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Three-year effects of a multidomain lifestyle intervention on impulsivity: Results from a randomized clinical trial

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Short Title: Effects of a multidomain lifestyle intervention on impulsivity

Keywords: Randomized control trial (RCT); Multidomain lifestyle intervention; Mediterranean diet; Physical activity; Trait impulsivity; Behavioral impulsivity

Trial registration

Name of registry: Effect of an energy-restricted Mediterranean diet, physical activity and behavioral intervention on the primary prevention of cardiovascular disease.

Trial registration number: ISRCTN 89898870

Date of registration: 24/Apr/2014

URL: http://www.isrctn.com/ISRCTN89898870

Abbreviations

RCT, Randomized Control Trial

IIG, intensive intervention group

CG, control group

MedDiet, Mediterranean diet

BMI, body mass index

ADHD, Attention-Deficit/Hyperactivity Disorder

SD, standard deviation

MICE, multivariate imputation by chained equations

MLE, maximum likelihood estimations

CCA, complete case analysis

UPPS-P, Impulsive Behavior Scale

CPT, Conners' Continuous Performance Test third edition

IGT, Iowa Gambling Task

SCWT, Stroop Color Word Test

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ABSTRACT

Introduction: Research has consistently shown associations between elevated impulsivity and adverse physical and mental health outcomes. Specifically, impulsivity has been associated with higher body mass index and cardiometabolic issues. However, evidence from randomized clinical trials (RCTs) on whether impulsivity is responsive to a multidomain lifestyle intervention in older adults with overweight or obesity who are at high cardiovascular risk is limited.

Methods: Participants from the PREDIMED-Plus-Cognition sub-study, followed for 3 years as part of the PREDIMED-Plus RCT, were included. Eligible participants had overweight or obesity and metabolic syndrome at baseline. Participants were randomly allocated to either an intensive intervention group (IIG), with an energy-restricted Mediterranean diet (MedDiet), physical activity, and behavioral support, or to a control group (CG), advised to follow an *ad libitum* MedDiet. The primary outcome of the current study was the evaluation of impulsivity, which was only assessed in participants from the PREDIMED-Plus-Cognition sub-study. Trait impulsivity was assessed using the UPPS-P Impulsive Behavior Scale and behavioral impulsivity through 4 neuropsychological evaluations at baseline, 1-year, and 3-year follow-ups. Z-score composites for Global, Trait, and Behavioral Impulsivity were estimated. Multivariate linear mixed models were used to assess the effect of the PREDIMED-Plus intervention on impulsivity among the participants who participated in the PREDIMED-Plus-Cognition sub-study.

Results: A total of 306 participants (CG: n=156; IIG: n=150; mean age [SD]: 65.0 [4.7] years; 45.7% female) had impulsivity data at baseline. Compared to the CG, participants in the IIG exhibited decreases in Trait Impulsivity at 1 year (mean z-score change [95%CI]: -0.26 [-0.49, -0.03]), and in Global (-0.28 [-0.52, -0.03]) and Behavioral (-0.28 [-0.54, -0.02]) Impulsivity at 3-year follow-up.

Conclusion: An intensive lifestyle intervention combining MedDiet, physical activity, and behavioral support resulted in a long-term reduction of impulsivity among older adults at high cardiometabolic risk. Public health guidelines may consider multidomain lifestyle intervention strategies to decrease impulsivity.

INTRODUCTION

Although impulsivity can be adaptive in some contexts [1], elevated levels are consistently linked to risky lifestyle behaviors [2], poor health outcomes [3,4], psychiatric conditions [1,5], suicidality [6], and reduced quality of life [5], underscoring the need for strategies to mitigate its negative health outcomes.

Impulsivity arises from a complex interplay between genetic and environmental factors [1,7], resulting in a multifaceted construct involving both personality traits and behavioral responses [8]. As a personality trait, impulsivity is characterized by an urgency to respond rashly to emotional states, lack of premeditation, and sensation-seeking [8]. Behavioral impulsivity reflects the manifestation of trait impulsivity in observable actions, typically characterized by high reward sensitivity and risky decision-making and usually associated with altered prefrontal cortex activity [8]. Impulsivity is further related to serotonin and dopamine pathways and the brain's reward system, mechanisms underpinning addictive behavior [9,10]. Therefore, a global measure of impulsivity aims to capture its overall nature by encompassing both the personality predisposition to act on impulses and the cognitive impulsivity reflected in behaviors [8].

Lifestyle interventions promoting physical activity or dietary changes may mitigate the adverse consequences of high impulsivity. A meta-analysis of individuals with Attention-Deficit/Hyperactivity Disorder (ADHD), a condition characterized by elevated impulsivity [1], found that physical activity may reduce impulsivity [11]. Dietary interventions targeting serotonin and dopamine pathways have also shown potential to reduce impulsivity [12,13], but studies of healthy patterns—such as the Mediterranean (MedDiet) or Nordic diets—report inconclusive results in various populations [14–16]. Remarkably, a multimodal intervention without a control group in Spanish adolescents—including cognitive behavioral therapy, physical activity, and dietary counseling—was associated with reductions in impulsivity [17].

Targeting impulsivity in older adults with overweight or obesity at high cardiovascular risk is particularly relevant, as this growing population experiences reduced quality of life and a substantial burden of cardiovascular morbidity and mortality [18]. In individuals with obesity—particularly those with diabetes—associations between heightened impulsivity and poorer glycemic control and adherence to treatment have been identified [19–21]. This suggests that impulsivity may hinder the adoption and maintenance of healthy lifestyle changes, thereby limiting health improvements. Evidence from a psychological-behavioral intervention indicates that reductions in impulsivity can be accompanied by improvements in mental health and weight status [22], but singular pharmacological treatments have yielded inconsistent results in mitigating impulsivity [23], and systematic reviews of isolated lifestyle, psychological, and

brain stimulation interventions report a lack of robust reliable randomized controlled trials (RCTs) [11,23–25]. Moreover, most existing studies have focused on children and young adults with ADHD or addiction, leaving the impact of intensive multidomain lifestyle interventions on impulsivity largely unexplored in older adults without psychiatric disorders. Multidomain programs promoting healthy diets and physical activity combined with behavioral support may reduce impulsivity through several mechanisms, including enhanced executive function and goal-setting, modulation of dopaminergic and serotonergic pathways, and reduced neuroinflammation [26,27]. Such reductions in impulsivity could, in turn, facilitate adherence to sustained lifestyle changes, contributing to improvements in weight management, cardiovascular risk, and quality of life.

The primary question of the present study is whether a multidomain lifestyle intervention—combining an energy-restricted MedDiet, physical activity, and behavioral support—can modulate impulsivity, considered an intermediate outcome in the PREDIMED-Plus trial. It was hypothesized that the intervention would decrease a global measure of impulsivity, as well as trait and behavioral impulsivity. Understanding these effects could inform non-pharmacological strategies to reduce impulsivity-related health risks and improve well-being.

METHODS

Study design

This study was conducted using data from participants randomized to the PREDIMED-Plus-Cognition sub-study within the PREDIMED-Plus trial. The PREDIMED-Plus is a 6-year, multicenter, randomized, parallel-group clinical trial conducted across 23 Spanish centers. The study's primary objective is to assess the effect of a multidomain lifestyle intervention on the prevention of cardiovascular disease, focusing on weight loss maintenance. Psychological and neuropsychological measures were pre-specified in the study protocol as intermediate endpoints. PREDIMED-Plus participants were recruited between September 2013 and December 2016, and were randomly assigned in a 1:1 ratio to either the intensive intervention group (IIG) or the control group (CG) using a centrally controlled, computer-generated random-number internet-based system. The personnel who enrolled participants did not have access to the random allocation sequence. The randomization process was stratified by study center, sex, and age categories (<65 years, 65–70 years, and >70 years). Household couples were randomized together as the randomization unit. The study protocol has been described elsewhere [28] and is available at: http://www.predimedplus.com. The trial was registered in the International Standard Randomized Controlled Trial registry: http://www.isrctn.com/ISRCTN89898870.

Participants were not involved in the design, conduct, or reporting of the PREDIMED-Plus-Cognition sub-study. The study protocol of the PREDIMED-Plus Cognition sub-study was distributed to all participating research centers of this sub-study. There were no significant changes to the sub-study protocol after it commenced. Sample size was driven by voluntary enrollment of PREDIMED-Plus participants into the sub-study. Participating centers in the sub-study were those that confirmed the availability of a neuropsychologist qualified to comply with the sub-study protocol, resulting in a total of 4 of the 23 centers. The participation in the PREDIMED-Plus-Cognition sub-study was voluntary for participants involved in the primary trial. Neuropsychologists conducted impulsivity assessments for the sub-study, while intervention visits and data collection within the PREDIMED-Plus study were performed by trained staff, including dietitians and nurses. No interim analyses or stopping guidelines were applied for the sub-study.
The CONSORT checklist is provided as a **Supplementary File**.

Study population

Eligible participants were men aged 55 to 75 years and women aged 60 to 75 years with overweight or obesity (27 kg/m^2 ≥ BMI < 40 kg/m^2) and meeting at least three criteria for metabolic syndrome at baseline. Participants with cardiovascular disease and other chronic illnesses such as cancer and severe depression at enrollment were excluded. Other exclusion criteria have been reported elsewhere [28].

As part of the initial PREDIMED-Plus population (n=6,874), the current analysis included participants from the PREDIMED-Plus-Cognition sub-study (n=486) who were recruited and randomized in 4 Spanish centers: Hospital del Mar Research Institute, Bellvitge University Hospital, Universitat Rovira i Virgili, and Universidad de Valencia. For the main analyses, only participants having all impulsivity assessments at baseline were considered (n=306). A detailed flowchart of the studied participants is shown in **Supplementary Figure 1**.

Intervention

Participants in the IIG received recommendations to increase their adherence to an energy-restricted MedDiet and physical activity levels, along with behavioral support. Detailed information can be found elsewhere [28]. The initial dietary recommendations aimed to achieve a 30% energy reduction, limiting the intake of specific foods such as processed meat, butter, margarine, cream, sweetened beverages, added sugars, biscuits, and refined cereals, while promoting fruits, vegetables, legumes, whole grains, and white meat to align with the caloric restriction characteristic of a MedDiet for the purpose of weight loss. Participants were also encouraged to gradually increase their aerobic physical activity, aiming for at least 45 minutes of walking per day or an equivalent activity for 6 days per week, along with exercises to

enhance strength, flexibility, and balance. During the first year of follow-up, participants were monitored 3 times per month through an individual motivational interview, a telephone consultation, and a group session, resulting in 36 contacts per year. Thereafter, the participants received monthly group sessions, individual sessions every 3 months, and two phone calls every 3 months, resulting in 24 contacts per year. In contrast, participants in the CG received general usual care recommendations to follow an energy-unrestricted MedDiet, without promotion of physical activity. These recommendations were delivered through an individual visit and a group session every 6 months, resulting in 2 contacts per year for participants in the CG. Participants in both groups continued their usual medical care without restrictions. No harms related to the intervention or assessments were recorded or expected in this sub-study. All participants freely received extra virgin olive oil (1L/month) to reinforce their adherence.

Impulsivity

The neuropsychologists evaluating impulsivity measures were blinded to group allocation. Trait and behavioral impulsivity measurements were assessed at baseline, 1-year, and 3-year follow-up visits.

Trait impulsivity was evaluated using the Impulsive Behavior Scale (UPPS-P) [29], validated for the Spanish population [30]. The UPPS-P assesses five personality subfactors related to impulsivity: negative urgency, (lack of) premeditation, (lack of) perseverance, sensation seeking, and positive urgency. Scores for each dimension and a total score of the UPPS-P were calculated by adding respective items, with higher scores indicating higher impulsivity. Cronbach's α values indicate excellent internal consistency for the UPPS-P total score at baseline (α=0.91) and 1-year (α=0.92) and 3-year (α=0.90) follow-ups.

