0.07 (0.14)	0.07	0.613
Effect of baseline characteristics on the mean rate of change in QOL																			
$QOL_{T0} \rightarrow \Delta QOL$	β_2	-0.26 (0.06)	-0.30	**<0.001**	-0.24 (0.06)	-0.28	**<0.001**	-0.24 (0.06)	-0.28	**<0.001**	-0.24 (0.06)	-0.29	**<0.001**	-0.25 (0.06)	-0.29	**<0.001**	-0.2 (0.06)	-0.24	**0.001**
$COG_{T0} \rightarrow \Delta QOL$	γ_1	0.05 (0.05)	0.16	0.262	-0.04 (0.05)	-0.10	0.405	0.09 (0.05)	0.16	0.073	-0.02 (0.06)	-0.02	0.709	0.02 (0.04)	0.07	0.592	-0.03 (0.04)	-0.12	0.451
IG → ΔQOL		0.47 (0.12)	0.22	**<0.001**	0.3 (0.12)	0.14	**0.012**	0.51 (0.12)	0.24	**<0.001**	0.29 (0.12)	0.14	**0.016**	0.5 (0.12)	0.23	**<0.001**	0.35 (0.13)	0.16	**0.006**
Gender [women] → ΔQOL		-0.33 (0.13)	-0.15	**0.009**	-0.32 (0.13)	-0.15	**0.016**	-0.34 (0.13)	-0.16	**0.007**	-0.29 (0.13)	-0.13	**0.033**	-0.36 (0.13)	-0.17	**0.005**	-0.31 (0.14)	-0.14	**0.027**
Age → ΔQOL		0.03 (0.09)	0.02	0.785	-0.13 (0.09)	-0.12	0.138	0.00 (0.07)	0.00	0.977	-0.09 (0.07)	-0.08	0.194	-0.02 (0.09)	-0.02	0.825	-0.14 (0.1)	-0.14	0.166
Education years → ΔQOL		-0.04 (0.06)	-0.03	0.555	0.02 (0.07)	0.02	0.735	0.01 (0.06)	0.01	0.831	0.00 (0.06)	0	0.971	-0.01 (0.06)	-0.01	0.811	0.04 (0.08)	0.04	0.615
IQ → ΔQOL		-0.17 (0.11)	-0.16	0.127	-0.01 (0.1)	-0.01	0.936	-0.18 (0.09)	-0.17	**0.043**	-0.07 (0.07)	-0.06	0.331	-0.1 (0.1)	-0.09	0.329	0 (0.12)	0	0.994
Cholesterol treatment → ΔQOL		-0.13 (0.12)	-0.06	0.281	-0.02 (0.12)	-0.01	0.871	-0.14 (0.12)	-0.07	0.230	-0.03 (0.12)	-0.01	0.821	-0.13 (0.12)	-0.06	0.273	-0.01 (0.13)	0	0.958
Use of tranquilizers/sedatives → ΔQOL		-0.10 (0.16)	-0.04	0.541	0.1 (0.16)	0.04	0.515	-0.09 (0.16)	-0.04	0.554	0.10 (0.16)	0.04	0.526	-0.08 (0.16)	-0.03	0.632	0.16 (0.17)	0.06	0.341