Four behavioral measures of impulsivity were assessed using three neuropsychological tasks. The Conners' Continuous Performance Test (CPT) is a 14-minute computerized task in which participants press the spacebar whenever any letter except 'X'. The CPT commission and perseveration scores were used to evaluate inattentiveness and anticipatory responses, respectively, with higher scores reflecting greater impulsivity [31]. The Iowa Gambling Task (IGT) is a computerized task where participants make 100 card selections from four decks, aiming to maximize monetary gain. Individuals with high impulsivity tend to select decks with high immediate rewards despite long-term losses, indicative of a preference for immediate over delayed gains. Higher IGT scores indicate better decision-making performance and, therefore, lower impulsivity [32]. The Stroop Color Word Test (SCWT) consists of three timed tasks requiring participants to name colors or words under congruent and incongruent conditions. The SCWT interference score is derived from performance in the incongruent condition, which requires cognitive inhibition of a prepotent response. Higher SCWT interference scores reflect

greater inhibitory control and cognitive flexibility, which is indicative of lower impulsivity [33]. Additional details are provided in the **Supplementary Methods**.

Covariates

Potential confounders of the PREDIMED-Plus intervention effect on impulsivity were assessed at baseline. Intervention-related covariates included study center and participants sharing household. Sociodemographic covariates were self-reported, including sex, age, educational level, and marital status. Lifestyle covariates included self-reported smoking status, alcohol and total energy intakes estimated from a validated 143-item Food Frequency Questionnaire [34], adherence to the 17-item energy-restricted MedDiet [35], physical activity from the Regicor Short Physical Activity Questionnaire [36], and obesity (BMI>30 kg/m^2) determined by anthropometric measures conducted by study staff. Disease history covariates encompassed self-reported hypercholesterolemia and hypertension, type 2 diabetes diagnosis per American Diabetes Association criteria [37], self-reported diabetes medication use (see **Supplementary Methods**), and depressive symptomatology determined by a Beck Depression Inventory-II score ≥14 [38].

Statistical analysis

The PREDIMED-Plus-Cognition database, updated in October 2024, was used for the present analyses.

To facilitate comparisons across impulsivity assessments, z-scores were generated for each impulsivity measurement, and z-score composites for Global, Trait, and Behavioral Impulsivity constructs were further obtained following specified methods [39] (see **Supplementary Methods**). Pearson correlation analyses were conducted to assess correlations between impulsivity assessments.

Baseline participant characteristics are presented as numbers and percentages for qualitative variables and as mean ± standard deviation (SD) for quantitative variables, with differences between CG and IIG examined using chi-square and t-tests, as appropriate, as this analysis used a sub-cohort within the PREDIMED-Plus.

For the main analysis, a complete case analysis (CCA) was conducted to select participants without missing values at baseline (n=306), and maximum likelihood estimation (MLE) was used to handle missing data over follow-ups. This approach ensured comparability across Global, Trait, and Behavioral impulsivity measures within the same population, and maximized the use of observed impulsivity evaluations. Additional rationale for the selection of this approach is presented in **Supplementary Methods**. Linear mixed models were performed to assess the effect of the PREDIMED-Plus intervention (difference between IIG and CG) on

impulsivity z-score changes. A total of three models were fitted, and the covariates were adjusted at baseline. Additional details are in **Supplementary Methods**. Random effects were hierarchically established at three levels: center, participants sharing a household, and individual. A random slope was specified for the individual level across time points. An unstructured covariance was specified.

Several sensitivity analyses were performed. First, a per-protocol analysis was conducted based on the intervention targets: a ≥5% reduction in body mass index (BMI), a ≥5% increase in leisure time physical activity, and a 17-point Mediterranean diet score of >13 points. Second, interactions by age (<65; ≥65 years), sex, MedDiet adherence (based on the median: <8; ≥8 points), and presence of obesity (no; yes) or type 2 diabetes (no; yes) were assessed at baseline using the likelihood ratio test. Third, given the considerable missing data on impulsivity assessments (for Global Impulsivity: 37.0% missing at baseline, 43.4% at 1-year, and 61.5% at 3-year follow-ups), several additional analyses were performed to confirm the robustness of the results. These analyses included: (1) a CCA at baseline with multivariate imputation by chained equations (MICE) across follow-ups; (2) MICE across all time points; (3) MLE across all time points; (4) a CCA across all time points. Detailed information in **Supplementary Methods**.

The STATA-18 software program (StataCorp) was used to perform the statistical analyses, and significance was defined as $p<0.05$.

RESULTS

Population characteristics

Of the 486 individuals participating in the PREDIMED-Plus-Cognition study, 306 had complete baseline data; among them, 126 had complete 3-year follow-up data on impulsivity (**Supplementary Figure 1**). A comparison of the general characteristics of the PREDIMED-Plus cohort (n=6,874) with the total PREDIMED-Plus-Cognition sub-study (n=486) and the total population included in the main analysis (n=306) is displayed in **Supplementary Table 1**.

Population baseline characteristics according to the PREDIMED-Plus study arm groups are shown in **Table 1**. Similar population characteristics were shown when comparing the IIG and CG. For the total population included in the main analysis (n=306), the mean age was 65.0 ± 4.7 years, and females represented 45.7% of participants. Nearly 50% of participants had primary school education, 80% were married, and 13% were current smokers. Alcohol and total energy intakes were 9.6 ± 11.1 g/day and 2452 ± 619 kcal/day, respectively. Adherence to the MedDiet was 7.8 ± 2.5 points. Around three-quarters of participants presented obesity, hypercholesterolemia, and hypertension. Baseline type 2 diabetes prevalence was 26.8%, with

76.8% of these participants taking type 2 diabetes medications. In addition, 15.7% of participants showed depressive symptoms. Impulsivity assessments at baseline were similar for CG and IIG. A correlation matrix of impulsivity assessments at baseline is shown in **Supplementary Table 2**.

Within- and between-group intervention effects on impulsivity changes

The effect of the PREDIMED-Plus intervention on 3-year z-score changes in impulsivity constructs is shown in **Table 2**, with linear predictions graphically displayed in **Figure 1**. In the fully-adjusted model, significant between-group differences across the overall follow-up were observed for Behavioral Impulsivity ($p<0.01$), while Global and Trait Impulsivity did not reach statistical significance (both $p\leq0.08$). Between-group z-score changes in impulsivity constructs from baseline to the 1-year follow-up revealed that the PREDIMED-Plus intervention resulted in a decrease in Trait Impulsivity (mean z-score change [95% CI]: -0.26 [-0.49, -0.03]; p=0.03), a non-significant increase in Behavioral Impulsivity (0.25 [-0.02, 0.52]; p=0.07), and no significant change in Global Impulsivity. At the 3-year follow-up, the IIG in comparison to CG had a significantly lower Global (-0.28 [-0.52, -0.03]; p=0.03) and Behavioral (-0.28 [-0.54, -0.02]; p=0.03) Impulsivity, but no differences were observed for Trait Impulsivity. Within-group z-score changes in impulsivity constructs from baseline to the 1-year follow-up revealed only a significant decrease in Behavioral Impulsivity (-0.22 [-0.40, -0.04]; p=0.02) in the CG group. At the 3-year follow-up, participants in both study arm groups showed decreases in Global (CG: -0.20 [-0.37, -0.03]; p=0.03); IIG: -0.48 [-0.66, -0.30]; $p<0.01$) and Behavioral (CG: -0.20 [-0.38, -0.02]; p=0.03); IIG: -0.48 [-0.67, -0.29]; $p<0.01$) Impulsivity, and only those in the IIG additionally showed significant decreases in Trait Impulsivity (-0.19 [-0.33, -0.05]; $p<0.01$).

The effect of the PREDIMED-Plus intervention on each specific trait and behavioral impulsivity z-score is shown in **Supplementary Table 3**, and on original values in **Supplementary Table 4**. Compared to baseline values, the IIG exhibited a mean decrease of -4.35 points in the total UPPS-P original score (95% CI: -7.56, -1.14; $p<0.01$), and a mean increase of 8.81 points in the IGT (3.25, 14.38; $p<0.01$) and 2.19 in the SCWT (0.72, 3.66; $p<0.01$) at the 3-year follow-up. The overall intervention effect across follow-ups was statistically significant for the IGT (p=0.02), but not for the total UPPS-P and SCWT.

Sensitivity analyses

None of the assessed interactions were found to be statistically significant. Per-protocol analyses revealed that, compared to participants in the CG, those in the IIG who adhered to the Mediterranean diet goals exhibited the largest decreases in Global Impulsivity at the 3-year follow-up (-0.66 [-1.11, -0.20]; $p<0.01$), followed by those who increased their leisure time

physical activity by 5% (-0.34 [-0.66, -0.01]; p=0.04). No significant reduction was observed among individuals with a 5% BMI decrease alone. Concomitant achievement of these goals further indicated decreases in Global Impulsivity at 3 years (**Supplementary Table 5**).

Sensitivity analyses addressing missing data on impulsivity indicated that the direction of the between-group effects on impulsivity constructs was consistent with the main analyses, although statistical significance varied by method. Compared with the main model, conducting CCA at baseline and MICE across follow-ups revealed a significant between-group decrease in Trait Impulsivity at 3 years (**Supplementary Table 6**). MICE across all time points showed a significant between-group increase in Behavioral Impulsivity at 1 year (**Supplementary Table 7**). MLE across all time points also indicated a significant between-group increase in Behavioral Impulsivity at 1 year, while the decrease observed at 3 years was no longer significant (**Supplementary Table 8**). In contrast, CCA across all time points did not show a significant between-group decrease in Trait Impulsivity at 1 year (**Supplementary Table 9**). Moreover, when considering the overall intervention effect across follow-ups, these sensitivity analyses revealed additional statistically significant effects compared with the main model (**Supplementary Tables 6–9**).

DISCUSSION

The present results offer novel insights into the effects of a multidomain lifestyle intervention on impulsivity over 3 years in older adults at high cardiovascular risk who participated in the PREDIMED-Plus-Cognition sub-study within the PREDIMED-Plus RCT. Our findings provide support for potential benefits of promoting an energy-restricted MedDiet and physical activity with behavioral support in modulating impulsivity.

Evidence from a recent RCT of a multidomain lifestyle intervention in older adults at high cardiovascular risk indicated that adherence to intervention goals decreased with aging but increased with higher self-efficacy [40]. Among older adults with type 2 diabetes and obesity, greater behavioral impulsivity has been observed compared to healthy individuals, and higher trait impulsivity predicted poorer diabetes self-management, suboptimal glycemic control, and greater weight gain [21,41]. Therefore, reducing impulsivity in older adults with unhealthy profiles may enhance adherence to lifestyle modifications, ultimately contributing to improved cardiometabolic status.

Research on isolated lifestyle interventions and impulsivity remains inconsistent and has been conducted primarily in young individuals with ADHD, leaving a paucity of evidence in older populations without psychiatric disorders. A meta-analysis reported that among studies involving individuals with ADHD, only 3 of 23 included adults; of these, 2 found no effects of

physical activity interventions on attention or hyperactivity, while the remaining study reported reductions in emotional problems [11]. Dietary interventions targeting impulsivity mainly focused on specific nutrients rather than modifying overall dietary patterns. Acute tryptophan depletion, which reduces serotonin availability, may heighten impulsivity in young populations with ADHD, but findings in adults have been inconsistent [13].

To the best of our knowledge, the present study is the first RCT assessing combined effects of an energy-restricted MedDiet, physical activity, and behavioral support on impulsivity. Given impulsivity's multifaceted nature, aggregating assessments into Global, Trait, and Behavioral z-scores may offer a more comprehensive evaluation than only examining isolated characteristics, as previously suggested [8]. Within this scope, an overall interpretation of the main and sensitivity analyses addressing missing data indicated that the effect of the PREDIMED-Plus intervention (IIG vs. CG) revealed distinct trajectories for trait and behavioral impulsivity. Trait Impulsivity showed a decreasing trend at 1 year, while these reductions became smaller or negligible at 3 years. Behavioral Impulsivity showed a trend to increase at 1 year and to decrease at 3 years. The divergent trajectories of Trait and Behavioral Impulsivity observed at the initial time point probably contributed to the absence of an effect on Global Impulsivity. However, the subsequent convergence of reductions may have yielded a significant decrease in Global Impulsivity at the final follow-up.

It has been suggested that the short-term RCTs effects may be insufficient to determine long-term impacts [42]. Our findings indicate that an intensive multidomain lifestyle intervention may have distinct short- and long-term effects on trait and behavioral impulsivity. A recent 4-week RCT with 30 healthy adults found that at least 8 hours of time-restricted feeding increased both trait and behavioral impulsivity [43]. Similarly, our results suggest a potential transient increase in behavioral impulsivity at 1 year, possibly due to the high cognitive load associated with an intensive intervention [44], which in the present trial involved 24–36 contacts per year while only 2 in the CG. In contrast, the intervention effect revealed its larger decreases in trait impulsivity at 1 year. Although personality traits are generally considered stable, impulsivity appears to be relatively malleable [7]. These findings suggest that the intensity of counseling and behavioral support may differentially influences self-perceived trait impulsivity tendencies over time. Overall, the observed trajectories of trait and behavioral impulsivity highlight differential short- and long-term responsiveness to lifestyle interventions, underscoring the need to monitor both dimensions.

It is important to note that significant benefits were observed in both the IIG and the active CG. Therefore, future clinical trials should assess not only the potentially greater long-term effects of intensive multidomain lifestyle interventions on impulsivity demonstrated in our IIG but also

their cost-effectiveness, given that even the less intensive approach in the CG—consisting of *ad libitum* MedDiet advice combined with annual follow-up—also yielded reductions in impulsivity.

Our per-protocol analyses indicated that participants with higher compliance with the Mediterranean diet goals exhibited the largest decreases in impulsivity over the 3 years of follow-up. Concomitant adherence to physical activity and weight reduction goals was also associated with decreased impulsivity at 3 years. These findings may be explained by multiple underlying mechanisms. First, adhering to an energy-restricted MedDiet may enhance brain function and self-regulation through its anti-inflammatory and neuroprotective properties. MedDiet components—such as antioxidants, polyphenols, and polyunsaturated fatty acids—have been found to promote synaptic plasticity, brain-derived neurotrophic factor expression, and dopaminergic and serotonergic neurotransmitter balance, while also reducing oxidative stress and neuroinflammation [26,45]. Additionally, diet-gut-brain axis interactions have been proposed as important contributors to these pathways, with impulsivity potentially playing a role in the process [46,47]. Second, physical activity may reduce impulsivity by improving brain function. Aerobic exercise has been linked to improved prefrontal cortex activity and connectivity within neural networks involved in impulsivity regulation, which are crucial for emotional reactivity, cognitive flexibility, decision-making, and inhibitory control [1,10,48,49]. Moreover, physical activity is suggested to enhance brain-derived neurotrophic factor expression and dopamine and serotonin signaling [27,50,51], potentially reducing impulsivity. Furthermore, endorphin and serotonin release during exercise may further ameliorate mood disturbances and emotional reactivity through changes in the hypothalamic–pituitary–adrenal axis [27,51]. Third, the PREDIMED-Plus intervention showed beneficial effects on adiposity and body composition [52], suggesting reductions in brain oxidative stress and inflammation, which in turn may lower impulsivity [4,20]. Fourth, the behavioral support in the PREDIMED-Plus intervention may have reinforced social interactions, self-monitoring, goal setting, and cognitive strategies, may reducing impulsivity predispositions and behaviors [23,24]. Consequently, the multifaceted intervention—combining diet, physical activity, and behavioral reinforcement for weight loss—may have produced a synergistic effect influencing multiple biological and psychological pathways leading to decreased impulsivity. Our findings and their biological plausibility are especially relevant, as the long-term effectiveness of weight-loss interventions is often modest and dependent on sustained adherence [53], in which impulsivity is probably playing a role.

Strengths of our study include the translational RCT design, relatively large sample size, long follow-up, and comprehensive impulsivity evaluations. The multidomain intervention enabled the examination of combined rather than isolated lifestyle effects. Moreover, the PREDIMED-

Plus intervention was found to improve diet, physical activity, and BMI [52,54,55], suggesting that combined lifestyle changes and behavioral support underlie reductions in impulsivity. Limitations include that impulsivity was obtained using self-report and cognitive measurements, which are susceptible to bias, although measurements administered by neuropsychologists. Our population consisted of older adults at high cardiovascular risk participating in a clinical trial, limiting generalizability to other populations as younger individuals or those with psychiatric conditions. Analyses were restricted to 4 of the 23 participating research centers participating in the PREDIMED-Plus study, also limiting the generalizability of the results. Considerable missing data on outcomes were present, which could impact validity. To address this, extensive sensitivity analyses were performed, revealing some discrepancies in statistical significance that warrant a cautious interpretation of the findings. Multiple comparisons correction was not conducted because the CCA is already conservative due to the extensive missingness, and the likelihood of false negative results is higher than that of false positives in this case. Indeed, the comparison of the results between sensitivity and main analyses suggested that the latter may be conservative in terms of statistical significance while maintaining similar directional trends. In addition, our study found small or negligible correlations between trait and behavioral impulsivity measures, consistent with prior reports [8]. There is an emerging debate concerning the validity of current impulsivity assessments [56,57], and the present work should be considered within this ongoing discussion. Finally, potential genetics interferences of impulsivity are not considered. Nevertheless, our models were controlled for extensive confounding factors.

CONCLUSION

Given the well-documented detrimental links between impulsivity and health outcomes, interventions targeting impulsivity may have important public health implications. This study provides novel evidence that promoting a healthy diet, physical activity, and behavioral support can produce long-term reductions in impulsivity among older adults at high cardiovascular risk without psychiatric conditions. Although effects observed were small to moderate, scaling such interventions at the population level could meaningfully improve health outcomes. These findings suggest that multidomain lifestyle interventions may help mitigate impulsivity-related medical and mental health problems, highlighting the value of sustained behavioral change in public health initiatives. Future research should replicate these findings in other populations and examine the potential benefits of combining lifestyle interventions with pharmacological or psychological treatments.

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ETHICS STATEMENT

All participants gave written informed consent. The study was approved by all participating institutions' Research Ethics Committees in accordance with the Declaration of Helsinki (CEIC del Hospital de Bellvitge, Hospital Universitari de Bellvitge: PR240/13; CEIC Parc de Salut Mar and IDIAP Jordi Gol, IMIM: PI13/120; CEIC of Human Subjects, University of Valencia: 2011-005398-22; CEIC del Hospital Universitari Sant Joan de Reus and IDIAB Jordi Gol, Universitat Rovira i Virgili: 13-07-25/7proj2).

CONFLICT OF INTERESTS

JS-S received research support from ISCIII, Ministerio de Educación y Ciencia, Generalitat de Catalunya, the European Commission, and NIH; consulting fees or travel expenses from Instituto Danone; nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, Almond Board of California, Pistachio Growers, and Borges S.A.; served on the board and received institutional grants from the International Nut and Dried Foundation; served on the Danone Institute International Scientific Board (non-payed member); and received personal fees from Instituto Danone Spain. FF-A and SJ-M received consultancy and speaker fees from Novo Nordisk. BF received educational speaking fees and travel support from Medice. All other authors declare no financial or commercial conflicts of interest. None of the sponsors played any role in study design, data collection, analysis, interpretation, manuscript preparation, or the decision to publish.

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AUTHOR CONTRIBUTIONS

Principal PREDIMED-Plus-Cognition investigators RdlT, DC, SJ-M, FF-A, and JS-S contributed to study design and data extraction. CG-M conducted statistical analyses and, with SS, interpreted results. CG-M and JS-S drafted the manuscript. CG-M, SS, LC-B, HJM-E, NB, LF, DC, AC-R, RdlT, SJ-M, XP, MF, RF-C, SM, BF, JH, FF-A, JS-S reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, allowing access to external researchers for studies following the project purposes. Interested researchers may contact the PREDIMED-Plus Steering Committee chair at: predimed_plus_scommitte@googlegroups.com. Requests will be reviewed by the Steering Committee. Further enquiries can be directed to the corresponding author.

REFERENCES

1 Dalley JW, Robbins TW. Fractionating impulsivity: neuropsychiatric implications. Nat Rev Neurosci. 2017 Mar;18(3):158–71.

2 Lee RSC, Hoppenbrouwers S, Franken I. A Systematic Meta-Review of Impulsivity and Compulsivity in Addictive Behaviors. Neuropsychol Rev. 2019 Mar;29(1):14–26.

3 Gómez-Martínez C, Paolassini-Guesnier P, Fezeu L, Srour B, Hercberg S, Touvier M, et al. Trait impulsivity is associated with an increased risk of type 2 diabetes incidence in adults over 8 years of follow-up: results from the NutriNet-Santé cohort. BMC Med. 2024 Aug;22(1):332.

4 Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. Psychol Bull. 2017 Aug;143(8):868–902.

5 Chamberlain SR, Stochl J, Redden SA, Grant JE. Latent traits of impulsivity and compulsivity: toward dimensional psychiatry. Psychol Med. 2018 Apr;48(5):810–21.

6 Moore FR, Doughty H, Neumann T, McClelland H, Allott C, O'Connor RC. Impulsivity, aggression, and suicidality relationship in adults: A systematic review and meta-analysis. EClinicalMedicine. 2022 Mar;45:101307.

7 Liu M, Argyriou E, Cyders MA. Developmental Considerations for Assessment and Treatment of Impulsivity in Older Adults. In: de Wit H, Jentsch JD, editors. Current Topics in Behavioral Neurosciences. Berlin/Heidelberg, Germany: Springer Cham; 2020; pp 165–77.

8 Sharma L, Markon KE, Clark LA. Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. Psychol Bull. 2014;140(2):374–408.

9 Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. Neuroscience. 2012 Jul;215:42–58.

10 Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol. 2013 Sep;108:44–79.

11 Xie Y, Gao X, Song Y, Zhu X, Chen M, Yang L, et al. Effectiveness of Physical Activity Intervention on ADHD Symptoms: A Systematic Review and Meta-Analysis. Front Psychiatry. 2021 Oct;12. DOI: 10.3389/fpsyt.2021.706625

12 van Kooten MJ, Veldhuizen MG, de Araujo IE, O'Malley SS, Small DM. Fatty acid amide supplementation decreases impulsivity in young adult heavy drinkers. Physiol Behav. 2016 Mar;155:131–40.

13 Dinu LM, Phattharakulnij N, Dommett EJ. Tryptophan modulation in individuals with attention deficit hyperactivity disorder: a systematic review. J Neural Transm. 2022 Apr;129(4):361–77.

14 Sørensen LB, Dyssegaard CB, Damsgaard CT, Petersen RA, Dalskov S-M, Hjorth MF, et al. The effects of Nordic school meals on concentration and school performance in 8- to 11-year-old children in the OPUS School Meal Study: a cluster-randomised, controlled, cross-over trial. British Journal of Nutrition. 2015 Apr;113(8):1280–91.

15 San Mauro Martin I, Sanz Rojo S, González Cosano L, Conty de la Campa R, Garicano Vilar E, Blumenfeld Olivares JA. Impulsiveness in children with attention-deficit/hyperactivity disorder

after an 8-week intervention with the Mediterranean diet and/or omega-3 fatty acids: A randomised clinical trial. Neurología. 2022 Sep;37(7):513–23.

16 Rucklidge J, Taylor M, Whitehead K. Effect of Micronutrients on Behavior and Mood in Adults With ADHD: Evidence From an 8-Week Open Label Trial With Natural Extension. J Atten Disord. 2011 Jan;15(1):79–91.

17 Delgado-Rico E, Río-Valle JS, Albein-Urios N, Caracuel A, González-Jiménez E, Piqueras MJ, et al. Effects of a multicomponent behavioral intervention on impulsivity and cognitive deficits in adolescents with excess weight. Behavioural Pharmacology. 2012 Sep;23(5 and 6):609–15.

18 Ahmed SK, Mohammed RA. Obesity: Prevalence, causes, consequences, management, preventive strategies and future research directions. Metabol Open. 2025 Sep;27:100375.

19 Steward T, Miranda-Olivos R, Soriano-Mas C, Fernández-Aranda F. Neuroendocrinological mechanisms underlying impulsive and compulsive behaviors in obesity: a narrative review of fMRI studies. Rev Endocr Metab Disord. 2019 Sep;20(3):263–72.