Prediabetes → ΔQOL		0.09 (0.16)	0.03	0.590	0.05 (0.19)	0.02	0.790	0.07 (0.16)	0.02	0.657	0.05 (0.19)	0.02	0.788	0.06 (0.16)	0.02	0.726	0.06 (0.2)	0.02	0.779
Diabetes → ΔQOL		-0.17 (0.14)	-0.07	0.248	-0.08 (0.14)	-0.04	0.549	-0.19 (0.14)	-0.08	0.183	-0.10 (0.14)	-0.04	0.47	-0.18 (0.15)	-0.08	0.209	-0.09 (0.14)	-0.04	0.531
Smoking → ΔQOL		-0.35 (0.20)	-0.11	0.078	-0.16 (0.17)	-0.05	0.330	-0.34 (0.21)	-0.10	0.095	-0.15 (0.17)	-0.05	0.372	-0.36 (0.2)	-0.11	0.077	-0.19 (0.17)	-0.06	0.282
Effect of baseline QOL on the mean rate of change in COG	γ_2	0.00 (0.09)	0.00	0.985	-0.05 (0.09)	-0.06	0.573	0.12 (0.12)	0.14	0.316	0.09 (0.06)	0.08	0.134	-0.05 (0.11)	-0.06	0.627	-0.13 (0.19)	-0.13	0.5
Coupled change ΔCOG ↔ ΔQOL	δ_2	0.73 (0.27)	0.73	**0.008**	0.88 (0.3)	0.88	**0.003**	-0.11 (0.36)	-0.11	0.764	0.15 (0.16)	0.15	0.348	0.83 (0.31)	0.83	**0.007**	1.16 (0.46)	1.16	**0.011**
Baseline covariance COG_{T0} ↔ QOL_{T0}	δ_1	0.13 (0.11)	0.13	0.251	0.08 (0.08)	0.08	0.358	-0.02 (0.12)	-0.02	0.878	0.03 (0.05)	0.03	0.495	0.17 (0.14)	0.17	0.221	0.3 (0.22)	0.3	0.164
Effect of baseline characteristics on baseline QOL																			
IG → QOL_{T0}		-0.06 (0.13)	-0.02	0.647	-0.07 (0.13)	-0.03	0.618	-0.06 (0.14)	-0.03	0.634	-0.07 (0.13)	-0.03	0.622	-0.06 (0.14)	-0.03	0.638	-0.09 (0.14)	-0.03	0.526
Gender [women] → QOL_{T0}		-0.85 (0.15)	-0.34	**<0.001**	-0.87 (0.15)	-0.34	**<0.001**	-0.86 (0.15)	-0.34	**<0.001**	-0.88 (0.15)	-0.34	**<0.001**	-0.86 (0.15)	-0.34	**<0.001**	-0.91 (0.15)	-0.35	**<0.001**
Age → QOL_{T0}		0.16 (0.08)	0.13	**0.039**	0.16 (0.08)	0.12	**0.05**	0.16 (0.08)	0.13	**0.040**	0.16 (0.08)	0.12	**0.049**	0.16 (0.08)	0.13	**0.039**	0.15 (0.08)	0.11	0.075