20 Testa G, Mora-Maltas B, Camacho-Barcia L, Granero R, Lucas I, Agüera Z, et al. Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile to Self-Reported Dimensions in Clinical Samples with and without Diabetes. Nutrients. 2021 Dec;13(12):4426.

21 Hadj-Abo A, Enge S, Rose J, Kunte H, Fleischhauer M. Individual differences in impulsivity and need for cognition as potential risk or resilience factors of diabetes self-management and glycemic control. PLoS One. 2020 Jan;15(1):e0227995.

22 Boswell RG, Gueorguieva R, Grilo CM. Change in impulsivity is prospectively associated with treatment outcomes for binge-eating disorder. Psychol Med. 2023 May;53(7):2789–97.

23 Anderson AC, Youssef GJ, Robinson AH, Lubman DI, Verdejo-Garcia A. Cognitive boosting interventions for impulsivity in addiction: a systematic review and meta-analysis of cognitive training, remediation and pharmacological enhancement. Addiction. 2021 Dec;116(12):3304–19.

24 Rung JM, Madden GJ. Experimental reductions of delay discounting and impulsive choice: A systematic review and meta-analysis. J Exp Psychol Gen. 2018 Sep;147(9):1349–81.

25 Yang C-C, Völlm B, Khalifa N. The Effects of rTMS on Impulsivity in Normal Adults: a Systematic Review and Meta-Analysis. Neuropsychol Rev. 2018 Sep;28(3):377–92.

26 Franco GA, Interdonato L, Cordaro M, Cuzzocrea S, Di Paola R. Bioactive Compounds of the Mediterranean Diet as Nutritional Support to Fight Neurodegenerative Disease. Int J Mol Sci. 2023 Apr;24(8):7318.

27 Heijnen S, Hommel B, Kibele A, Colzato LS. Neuromodulation of Aerobic Exercise—A Review. Front Psychol. 2016 Jan;6(JAN). DOI: 10.3389/fpsyg.2015.01890

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

29 Lynam DR, Smith GT, Whiteside SP, Cyders MA. The UPPS–P: Assessing five personality pathways to impulsive behavior. West Lafayette: Purdue University; 2006.

30 Verdejo-García A, Lozano Ó, Moya M, Alcázar MÁ, Pérez-García M. Psychometric Properties of a Spanish Version of the UPPS–P Impulsive Behavior Scale: Reliability, Validity and Association With Trait and Cognitive Impulsivity. J Pers Assess. 2010 Jan;92(1):70–7.

31 Keith Conners C, Sitarenios G, Ayearst LE. Conners' Continuous Performance Test Third Edition. Encyclopedia of Clinical Neuropsychology. Cham: Springer International Publishing; 2018; pp 929–33.

32 Bechara A, Damasio H, Tranel D, Damasio AR. Deciding Advantageously Before Knowing the Advantageous Strategy. Science (1979). 1997 Feb;275(5304):1293–5.

33 Golden C. Manual STROOP-Test de Colores y Palabras. 3rd ed. Madrid, Spain: TEA Ediciones; 2001.

34 Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. British Journal of Nutrition. 2010 Jun;103(12):1808–16.

35 Schröder H, Zomeño MD, Martínez-González MA, Salas-Salvadó J, Corella D, Vioque J, et al. Validity of the energy-restricted Mediterranean Diet Adherence Screener. Clinical Nutrition. 2021 Aug;40(8):4971–9.

36 Molina L, Sarmiento M, Peñafiel J, Donaire D, Garcia-Aymerich J, Gomez M, et al. Validation of the Regicor Short Physical Activity Questionnaire for the Adult Population. PLoS One. 2017 Jan;12(1):e0168148.

37 American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan;45(Suppl 1):S17–38.

38 Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.

39 Tuligenga RH, Dugravot A, Tabák AG, Elbaz A, Brunner EJ, Kivimäki M, et al. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. Lancet Diabetes Endocrinol. 2014 Mar;2(3):228–35.

40 Wittmann FG, Pabst A, Zülke A, Luppa M, Oey A, Boekholt M, et al. Adherence to a lifestyle intervention – just a question of self-efficacy? Analysis of the AgeWell.de-intervention against cognitive decline. Alzheimers Res Ther. 2024 Jun;16(1):133.

41 Testa G, Camacho-Barcia L, Gómez-Martínez C, Mora-Maltas B, de la Torre R, Pintó X, et al. Impulsive Personality Traits Predicted Weight Loss in Individuals with Type 2 Diabetes after 3 Years of Lifestyle Interventions. J Clin Med. 2022 Jun;11(12):3476.

42 Norrie J. The importance of long-term follow-up in clinical trials. Lancet Glob Health. 2023 Jul;11(7):e995–6.

43 Güner E, Aktaç Ş. Time-restricted feeding can increase food-related impulsivity: a randomized controlled trial. Nutr Neurosci. 2025 Jan;28(1):28–36.

44 Finn EB, Whang C, Hong PH, Costa SA, Callahan EA, Huang TT-K. Strategies to improve the implementation of intensive lifestyle interventions for obesity. Front Public Health. 2023 Jul;11. DOI: 10.3389/fpubh.2023.1202545

45 Maia JM, Solon IG, Soriano RN, Branco LGS. Exploring the links between pro-inflammatory diets, gut dysbiosis, serotonin, and their implications for psychiatric and neurodegenerative disorders. Brain Behavior and Immunity Integrative. 2024 Dec;8:100097.

46 Konstanti P, Gómez-Martínez C, Muralidharan J, Vioque J, Corella D, Fitó M, et al. Faecal microbiota composition and impulsivity in a cohort of older adults with metabolic syndrome. Sci Rep. 2024 Nov;14(1):28075.

47 Zhang R, Zhang M, Wang P. The intricate interplay between dietary habits and cognitive function: insights from the gut-brain axis. Front Nutr. 2025 Jan;12. DOI: 10.3389/fnut.2025.1539355

48 Mehren A, Diaz Luque C, Brandes M, Lam AP, Thiel CM, Philipsen A, et al. Intensity-Dependent Effects of Acute Exercise on Executive Function. Neural Plast. 2019 Jun;2019:1–17.

49 Damrongthai C, Kuwamizu R, Suwabe K, Ochi G, Yamazaki Y, Fukuie T, et al. Benefit of human moderate running boosting mood and executive function coinciding with bilateral prefrontal activation. Sci Rep. 2021 Nov;11(1):22657.

50 Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res. 2015 Jan;60:56–64.

51 Bhattacharya P, Chatterjee S, Roy D. Impact of exercise on brain neurochemicals: a comprehensive review. Sport Sci Health. 2023 Jun;19(2):405–52.

52 Konieczna J, Ruiz-Canela M, Galmes-Panades AM, Abete I, Babio N, Fiol M, et al. An Energy-Reduced Mediterranean Diet, Physical Activity, and Body Composition. JAMA Netw Open. 2023 Oct;6(10):e2337994.

53 Kheniser K, Saxon DR, Kashyap SR. Long-Term Weight Loss Strategies for Obesity. J Clin Endocrinol Metab. 2021 Jun;106(7):1854–66.

54 Sayón-Orea C, Razquin C, Bulló M, Corella D, Fitó M, Romaguera D, et al. Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome. JAMA. 2019 Oct;322(15):1486.

55 Schröder H, Cárdenas-Fuentes G, Martínez-González MA, Corella D, Vioque J, Romaguera D, et al. Effectiveness of the physical activity intervention program in the PREDIMED-Plus study: a randomized controlled trial. International Journal of Behavioral Nutrition and Physical Activity. 2018 Dec;15(1):110.

56 Huang Y, Luan S, Wu B, Li Y, Wu J, Chen W, et al. Impulsivity is a stable, measurable, and predictive psychological trait. Proceedings of the National Academy of Sciences. 2024 Jun;121(24). DOI: 10.1073/pnas.2321758121

57 Strickland JC, Johnson MW. Rejecting impulsivity as a psychological construct: A theoretical, empirical, and sociocultural argument. Psychol Rev. 2021 Mar;128(2):336–61.

Figure 1. Graphical representation of linear predictions for the effect of the PREDIMED-Plus intervention on changes in impulsivity constructs.

Table 1. Population characteristics.

Characteristics		Study arm		
	All (n=306)	CG (n=156)	IIG (n=150)	p
Sex (female)	140 (45.75)	69 (44.23)	71 (47.33)	0.586
Age (in years)	65.03 ± 4.72	64.52 ± 4.68	65.56 ± 4.71	0.054
Educational level				0.382
Primary school or less	146 (47.71)	71 (45.51)	75 (50.00)	
High school	97 (31.70)	48 (30.77)	49 (32.67)	
College	63 (20.59)	37 (23.72)	26 (23.72)	
Civil status				0.090
Single, divorced or separated	33 (10.78)	13 (8.33)	20 (13.33)	
Married	246 (80.39)	133 (85.26)	113 (75.33)	
Widower	27 (8.80)	10 (6.41)	17 (11.33)	
Smoking status				0.062
Never	140 (45.75)	62 (39.74)	78 (52.00)	
Former	126 (41.18)	74 (47.44)	52 (34.67)	
Current	40 (13.07)	20 (12.82)	20 (13.33)	
Alcohol intake (g/day)	9.64 ± 11.12	9.37 ± 11.71	9.91 ± 12.57	0.695
Adherence to Mediterranean diet (0-17 points)	7.81 ± 2.47	7.93 ± 2.51	7.68 ± 2.42	0.377
Total energy intake (kcal/day)	2452 ± 619	2461 ± 600	2443 ± 641	0.805
Physical activity (MET min/week)	2471 ± 2019	2353 ± 2031	2593 ± 2006	0.300
BMI (kg/m²)	32.51 ± 3.38	32.43 ± 3.16	32.58 ± 3.59	0.705
Obesity (BMI≥30 kg/m2)	226 (73.86)	118 (75.64)	108 (72.00)	0.469
Hypercholesterolemia (yes)	223 (72.88)	113 (72.44)	110 (73.33)	0.860
Hypertension (yes)	254 (83.01)	125 (80.13)	129 (86.00)	0.172
HbA1c (%)	6.12 ± 0.86	6.18 ± 0.98	6.06 ± 0.73	0.206
Type 2 diabetes (yes)	82 (26.80)	35 (22.44)	47 (31.33)	0.079
Medication for diabetes (yes)	63 (76.83)	23 (74.29)	37 (78.72)	0.638
Depressive symptomatology (BDI-II score; 0-63 points)	7.82 ± 6.86	7.97 ± 6.75	7.66 ± 7.00	0.689
Depressive symptomatology (yes; BDI-II≥14)	48 (15.69)	24 (15.38)	24 (16.00)	0.882
UPPS-P total score (59-236 points)	106.8 ± 21.36	107.6 ± 21.38	106.1 ± 21.38	0.532
UPPS-P Negative Urgency (12-48points)	22.56 ± 8.03	22.83 ± 8.10	22.26 ± 7.98	0.533
UPPS-P Positive Urgency (14-56 points)	24.08 ± 7.01	24.32 ± 6.80	23.84 ± 7.25	0.550
UPPS-P Lack of Premeditation (11-44 points)	19.40 ± 5.47	19.3 ± 5.59	19.45 ± 5.37	0.856
UPPS-P Lack of Perseverance (10-40 points)	18.73 ± 5.06	19.11 ± 5.00	18.35 ± 5.10	0.192
UPPS-P Sensation Seeking (12-48 points)	22.08 ± 6.01	22.00 ± 5.88	22.17 ± 6.16	0.809
CPT-Commissions	21.70 ± 15.03	21.69 ± 15.40	21.71 ± 14.70	0.992
CPT-Perseverations	0.78 ± 3.20	0.89 ± 4.02	0.66 ± 2.04	0.532
Iowa Gambling Task	2.47 ± 21.28	3.03 ± 20.21	1.89 ± 22.38	0.642
Stroop Color Word Test	-2.17 ± 7.51	-1.48 ± 7.72	-2.89 ± 7.24	0.102

Abbreviations: CG, control group; IIG, intensive intervention group; BDI-II, Beck Depression Inventory-II; UPPS-P, Impulsive Behavior Scale; CPT, Conners' Continuous Performance Test.

Values are numbers and percentages for qualitative variables and mean ± standard deviation (SD) for quantitative variables, with differences between CG and IG examined using chi-square and t-tests, as appropriate.