Education years → QOL_{T0}		0.16 (0.07)	0.12	**0.027**	0.16 (0.07)	0.13	**0.021**	0.16 (0.07)	0.13	**0.025**	0.17 (0.07)	0.13	**0.021**	0.16 (0.07)	0.13	**0.025**	0.17 (0.07)	0.13	**0.022**
IQ → QOL_{T0}		0.07 (0.07)	0.06	0.334	0.06 (0.07)	0.05	0.393	0.06 (0.07)	0.05	0.381	0.06 (0.07)	0.05	0.401	0.07 (0.07)	0.05	0.378	0.08 (0.08)	0.06	0.318
Cholesterol treatment → QOL_{T0}		-0.25 (0.14)	-0.10	0.072	-0.24 (0.14)	-0.10	0.076	-0.24 (0.14)	-0.10	0.080	-0.25 (0.14)	-0.10	0.076	-0.24 (0.14)	-0.09	0.081	-0.25 (0.14)	-0.10	0.075
Use of tranquilizers/sedatives → QOL_{T0}		-1.11 (0.18)	-0.37	**<0.001**	-1.07 (0.18)	-0.35	**<0.001**	-1.12 (0.18)	-0.37	**<0.001**	-1.08 (0.18)	-0.36	**<0.001**	-1.12 (0.18)	-0.37	**<0.001**	-1.11 (0.18)	-0.36	**<0.001**
Prediabetes → QOL_{T0}		0.16 (0.19)	0.05	0.407	0.17 (0.2)	0.05	0.392	0.17 (0.20)	0.05	0.382	0.17 (0.20)	0.05	0.384	0.17 (0.20)	0.05	0.385	0.16 (0.21)	0.04	0.434
Diabetes → QOL_{T0}		-0.04 (0.16)	-0.02	0.784	-0.02 (0.16)	-0.01	0.883	-0.04 (0.16)	-0.01	0.809	-0.02 (0.16)	-0.01	0.893	-0.04 (0.16)	-0.02	0.796	-0.01 (0.17)	0.00	0.941
Smoking → QOL_{T0}		0.13 (0.21)	0.03	0.550	0.17 (0.21)	0.04	0.410	0.13 (0.21)	0.03	0.549	0.17 (0.21)	0.04	0.414	0.13 (0.21)	0.03	0.550	0.20 (0.22)	0.05	0.360

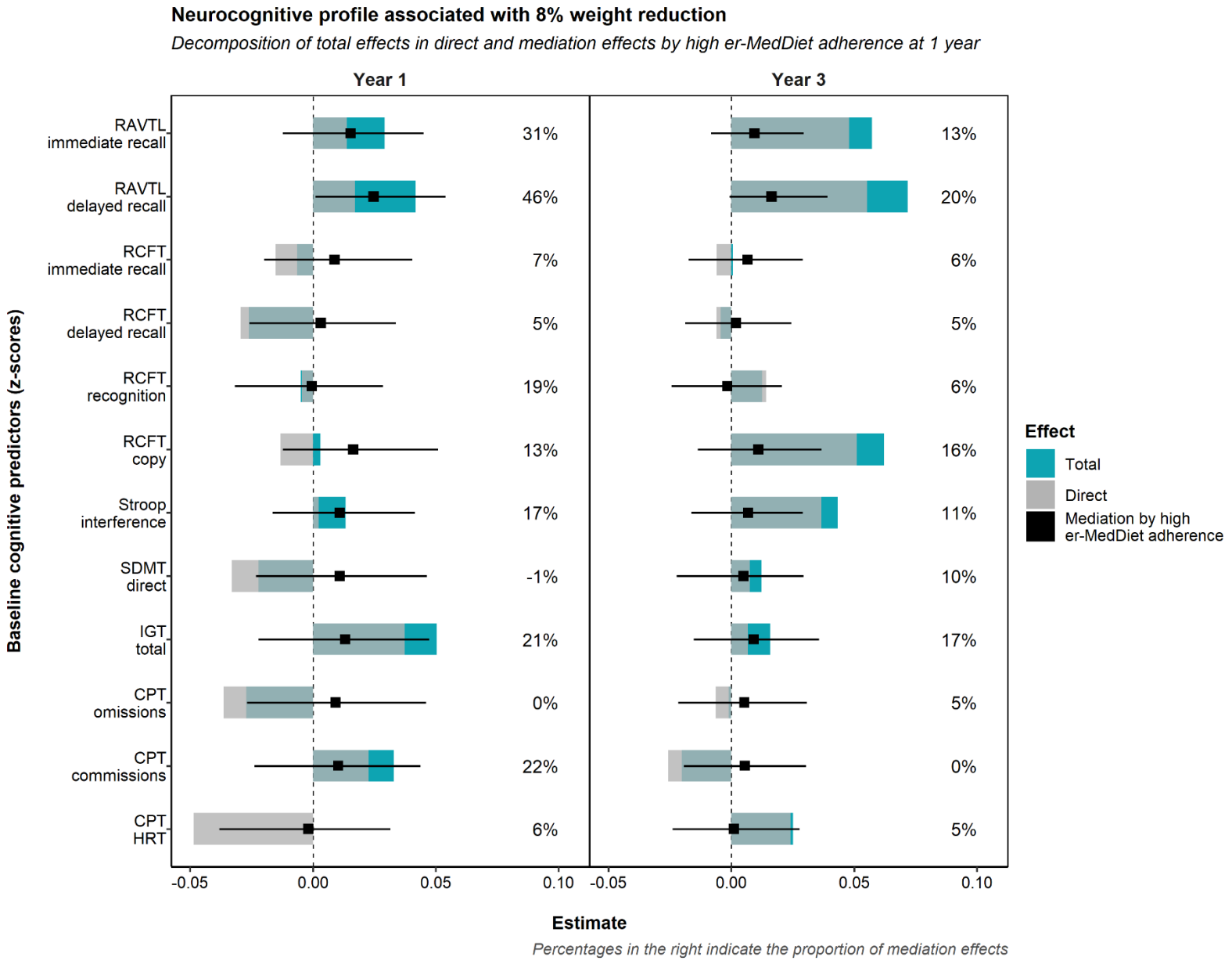
Model Fit Indexes	CFI=0.91; TLI=0.9; RMSEA=0.04; SRMR=0.07	CFI=0.89; TLI=0.87; RMSEA=0.05; SRMR=0.08	CFI=0.93; TLI=0.91; RMSEA=0.05; SRMR=0.07	CFI=0.92; TLI=0.89; RMSEA=0.05; SRMR=0.08	CFI=0.9; TLI=0.88; RMSEA=0.05; SRMR=0.07	CFI=0.9; TLI=0.88; RMSEA=0.05; SRMR=0.07

IQ = intelligence quotient. IG= Intervention group. Est_{STD}= standardized estimate. → = regression path. ↔ = correlation path. CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.
*Those parameters that only refer to cognition (Factor loadings for COG, mean rate of change for COG and the effect of baseline characteristics on baseline COG or on the mean rate of change for COG) are not included since they are equivalent to ones from Supplementary Table 7.

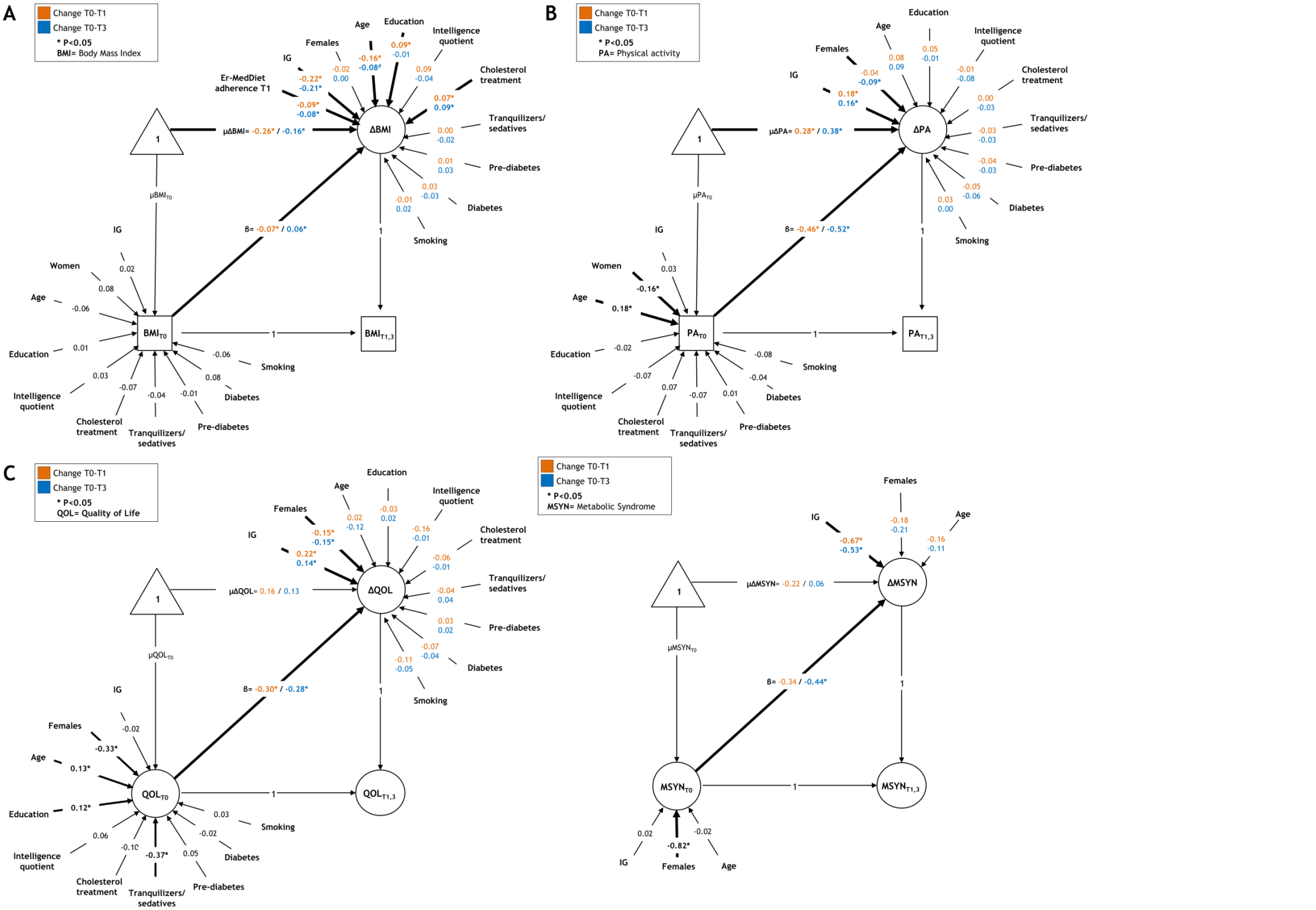
Supplementary Table 11. Bivariate latent change score models of metabolic syndrome (MSYN) and Cognition (COG)

		COG= Global Cognition						COG= Memory						COG= Executive functions					
		T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change			T0-T1 change			T0-T3 change		
Parameter	**Label**	**Est (SE)**	**EstSTD**	**P**	**Est (SE)**	**EstSTD**	**P**	**Est (SE)**	**EstSTD**	**P**	**Est (SE)**	**EstSTD**	**P**	**Est (SE)**	**EstSTD**	**P**	**Est (SE)**	**EstSTD**	**P**
Factor loadings for MSYN																			
Waist	λ_1	0.25 (0.02)	0.45	**<0.001**	0.33 (0.03)	0.49	**<0.001**	0.3 (0.03)	0.48	**<0.001**	0.33 (0.03)	0.49	**<0.001**	0.27 (0.05)	0.47	**<0.001**	0.33 (0.03)	0.49	**<0.001**
Triglycerides	λ_2	0.09 (0.02)	0.15	**<0.001**	0.13 (0.03)	0.19	**<0.001**	0.1 (0.02)	0.15	**<0.001**	0.12 (0.03)	0.18	**<0.001**	0.08 (0.03)	0.14	**0.005**	0.13 (0.03)	0.19	**<0.001**
HDL-cholesterol	λ_3	0.13 (0.02)	0.23	**<0.001**	0.15 (0.02)	0.24	**<0.001**	0.16 (0.03)	0.27	**<0.001**	0.15 (0.02)	0.24	**<0.001**	0.14 (0.03)	0.27	**<0.001**	0.15 (0.02)	0.24	**<0.001**
Systolic blood pressure	λ_4	0.14 (0.02)	0.24	**<0.001**	0.15 (0.03)	0.22	**<0.001**	0.16 (0.03)	0.25	**<0.001**	0.15 (0.03)	0.22	**<0.001**	0.14 (0.03)	0.24	**<0.001**	0.15 (0.03)	0.22	**<0.001**