Table 2. Effect of the PREDIMED-Plus intervention on changes in impulsivity constructs.

Impulsivity constructs	Model	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
				Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
Global Impulsivity	Crude	CG	Ref.	-0.055 (-0.238, 0.128)	0.554†	-0.196 (-0.363, -0.028)	0.022†	
		IIG	Ref.	-0.108 (-0.296, 0.081)	0.265‡	-0.499 (-0.683, -0.315)	<0.001‡	
		Difference	Ref.	-0.052 (-0.315, 0.211)	0.697#	-0.303 (-0.552, -0.055)	0.017#	0.056*
	Minimally adjusted	CG	Ref.	-0.057 (-0.239, 0.126)	0.544	-0.198 (-0.366, -0.030)	0.021	
		IIG	Ref.	-0.092 (-0.281, 0.097)	0.340	-0.491 (-0.675, -0.307)	<0.001	
		Difference	Ref.	-0.035 (-0.298, 0.228)	0.792	-0.293 (-0.543, -0.044)	0.021	0.064
	Fully adjusted	CG	Ref.	-0.045 (-0.228, 0.138)	0.629	-0.200 (-0.368, -0.032)	0.019	
		IIG	Ref.	-0.088 (-0.277, 0.101)	0.359	-0.477 (-0.659, -0.296)	<0.001	
		Difference	Ref.	-0.043 (-0.307, 0.220)	0.748	-0.277 (-0.524, -0.030)	0.028	0.085
Trait Impulsivity	Crude	CG	Ref.	0.131 (-0.029, 0.291)	0.109	-0.062 (-0.194, 0.071)	0.363	
		IIG	Ref.	-0.145 (-0.310, 0.021)	0.087	-0.208 (-0.350, -0.066)	0.004	
		Difference	Ref.	-0.275 (-0.506, -0.045)	0.019	-0.147 (-0.341, 0.048)	0.139	0.051
	Minimally adjusted	CG	Ref.	0.129 (-0.031, 0.289)	0.115	-0.063 (-0.196, 0.070)	0.352	
		IIG	Ref.	-0.136 (-0.302, 0.030)	0.109	-0.201 (-0.343, -0.058)	0.006	
		Difference	Ref.	-0.269 (-0.509, -0.029)	0.028	-0.146 (-0.344, 0.051)	0.146	0.066
	Fully adjusted	CG	Ref.	0.131 (-0.031, 0.292)	0.112	-0.051 (-0.183, 0.081)	0.450	
		IIG	Ref.	-0.126 (-0.292, 0.041)	0.139	-0.191 (-0.333, -0.050)	0.008	
		Difference	Ref.	-0.256 (-0.488, -0.025)	0.030	-0.140 (-0.334, 0.053)	0.155	0.075
Behavioral Impulsivity	Crude	CG	Ref.	-0.214 (-0.398, -0.029)	0.023	-0.203 (-0.378, -0.028)	0.023	
		IIG	Ref.	0.017 (-0.176, 0.211)	0.859	-0.473 (-0.662, -0.284)	<0.001	
		Difference	Ref.	0.231 (-0.036, 0.498)	0.090	-0.270 (-0.527, -0.012)	0.040	0.003
	Minimally adjusted	CG	Ref.	-0.216 (-0.399, -0.032)	0.022	-0.198 (-0.374, -0.023)	0.027	
		IIG	Ref.	0.024 (-0.169, 0.217)	0.809	-0.481 (-0.670, -0.291)	<0.001	
		Difference	Ref.	0.239 (-0.027, 0.506)	0.078	-0.282 (-0.540, -0.024)	0.032	0.002
	Fully adjusted	CG	Ref.	-0.221 (-0.404, -0.037)	0.019	-0.200 (-0.376, -0.024)	0.026	
		IIG	Ref.	0.028 (-0.164, 0.221)	0.774	-0.478 (-0.666, -0.289)	<0.001	
		Difference	Ref.	0.249 (-0.017, 0.515)	0.067	-0.278 (-0.536, -0.020)	0.035	0.001

Abbreviations: CG, control group; IIG, intensive intervention group.

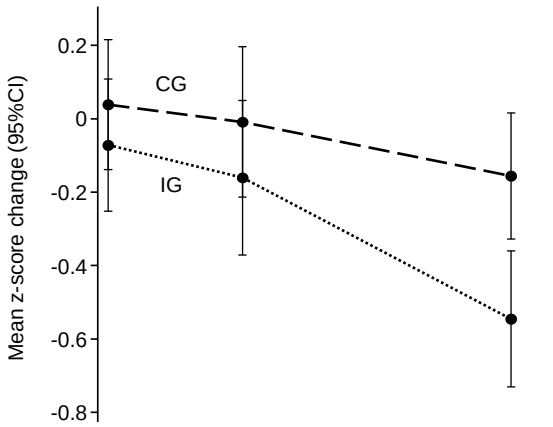
Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score changes. The term “difference” results from the comparison between IIG and CG. All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.
Crude model: unadjusted.
Minimally adjusted model: sex, age, educational level, and marital status.
Fully adjusted model: minimally adjusted model + smoking status, alcohol intake, 17-point Mediterranean diet, total energy intake, physical activity, obesity, hypercholesterolemia, hypertension, type 2 diabetes, diabetes medication use, and depressive symptomatology.
† (all such values) P-values within CG at specific follow-up points.
‡ (all such values) P-values within IIG at specific follow-up points.
# (all such values) P-values comparing IIG and CG at specific follow-up points.
* (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

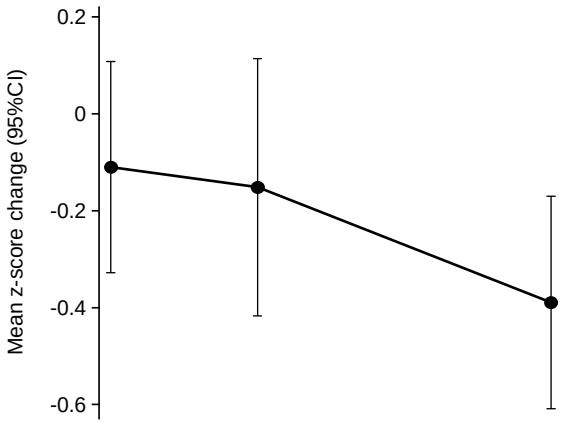
Impulsivity construct

PREDIMED-Plus intervention effect within study arm groups

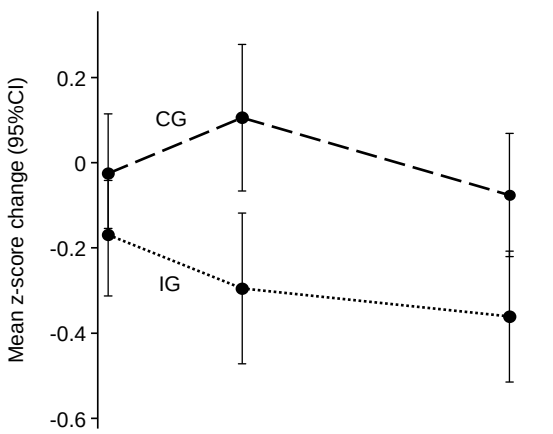
PREDIMED-Plus intervention effect between study arm groups

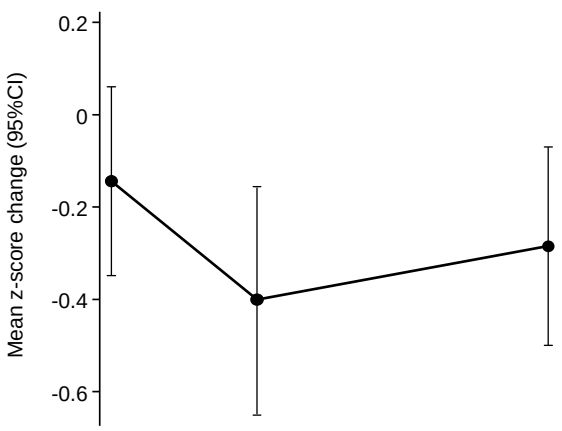
GLOBAL IMPULSIVITY



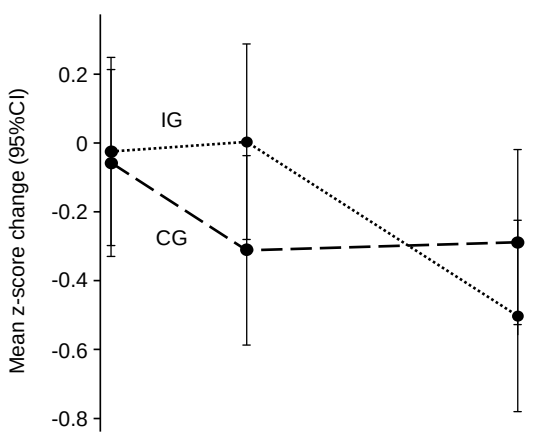


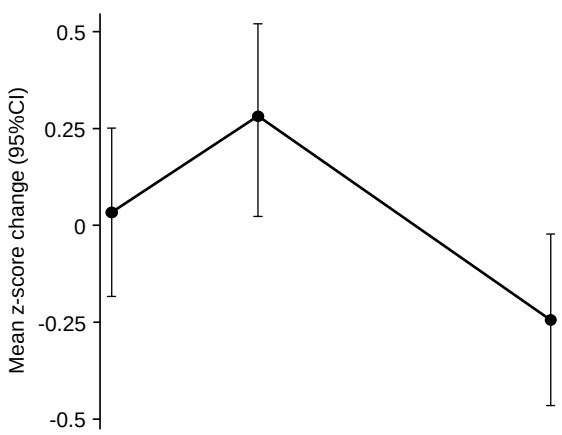
TRAIT IMPULSIVITY





BEHAVIORAL IMPULSIVITY





Supplementary Methods

Impulsivity

The CPT [1] is a computer-based task in which participants have to press the space bar in response to visual stimuli over 14 minutes. The CPT reports several measures, and the commissions and perseveration scores were chosen as they are impulsivity-related measures [1]. The commission score reflects failed targets (e.g., responding to a non-target), while the perseveration score reflects random, repetitive, or anticipatory responses (e.g., hit reaction time <100ms). Higher scores in both CPT measurements reflect higher behavioral impulsivity. The IGT [2] is a computerized task to evaluate risky decision-making, which has also been proposed as a measure of behavioral impulsivity [3]. Four decks (A, B, C, and D) are presented to the participants, and they have to make a total of 100 deck selections. A reward or punishment appears in each selection, where the A and B decks represent the worst selection options due to final losses being higher than the final gain. The final aim is to win as much money as possible. A total score is obtained by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. Higher scores indicate better performance under risky decision-making and hence, lower impulsivity. The Spanish version of the Stroop Color and Word Test (SCWT) [4] consists of three different tasks in which participants have to name as many words as they are able to in a total time of 45 seconds. In the first task participants have to name the written color from a list of words specifying colors printed in black text. In the second task participants have to name the printed color from a list of words printed in the following format: "XXXXX". In the last task participants have to name the printed color in a list of words in which the written word naming a color and the printed color from the word are incongruent. A total interference score was obtained from the three tasks, assessing the participants' capacity to inhibit cognitive interference, providing a measure of inhibition control which is a cognitive function related to impulsivity [3]. Higher scores indicate higher inhibition control performance and then, lower impulsivity.

Covariates

A composite of diabetes medication use was obtained from self-reported use of insulin, insulin secretagogues, other noninsulin hypoglycemics, thiazolidinediones, metformin, other biguanides, sulfonylureas, alpha-glucosidase inhibitors, GLP-1 analogs, DPP-4 inhibitors, or SGLT2 inhibitors medications.

Statistical analysis

- *Impulsivity z-scores obtention*

Z-scores were obtained at each time point for the UPPS-P total score (Trait Impulsivity construct), each UPPS-P subscale, and all the behavioral impulsivity tests using the mean and SD of their respective baseline data. Moreover, at each time point, a behavioral impulsivity z-score (Behavioral Impulsivity construct) and a global impulsivity z-score (Global Impulsivity construct) were also calculated. The Behavioral Impulsivity z-score was obtained by averaging all the behavioral impulsivity z-score tests at each time point, always standardizing by the mean and SD of all the behavioral impulsivity z-score tests at baseline. The Global Impulsivity z-score was calculated by averaging the Trait Impulsivity and the Behavioral Impulsivity z-scores at each time point, always standardizing by the mean and SD of the Trait Impulsivity and the Behavioral Impulsivity z-scores at baseline.