Glucose	λ_5	0.06 (0.02)	0.11	**<0.001**	0.13 (0.03)	0.19	**<0.001**	0.07 (0.01)	0.12	**<0.001**	0.13 (0.03)	0.19	**<0.001**	0.05 (0.02)	0.08	**0.038**	0.13 (0.03)	0.19	**<0.001**
Mean rate of change in MSYN	$\mu\Delta$MSYN	-0.32 (0.3)	-0.22	0.282	0.09 (0.23)	0.07	0.696	-0.16 (0.24)	-0.11	0.515	0.06 (0.22)	0.04	0.79	0.06 (0.32)	0.04	0.85	0.11 (0.25)	0.08	0.657
Effect of baseline characteristics on the mean rate of change in MSYN																			
$MSYN_{T0} \rightarrow \Delta$MSYN	β_2	-0.28 (0.18)	-0.33	0.121	-0.39 (0.18)	-0.44	**0.030**	-0.43 (0.17)	-0.50	**0.01**	-0.39 (0.18)	-0.44	**0.03**	-0.58 (0.2)	-0.69	**0.003**	-0.39 (0.18)	-0.45	**0.03**
$COG_{T0} \rightarrow \Delta$MSYN	γ_1	-0.24 (0.12)	-0.30	0.053	-0.03 (0.1)	-0.03	0.783	-0.17 (0.13)	-0.15	0.194	-0.08 (0.09)	-0.06	0.353	-0.2 (0.16)	-0.28	0.218	-0.05 (0.16)	-0.09	0.742
IG $\rightarrow \Delta$MSYN		-1.98 (0.25)	-0.66	**<0.001**	-1.38 (0.19)	-0.53	**<0.001**	-1.57 (0.24)	-0.57	**<0.001**	-1.38 (0.19)	-0.53	**<0.001**	-1.61 (0.38)	-0.55	**<0.001**	-1.37 (0.19)	-0.53	**<0.001**
Gender [women] $\rightarrow \Delta$MSYN		-0.66 (0.59)	-0.22	0.257	-0.56 (0.42)	-0.22	0.181	-0.84 (0.47)	-0.3	0.073	-0.5 (0.42)	-0.19	0.23	-1.57 (0.7)	-0.54	**0.025**	-0.61 (0.45)	-0.24	0.176
Age $\rightarrow \Delta$MSYN		-0.38 (0.19)	-0.25	0.047	-0.16 (0.12)	-0.12	0.19	-0.17 (0.12)	-0.12	0.172	-0.16 (0.09)	-0.12	0.081	-0.4 (0.27)	-0.27	0.141	-0.22 (0.27)	-0.17	0.421
Effect of baseline MSYN on the mean rate of change in COG	γ_2	0.18 (0.1)	0.31	0.063	-0.01 (0.06)	-0.02	0.811	0.3 (0.17)	0.43	0.07	-0.08 (0.08)	-0.1	0.284	0.11 (0.14)	0.19	0.412	0.01 (0.15)	0.02	0.925
Coupled change $\Delta COG \leftrightarrow \Delta MSYN$	δ_2	-0.27 (0.24)	-0.27	0.259	-0.05 (0.24)	-0.05	0.828	-0.35 (0.21)	-0.35	0.088	-0.05 (0.14)	-0.05	0.715	0.16 (0.24)	0.16	0.494	-0.1 (0.28)	-0.1	0.718
Baseline covariance $COG_{T0} \leftrightarrow MSYN_{T0}$	δ_1	-0.05 (0.22)	-0.05	0.837	-0.05 (0.12)	-0.05	0.672	-0.09 (0.22)	-0.09	0.667	0.09 (0.1)	0.09	0.369	0.03 (0.24)	0.03	0.91	-0.06 (0.24)	-0.06	0.815
Effect of baseline characteristics on baseline MSYN																			
IG $\rightarrow MSYN_{T0}$		0.08 (0.29)	0.02	0.785	0.04 (0.23)	0.01	0.848	0.07 (0.25)	0.02	0.762	0.04 (0.23)	0.01	0.854	0.08 (0.28)	0.02	0.771	0.04 (0.23)	0.01	0.849
Gender [women] $\rightarrow MSYN_{T0}$		-2.89 (0.43)	-0.82	**<0.001**	-2.13 (0.35)	-0.72	**<0.001**	-2.47 (0.37)	-0.77	**<0.001**	-2.12 (0.35)	-0.72	**<0.001**	-2.79 (0.65)	-0.81	**<0.001**	-2.13 (0.35)	-0.72	**<0.001**
Age $\rightarrow MSYN_{T0}$		-0.03 (0.16)	-0.02	0.841	-0.06 (0.12)	-0.04	0.598	-0.04 (0.14)	-0.02	0.795	-0.06 (0.12)	-0.04	0.622	-0.04 (0.15)	-0.02	0.79	-0.06 (0.12)	-0.04	0.604
Model Fit Indexes		CFI=0.91; TLI=0.9; RMSEA=0.05; SRMR=0.08			CFI=0.87; TLI=0.85; RMSEA=0.06; SRMR=0.09			CFI=0.94; TLI=0.93; RMSEA=0.06; SRMR=0.08			CFI=0.9; TLI=0.87; RMSEA=0.08; SRMR=0.1			CFI=0.91; TLI=0.89; RMSEA=0.05; SRMR=0.08			CFI=0.88; TLI=0.86; RMSEA=0.06; SRMR=0.08		

IQ = intelligence quotient. IG= Intervention group. Est_{STD}= standardized estimate. $\rightarrow$ = regression path. $\leftrightarrow$ = correlation path. CFI= comparative fit index. TLI=Tucker Lewis Index. RMSEA= root-mean-square error of approximation. SRMR= standardized root-mean-square residual.