- A*pproach to missing data and rationale for the main model selection*

The main analyses were conducted using Complete Case Analysis (CCA) at baseline and maximum likelihood estimation (MLE) for handling missing data over follow-ups. Baseline CCA (n=306) ensured comparability across Global, Trait, and Behavioral Impulsivity constructs by restricting analyses to participants with complete baseline data, anchoring impulsivity evaluations to the same analytic population. This is particularly relevant as baseline serves as the reference point for estimating longitudinal changes in impulsivity. MLE was then applied to the 1-year and 3-year follow-up data, making full use of all available observed repeated measures.

Alternative approaches include a pure CCA across all time points or multiple imputation by chained equations (MICE). A pure CCA would have restricted analyses to only 126 of 486 participants (26%), resulting in a substantial loss of power. MICE, in contrast, creates multiple imputed datasets and combines results across them, accounting for uncertainty due to missingness and allowing inclusion of all participants. Both MLE and MICE rely on the assumption that data are missing at random; however, participants with higher impulsivity may be more prone to dropout, potentially raising concerns about missing not at random mechanisms [5]. Because a large fraction of baseline impulsivity would otherwise require imputation and the adequacy of auxiliary predictors in capturing missingness mechanisms for unobserved impulsivity is uncertain under MICE, we favored baseline CCA combined with MLE for follow-ups. This combined approach preserves operational comparability across impulsivity constructs, avoids imputing a substantial portion of baseline values while maximizing the use of observed follow-up impulsivity data, and limits reliance on imputation models which under potential deviations from missing at random could introduce an additional layer of uncertainty by adding model-dependent imputation bias.

Nevertheless, several sensitivity analyses were performed using combinations of CCA, MLE, and MICE to assess the robustness of our findings and to explore that conclusions were not dependent on a particular approach to handling missing data.

- Covariate adjustment

Regarding covariate adjustment models, a total of three models were fitted. All models included random effects hierarchically specified at three levels (center, household, and individual), a random slope at the individual level across time points, and an unstructured covariance. The crude model was unadjusted. The minimally adjusted model (sociodemographics adjustment) included: sex (male; female), age (in years), educational level (primary school; secondary school; college), and marital status (single, divorced, or separated; married; widowed) at baseline. The fully adjusted model (lifestyle and disease adjustments) included: the minimally adjusted model + smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), diabetes medication use (no; yes), and depressive symptomatology (no; yes) at baseline.

- Sensitivity analyses with alternative approaches to handling missing data

Sensitivity analyses were performed to assess the robustness of the findings of the main analyses. To accomplish this aim, several additional analyses were conducted. These included:

(1) To conduct a CCA to select participants with complete data at baseline (n=306), but instead of using MLE for missing data over the follow-up as the main analyses, we performed a multivariate imputation by chained-equations (MICE) with fully conditioned specification (imputed datasets=20; seed=1234) on the Global Impulsivity z-score at 1-year (missing data=89/306; 29.1%) and 3-year (missing data=158/306; 51.6%) follow-ups, on the Trait Impulsivity z-score at 1-year (missing data=74/306; 24.18%) and 3-year (missing data=103/306; 33.6%) follow-ups, and on the Behavioral Impulsivity z-score at 1-year (missing data=53/306; 17.3%) and 3-year (missing data=140/306; 45.7%) follow-ups (**Supplementary Table 6**).

(2) To perform a MICE (imputed datasets=20; seed=1234) for all missing data at baseline, 1-year follow-up, and 3-year follow-up (n=486). This included the imputation of the Global Impulsivity z-score at baseline (missing data=180/486; 37.0%), 1-year (missing data=211/486; 43.4%), and 3-year (missing data=299/486; 61.5%) time points, the Trait Impulsivity z-score at baseline (missing data=117/486; 24.1%), 1-year (missing data=115/486; 23.6%), 3-year (missing data=155/486; 31.9%) time points, the Behavioral Impulsivity z-score at baseline (missing data=92/486; 18.9%), 1-year (missing data=160/486; 32.9%), and 3-year (missing data=272/486; 56.0%) time points, and the HbA1c (missing data=17/486; 3.5%) and hypercholesterolemia (missing data=1/486; 0.21%) covariates at baseline (**Supplementary Table 7**). The ancillary variables included in all MICE models were those included in the fully adjusted model.

(3) To perform a pure MLE analysis, which maximized the use of all available data across all assessed time points, even though some data was only available at a single time point (**Supplementary Table 8**).

(4) To conduct a pure CCA, which included only participants with complete data across all time points (**Supplementary Table 9**).

References

1 Keith Conners C, Sitarenios G, Ayearst LE. Conners' Continuous Performance Test Third Edition. Encyclopedia of Clinical Neuropsychology. Cham: Springer International Publishing; 2018; pp 929–33.

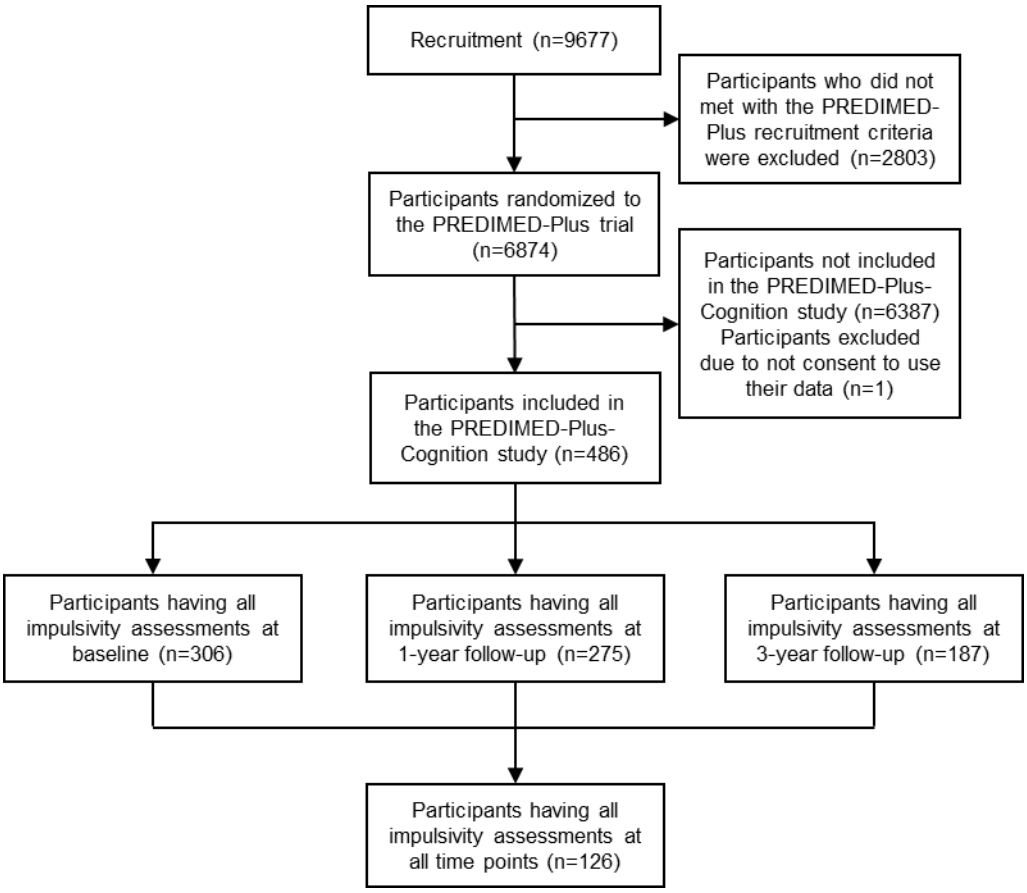
2 Bechara A, Damasio H, Tranel D, Damasio AR. Deciding Advantageously Before Knowing the Advantageous Strategy. Science (1979). 1997 Feb;275(5304):1293–5.

3 Sharma L, Markon KE, Clark LA. Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. Psychol Bull. 2014;140(2):374–408.

4 Golden C. Manual STROOP-Test de Colores y Palabras (3rd ed.). TEA Ediciones. Madrid, Spain; 2001.

5 Wittmann FG, Pabst A, Zülke A, Luppa M, Oey A, Boekholt M, et al. Adherence to a lifestyle intervention – just a question of self-efficacy? Analysis of the AgeWell.de-intervention against cognitive decline. Alzheimers Res Ther. 2024 Jun;16(1):133.

Supplementary Figure 1. Flowchart of the studied population.



Supplementary Table 1. Population characteristics according to PREDIMED-Plus participants included and not included in the PREDIMED-Plus-Cognition sub-study.

Characteristics	PREDIMED-Plus participants not included in the PREDIMED-Plus-Cognition sub-study (n=6,388)	PREDIMED-Plus participants included in the PREDIMED-Plus-Cognition sub-study (n=486)	p	PREDIMED-Plus-Cognition participants included in the main analyses (n=306) *	p
Intervention study arm (intervention group)	3166 (49.56)	240 (49.38)	0.393	150 (49.02)	0.853
Sex (female)	3089 (48.36)	245 (50.41)	0.336	140 (45.75)	0.436
Age (in years)	64.92 ± 4.93	65.24 ± 4.71	0.176	65.03 ± 4.72	0.724
Educational level			0.024		0.510
Primary school or less	3102 (48.56)	260 (53.50)		146 (47.71)	
High school	1845 (28.88)	141 (29.01)		97 (31.70)	
College	1441 (22.56)	85 (17.49)		63 (20.59)	
Civil status			0.411		0.260
Single, divorced or separated	840 (13.21)	54 (11.11)		33 (10.78)	
Married	4853 (76.33)	381 (78.40)		246 (80.39)	
Widower	665 (10.46)	51 (10.49)		27 (8.80)	
Smoking status			0.044		0.634
Never	2767 (43.51)	239 (49.18)		140 (45.75)	
Former	2795 (43.95)	188 (36.68)		126 (41.18)	
Current	798 (12.55)	59 (12.14)		40 (13.07)	
Alcohol intake (g/day)	11.39 ± 15.57	8.94 ± 11.74	<0.001	9.64 ± 11.12	0.052
Adherence to Mediterranean diet (0-17 points)	8.55 ± 2.68	7.77 ± 2.47	<0.001	7.81 ± 2.47	<0.001
Total energy intake (kcal/day)	2417 ± 636	2406 ± 585	0.719	2452 ± 619	0.339
Physical activity (MET min/week)	2470 ± 2320	2364 ± 2038	0.324	2471 ± 2019	0.994
BMI (kg/m²)	32.57 ± 3.46	32.52 ± 3.41	0.778	32.51 ± 3.38	0.759
Obesity (BMI≥30 kg/m2)	4693 (73.47)	353 (72.63)	0.689	226 (73.86)	0.880
Hypercholesterolemia (yes)	4408 (69.54)	356 (73.40)	0.091	223 (72.88)	0.263
Hypertension (yes)	5303 (83.02)	410 (84.36)	0.190	254 (83.01)	
HbA1c (%)	6.11 ± 0.88	6.14 ± 0.84	0.555	6.12 ± 0.86	0.831
Type 2 diabetes (yes)	1945 (30.45)	148 (30.45)	0.998	82 (26.80)	0.175
Medication for diabetes (yes)	1685 (86.63)	121 (81.76)	0.096	63 (76.83)	0.012
Depressive symptomatology (BDI-II score; 0-63 points)	8.49 ± 7.48	8.53 ± 6.91	0.893	7.82 ± 6.86	0.126
Depressive symptomatology (yes; BDI-II≥14)	1302 (20.47)	97 (19.96)	0.787	48 (15.69)	0.042

Values are mean ± standard deviation for quantitative variables and number (%) for qualitative variables.

Chi-square for qualitative variables and t-test for quantitative variables were performed comparing the total PREDIMED-Plus population with the total population of the PREDIMED-Plus-Cognition cohort and the total population of the PREDIMED-Plus-Cognition cohort included for the main analyses.

* Participants with data on all impulsivity assessments at baseline.

Supplementary Table 2. Correlation matrix of impulsivity assessments.

	Global Impulsivity	**Trait Impulsivity**	UPPS-P Positive Urgency	UPPS-P Negative Urgency	UPPS-P Premeditation	UPPS-P Perseverance	UPPS-P Sensation Seeking	**Behavioral Impulsivity**	CPT-Commissions	CPT-Perseverations	Iowa Gambling Task §	Stroop Color Word Test §
Global Impulsivity	1.00											
Trait Impulsivity	0.72***	1.00										
UPPS-P Positive Urgency	0.65***	0.83***	1.00									
UPPS-P Negative Urgency	0.57***	0.79***	0.72***	1.00								
UPPS-P Premeditation	0.42***	0.62***	0.28***	0.26***	1.00							
UPPS-P Perseverance	0.35***	0.55***	0.21***	0.26***	0.65***	1.00						
UPPS-P Sensation Seeking	0.36***	0.49***	0.35***	0.22***	0.07	-0.04	1.00					
Behavioral Impulsivity	0.76***	0.11#	0.16**	0.09	0.02	-0.01	0.06	1.00				
CPT-Commissions	0.50***	0.18**	0.18**	0.19***	0.15*	0.02	0.18*	0.54***	1.00			
CPT-Perseverations	0.45***	0.08	0.08	0.08	0.02	0.11*	0.03	0.57***	0.05	1.00		
Iowa Gambling Task §	-0.37***	0.02	-0.05	-0.02	0.05	0.07	0.04	-0.54***	-0.07	0.03	1.00	
Stroop Color Word Test §	-0.34***	0.02	-0.02	-0.01	0.07	-0.02	0.06	-0.50***	-0.06	-0.07	0.15**	1.00

Pearson correlation analyses were performed between z-scores of impulsivity constructs (in bold) and each specific impulsivity z-score assessment at baseline.

§ Higher scores on this test is indicative of lower impulsivity.

# $p<0.010$; * $p<0.05$; ** $p<0.01$; *** $p<0.001$

Supplementary Table 3. Effect of the PREDIMED-Plus intervention on impulsivity changes for each trait and behavioral impulsivity assessment (n=306).

Impulsivity assessment	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
UPPS-P Negative Urgency	CG	Ref.	0.029 (-0.109, 0.168)	0.679†	-0.178 (-0.324, -0.032)	0.017†	
	IIG	Ref.	-0.222 (-0.365, -0.078)	0.002‡	-0.245 (-0.400, -0.089)	<0.001‡	
	Difference	Ref.	-0.251 (-0.450, -0.052)	0.014#	-0.067 (-0.280, 0.147)	0.541#	0.044*
UPPS-P Positive Urgency	CG	Ref.	0.096 (-0.067, 0.259)	0.247	-0.065 (-0.214, 0.083)	0.388	
	IIG	Ref.	-0.095 (-0.263, 0.073)	0.269	-0.168 (-0.326, -0.010)	0.038	
	Difference	Ref.	-0.191 (-0.425, 0.043)	0.110	-0.102 (-0.319, 0.114)	0.355	0.262
UPPS-P Lack of Premeditation	CG	Ref.	0.139 (-0.029, 0.307)	0.106	0.167 (0.011, 0.323)	0.036	
	IIG	Ref.	0.061 (-0.113, 0.236)	0.491	-0.095 (-0.260, 0.069)	0.256	
	Difference	Ref.	-0.077 (-0.320, 0.165)	0.533	-0.262 (-0.552, -0.035)	0.023	0.072
UPPS-P Lack of Perseverance	CG	Ref.	0.054 (-0.098, 0.206)	0.486	-0.058 (-0.196, 0.080)	0.411	
	IIG	Ref.	-0.085 (-0.242, 0.071)	0.286	-0.068 (-0.215, 0.079)	0.367	
	Difference	Ref.	-0.139 (-0.357, 0.079)	0.211	-0.010 (-0.212, 0.192)	0.925	0.409
UPPS-P Sensation Seeking	CG	Ref.	0.123 (-0.027, 0.273)	0.108	-0.047 (-0.173, 0.078)	0.460	
	IIG	Ref.	-0.055 (-0.211, 0.101)	0.488	-0.063 (-0.196, 0.070)	0.355	
	Difference	Ref.	-0.078 (-0.395, 0.038)	0.106	-0.015 (-0.199, 0.168)	0.869	0.248
CPT Commissions	CG	Ref.	-0.142 (-0.257, -0.028)	0.015	-0.193 (-0.334, -0.052)	0.007	
	IIG	Ref.	-0.020 (-0.263, 0.073)	0.747	-0.200 (-0.354, -0.052)	0.011	
	Difference	Ref.	0.123 (-0.043, 0.289)	0.148	-0.007 (-0.215, 0.201)	0.945	0.242
CPT Perseverations	CG	Ref.	-0.183 (-0.422, 0.057)	0.135	-0.184 (-0.315, -0.053)	0.006	
	IIG	Ref.	0.124 (-0.125, 0.374)	0.328	-0.091 (-0.226, 0.044)	0.186	
	Difference	Ref.	0.307 (-0.039, 0.652)	0.082	0.093 (-0.096, 0.281)	0.335	0.220
Iowa Gambling Task §	CG	Ref.	0.111 (-0.090, 0.312)	0.277	0.080 (-0.162, 0.322)	0.518	
	IIG	Ref.	-0.077 (-0.288, 0.133)	0.472	0.408 (0.150, 0.666)	0.002	
	Difference	Ref.	-0.189 (-0.480, 0.103)	0.204	0.328 (-0.025, 0.682)	0.069	0.018
Stroop Color Word Test §	CG	Ref.	0.033 (-0.091, 0.156)	0.601	0.020 (-0.120, 0.160)	0.782	
	IIG	Ref.	0.129 (-0.001, 0.257)	0.050	0.221 (0.073, 0.369)	0.003	
	Difference	Ref.	0.096 (-0.083, 0.274)	0.294	0.201 (-0.002, 0.405)	0.053	0.151

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; CPT, Conners' Continuous Performance Test 3rd Edition; CCA, complete case analysis; MLE, maximum likelihood estimation.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on each specific trait and behavioral impulsivity z-score assessment over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, a CCA was conducted to select participants with complete baseline data (n=306), and MLE was used to handle missing data at the 1-year and 3-year follow-ups. All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), diabetes medication use (no; yes), and depressive symptomatology (no; yes) at baseline.

§ A negative coefficient value indicates higher impulsivity; † (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 4. Effect of the PREDIMED-Plus intervention on original impulsivity score changes for each trait and behavioral impulsivity assessment (n=306).

Impulsivity assessment	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean score change (95%CI)	p	Mean score change (95%CI)	p	p
UPPS-P Total score	CG	Ref.	2.97 (-0.69, 6.64)	0.112†	-1.16 (-4.16, 1.84)	0.450†	
	IIG	Ref.	-2.86 (-6.64, 0.93)	0.139‡	-4.35 (-7.56, -1.14)	0.008‡	
	Difference	Ref.	-5.83 (-11.10, -0.56)	0.030#	-3.19 (-7.59, 1.20)	0.155#	0.075*
UPPS-P Negative Urgency	CG	Ref.	0.22 (-0.81, 1.24)	0.679	-1.31 (-2.39, -0.24)	0.017	
	IIG	Ref.	-1.63 (-2.69, -0.58)	0.002	-1.80 (-2.95, -0.66)	<0.001	
	Difference	Ref.	-1.85 (-3.32, -0.38)	0.014	-0.49 (-2.06, 1.08)	0.541	0.044
UPPS-P Positive Urgency	CG	Ref.	0.79 (-0.55, 2.14)	0.247	-0.54 (-1.76, 0.69)	0.388	
	IIG	Ref.	-0.78 (-2.16, 0.60)	0.269	-1.38 (-2.69, -0.08)	0.038	
	Difference	Ref.	-1.57 (-3.50, 0.36)	0.110	-0.84 (-2.63, 0.94)	0.355	0.262
UPPS-P Lack of Premeditation	CG	Ref.	0.78 (-0.16, 1.72)	0.106	0.93 (0.06, 1.81)	0.036	
	IIG	Ref.	0.34 (-0.63, 0.32)	0.491	-0.53 (-1.46, 0.39)	0.256	
	Difference	Ref.	-0.43 (-1.79, 0.93)	0.533	-1.47 (-2.74, -0.20)	0.023	0.072
UPPS-P Lack of Perseverance	CG	Ref.	0.27 (-0.49, 1.02)	0.486	-0.29 (-0.97, 0.40)	0.411	
	IIG	Ref.	-0.42 (-1.20, 0.35)	0.286	-0.34 (-1.06, 0.39)	0.367	
	Difference	Ref.	-0.69 (-1.77, 0.39)	0.211	-0.05 (-1.05, 0.95)	0.925	0.409
UPPS-P Sensation Seeking	CG	Ref.	0.74 (-0.16, 1.65)	0.108	-0.29 (-1.05, 0.47)	0.460	
	IIG	Ref.	-0.33 (-1.28, 0.61)	0.488	-0.38 (-1.19, 0.43)	0.355	
	Difference	Ref.	-1.08 (-2.39, 0.23)	0.106	-0.09 (-1.20, 1.02)	0.869	0.248
CPT Commissions	CG	Ref.	-2.25 (-4.07, -0.44)	0.015	-3.05 (-5.28, -0.83)	0.007	
	IIG	Ref.	-0.31 (-2.21, 1.59)	0.747	-3.17 (-5.60, -0.74)	0.011	
	Difference	Ref.	1.94 (-0.69, 4.57)	0.148	-0.12 (-3.41, 3.18)	0.945	0.242
CPT Perseverations	CG	Ref.	-0.52 (-1.21, 0.16)	0.135	-0.53 (-0.90, -0.15)	0.006	
	IIG	Ref.	0.36 (-0.36, 1.07)	0.328	-0.26 (-0.65, 0.13)	0.186	
	Difference	Ref.	0.88 (-0.11, 1.87)	0.082	0.27 (-0.27, 0.81)	0.335	0.220
Iowa Gambling Task §	CG	Ref.	2.41 (-1.93, 6.75)	0.277	1.73 (-3.50, 6.95)	0.518	
	IIG	Ref.	-1.67 (-6.22, 2.88)	0.472	8.81 (3.25, 14.38)	0.002	
	Difference	Ref.	-4.08 (-10.37, 2.22)	0.204	7.09 (-0.54, 14.71)	0.069	0.018
Stroop Color Word Test §	CG	Ref.	0.33 (-0.90, 1.55)	0.601	0.20 (-1.19, 1.58)	0.782	
	IIG	Ref.	1.28 (-0.01, 2.55)	0.050	2.19 (0.72, 3.66)	0.003	
	Difference	Ref.	0.95 (-0.82, 2.72)	0.294	2.00 (-0.02, 4.01)	0.053	0.151

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; CPT, Conners' Continuous Performance Test 3rd Edition; CCA, complete case analysis; MLE, maximum likelihood estimation. Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on each raw score of trait and behavioral impulsivity assessment over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, a CCA was conducted to select participants with complete baseline data (n=306), and MLE was used to handle missing data at the 1-year and 3-year follow-ups. All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), diabetes medication use (no; yes), and depressive symptomatology (no; yes) at baseline.

§ A negative coefficient value indicates higher impulsivity; † (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 5. Effect of the PREDIMED-Plus intervention on changes in Global Impulsivity based on per-protocol analyses (n=306).