*Those parameters that only refer to cognition (Factor loadings for COG, mean rate of change for COG and the effect of baseline characteristics on baseline COG or on the mean rate of change for COG) are not included since they are equivalent to ones from Supplementary Table 7.



Supplementary Figure 1. Representation of the results of the causal mediation analysis testing the association between baseline cognitive scores and the achievement of the 8% weight loss goal after 1 and 3 years, mediated by high er-MedDiet adherence (yes/no) at 1 year in individuals allocated to the intervention group [N=240]. Blue bars represent total effects, grey bars represent average direct effects (ADE), black point ranges represent average causal mediation effects (ACME) and percentages in the right represent the proportion of mediation effects. 95% confidence intervals (95%CI) are only included for ACME. 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.


A
Change T0-T1
Change T0-T3
* P<0.05
BMI= Body Mass Index
ΔBMI
μΔBMI= -0.26* / -0.16*
μBMI$_{T0}$
β= -0.07* / 0.06*
BMI$_{T0}$
BMI$_{T1,3}$
Age
Education
Females
IG
Intelligence quotient
Er-MedDiet adherence T1
Cholesterol treatment
Tranquilizers/ sedatives
Pre-diabetes
Diabetes
Smoking
Women
Cholesterol treatment
Tranquilizers/ sedatives
B
Change T0-T1
Change T0-T3
* P<0.05
PA= Physical activity
ΔPA
μΔPA= 0.28* / 0.38*
μPA$_{T0}$
β= -0.46* / -0.52*
PA$_{T0}$
PA$_{T1,3}$
C
Change T0-T1
Change T0-T3
* P<0.05
QOL= Quality of Life
ΔQOL
μΔQOL= 0.16 / 0.13
μQOL$_{T0}$
β= -0.30* / -0.28*
QOL$_{T0}$
QOL$_{T1,3}$
Change T0-T1
Change T0-T3
* P<0.05
MSYN= Metabolic Syndrome
ΔMSYN
μΔMSYN= -0.22 / 0.06
μMSYN$_{T0}$
β= -0.34 / -0.44*
MSYN$_{T0}$
MSYN$_{T1,3}$

Supplementary Figure 2. Structural Equation Model (SEM) representations of the univariate part of bivariate latent change score models of global cognition, representing the effect of baseline characteristics on (A) baseline body mass index (BMIT0) and the mean rate of change in BMI (∆BMI); (B) baseline levels of PA (PA) (METs-minute/week) and the mean rate of change in PA (∆PA); (C) baseline levels of QoL (QOLT0) and the mean rate of change in QoL (∆QOL); (D) baseline levels of metabolic syndrome (MSYNT0) and the mean rate of change in MSYN (∆MSYN). 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. Bold lines refer to significant coefficients (<0.05 level). Measurement invariance of latent variables (QoL and MSYN) and correlated residual errors over time were assumed.