Per-protocol	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
BMI decrease of 5%	CG (n=25)	Ref.	0.027 (-0.358, 0.412)	0.890†	-0.230 (-0.591, 0.132)	0.213†	
	IIG (n=94)	Ref.	-0.049 (-0.246, 0.149)	0.630‡	-0.545 (-0.749, -0.342)	<0.001‡	
	Difference	Ref.	-0.076 (-0.508, 0.357)	0.514#	-0.316 (-0.730, 0.098)	0.135#	0.323*
Physical activity increase of 5%	CG (n=102)	Ref.	-0.072 (-0.310, 0.165)	0.551	-0.243 (-0.472, -0.015)	0.036	
	IIG (n=106)	Ref.	-0.052 (-0.275, 0.171)	0.648	-0.580 (-0.809, -0.352)	<0.001	
	Difference	Ref.	0.020 (-0.306, 0.347)	0.902	-0.337 (-0.659, -0.014)	0.041	0.089
17-point Mediterranean diet score > 13	CG (n=37)	Ref.	-0.115 (-0.589, 0.359)	0.635	0.011 (-0.360, 0.381)	0.955	
	IIG (n=85)	Ref.	0.064 (-0.227, 0.354)	0.667	-0.645 (-0.905, -0.385)	<0.001	
	Difference	Ref.	0.179 (-0.378, 0.735)	0.529	-0.655 (-1.107, -0.203)	0.005	0.007
2 goals	CG (n=38)	Ref.	-0.071 (-0.505, 0.362)	0.748	-0.140 (-0.484, 0.203)	0.424	
	IIG (n=104)	Ref.	-0.001 (-0.254, 0.252)	0.994	-0.619 (-0.848, -0.389)	<0.001	
	Difference	Ref.	0.070 (-0.432, 0.572)	0.784	-0.478 (-0.891, -0.066)	0.023	0.049
3 goals	CG (n=7)	Ref.	-0.037 (-0.847, 0.773)	0.929	0.011 (-0.601, 0.623)	0.971	
	IIG (n=49)	Ref.	0.060 (-0.175, 0.295)	0.615	-0.652 (-0.895, -0.408)	<0.001	
	Difference	Ref.	0.097 (-0.746, 0.940)	0.821	-0.663 (-1.321, -0.008)	0.048	0.088

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; BMI, body mass index; CCA, complete case analysis; MLE, maximum likelihood estimation.

The per-protocol analyses include an average decrease of 5% in BMI, an increase in leisure-time physical activity, and an increase in adherence to the Mediterranean diet, as measured by a score of >13 points. Additionally, participants who accomplished two or three goals were evaluated.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score constructs over three years of follow-up in the PREDIMED-Plus-Cognition sub-study under a per-protocol approach. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, a CCA was conducted to select participants with complete baseline data (n=306), and MLE was used to handle missing data at the 1-year and 3-year follow-ups. All models included random effects (center, household, and individual), random slope across time points, and independent covariance was specified (due to convergence problems resulting from the small number of participants).

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), and diabetes medication use (no; yes) at baseline.

† (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 6. Effect of the PREDIMED-Plus intervention on changes in impulsivity constructs with CCA at baseline and MICE over follow-ups (n=306).

Impulsivity constructs	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
Global Impulsivity	CG	Ref.	-0.065 (-0.208, 0.078)	0.373†	-0.215 (-0.340, -0.089)	0.001†	
	IIG	Ref.	-0.101 (-0.247, 0.045)	0.175‡	-0.476 (-0.604, -0.348)	<0.001‡	
	Difference	Ref.	-0.036 (-0.241, 0.169)	0.731#	-0.261 (-0.440, -0.082)	0.004#	0.009*
Trait Impulsivity	CG	Ref.	0.122 (-0.009, 0.252)	0.067	-0.046 (-0.151, 0.059)	0.388	
	IIG	Ref.	-0.117 (-0.250, 0.016)	0.085	-0.206 (-0.313, -0.099)	<0.001	
	Difference	Ref.	-0.239 (-0.425, -0.052)	0.012	-0.160 (-0.309, -0.010)	0.036	0.026
Behavioral Impulsivity	CG	Ref.	-0.188 (-0.352, -0.024)	0.025	-0.201 (-0.334, -0.067)	0.003	
	IIG	Ref.	0.013 (-0.154, 0.180)	0.878	-0.462 (-0.598, -0.326)	<0.001	
	Difference	Ref.	0.201 (-0.033, 0.436)	0.092	-0.261 (-0.452, -0.070)	0.007	<0.001

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; CCA, complete case analysis; MICE, multivariate imputation by chained-equations.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score constructs over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, a CCA was conducted to select participants with complete baseline data (n=306), and MICE was used to handle missing data at the 1-year and 3-year follow-ups. All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), and diabetes medication use (no; yes) at baseline.

† (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 7. Effect of the PREDIMED-Plus intervention on changes in impulsivity constructs with MICE across all time points (n=486).

Impulsivity constructs	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
Global Impulsivity	CG	Ref.	-0.029 (-0.131, 0.073)	0.575†	-0.197 (-0.282, -0.112)	<0.001†	
	IIG	Ref.	-0.088 (-0.192, 0.015)	0.094‡	-0.471 (-0.557, -0.385)	<0.001‡	
	Difference	Ref.	-0.059 (-0.205, 0.086)	0.425#	-0.274 (-0.395, -0.153)	<0.001#	<0.001*
Trait Impulsivity	CG	Ref.	0.139 (0.029, 0.249)	0.013	-0.098 (-0.208, 0.012)	0.080	
	IIG	Ref.	-0.161 (-0.273, -0.050)	0.005	-0.131 (-0.242, -0.019)	0.021	
	Difference	Ref.	-0.301 (-0.457, -0.144)	<0.001	-0.033 (-0.189, 0.124)	0.684	<0.001
Behavioral Impulsivity	CG	Ref.	-0.204 (-0.349, -0.059)	0.006	-0.263 (-0.359, -0.166)	<0.001	
	IIG	Ref.	0.147 (-0.001, 0.294)	0.050	-0.498 (-0.596, -0.400)	<0.001	
	Difference	Ref.	0.351 (0.144, 0.558)	0.001	-0.235 (-0.373, -0.098)	0.001	<0.001

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; MICE, multivariate imputation by chained-equations.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score constructs over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, MICE was conducted to impute missing data across all time points (n=486). All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. An unstructured covariance was specified. For this analysis, MICE was conducted to impute missing data across all time points (n=486). The term "difference" refers to the comparison of effects between IIG and CG.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), and diabetes medication use (no; yes) at baseline.

† (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 8. Effect of the PREDIMED-Plus intervention on changes in impulsivity constructs with MLE across all time points (n=486).

Impulsivity constructs	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
Global Impulsivity (n=373)	CG	Ref.	-0.041 (-0.225, 0.143)	0.664†	-0.171 (-0.337, -0.005)	0.043†	
	IIG	Ref.	-0.050 (-0.239, 0.139)	0.606‡	-0.468 (-0.644, -0.293)	<0.001‡	
	Difference	Ref.	-0.009 (-0.273, 0.255)	0.948#	-0.297 (-0.538, -0.056)	0.016#	0.044*
Trait Impulsivity (n=443)	CG	Ref.	0.115 (-0.041, 0.271)	0.109	-0.114 (-0.266, 0.038)	0.143	
	IIG	Ref.	-0.177 (-0.336, -0.017)	0.030	-0.196 (-0.354, -0.037)	0.015	
	Difference	Ref.	-0.292 (-0.515, -0.069)	0.010	-0.082 (-0.302, 0.137)	0.463	0.030
Behavioral Impulsivity (n=406)	CG	Ref.	-0.266 (-0.464, -0.069)	0.008	-0.231 (-0.386, -0.076)	0.003	
	IIG	Ref.	0.125 (-0.083, 0.333)	0.240	-0.432 (-0.594, -0.270)	<0.001	
	Difference	Ref.	0.391 (0.104, 0.678)	0.008	-0.201 (-0.424, 0.023)	0.078	<0.001

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; MLE, maximum likelihood estimation.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score constructs over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, MLE was conducted to address missing data across all time points (n=486). All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), and diabetes medication use (no; yes) at baseline.

† (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Supplementary Table 9. Effect of the PREDIMED-Plus intervention on changes in impulsivity constructs with CCA across all time points (n=126).

Impulsivity constructs	Study arm	Baseline	1-year follow-up		3-year follow-up		Overall follow-up
			Mean z-score change (95%CI)	p	Mean z-score change (95%CI)	p	p
Global Impulsivity	CG	Ref.	0.065 (-0.179, 0.309)	0.603†	-0.077 (-0.277, 0.122)	0.447†	
	IIG	Ref.	0.061 (-0.195, 0.316)	0.642‡	-0.426 (-0.635, -0.217)	<0.001‡	
	Difference	Ref.	-0.004 (-0.357, 0.349)	0.982#	-0.349 (-0.638, -0.059)	0.018#	0.044*
Trait Impulsivity	CG	Ref.	0.193 (-0.018, 0.403)	0.073	-0.051 (-0.212, 0.111)	0.539	
	IIG	Ref.	-0.052 (-0.273, 0.169)	0.644	-0.188 (-0.358, -0.019)	0.029	
	Difference	Ref.	-0.245 (-0.550, -0.061)	0.116	-0.138 (-0.372, 0.096)	0.249	0.227
Behavioral Impulsivity	CG	Ref.	-0.099 (-0.383, 0.186)	0.496	-0.062 (-0.286, -0.163)	0.590	
	IIG	Ref.	0.140 (-0.158, 0.438)	0.358	-0.429 (-0.665, -0.194)	<0.001	
	Difference	Ref.	0.239 (-0.173, 0.651)	0.256	-0.368 (-0.693, -0.043)	0.027	0.007

Abbreviations: CG, control group; IIG, intensive intervention group; 95%CI, 95% confidence interval; CCA, complete case analysis.

Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score constructs over three years of follow-up in the PREDIMED-Plus-Cognition sub-study. Within-group effects (for CG and IIG) and between-group effects (difference between CG and IIG) were evaluated. For this analysis, a pure CCA was conducted to select participants with complete data across all time points (n=126). All models included random effects (center, household, and individual), random slope across time points, and unstructured covariance.

Models were adjusted for sex (male; female), age (in years), educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), alcohol intake (g/day), 17-point Mediterranean diet (score), total energy intake (kcal/day), physical activity (MET min/week), obesity (no; yes), hypercholesterolemia (no; yes), hypertension (no; yes), type 2 diabetes (no; yes), and diabetes medication use (no; yes) at baseline.

† (all such values) P-values within CG at specific follow-up points; ‡ (all such values) P-values within IIG at specific follow-up points; # (all such values) P-values comparing IIG and CG at specific follow-up points; * (all such values) Overall p-values comparing IIG and CG over the duration of follow-up.

Section/topic	No	CONSORT 2025 checklist item description	Reported on page no.
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Title and structured abstract	1a	Identification as a randomised trial	1-4
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Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	2-3
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	6-7
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	16-17
Funding and conflicts of interest	5a	Sources of funding and other support (eg, supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	16
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Objectives	7	Specific objectives related to benefits and harms	6
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	7
Trial design	9	Description of trial design including type of trial (eg, parallel group, crossover), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-7
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	7
Trial setting	11	Settings (eg, community, hospital) and locations (eg, countries, sites) where the trial was conducted	6-7
Eligibility criteria	12a	Eligibility criteria for participants	7
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (eg, surgeons, physiotherapists)	7
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (eg, intervention manual) can be accessed	7-8
Outcomes	14	Prespecified primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome	8-9
Harms	15	How harms were defined and assessed (eg, systematically, non-systematically)	8
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	7
	16b	Explanation of any interim analyses and stopping guidelines	7
Randomisation:			7
Sequence generation	17a	Who generated the random allocation sequence and the method used	
	17b	Type of randomisation and details of any restriction (eg, stratification, blocking and block size)	7

			Reported on page no.
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (eg, central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	7
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	7
Blinding	20a	Who was blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts)	7
	20b	If blinded, how blinding was achieved and description of the similarity of interventions *NOTE: Neuropsychologists assessing impulsivity were blinded to group allocation. Intervention staff were not blinded due to the nature of the intervention.*	7
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	9-10
	21b	Definition of who is included in each analysis (eg, all randomised participants), and in which group	9-10
	21c	How missing data were handled in the analysis	9-10
	21d	Methods for any additional analyses (eg, subgroup and sensitivity analyses), distinguishing prespecified from post hoc	10
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	10
	22b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	6
	23b	If relevant, why the trial ended or was stopped	NA
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (eg, where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended (fidelity))	7-8
	24b	Concomitant care received during the trial for each group	8
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	10
Numbers analysed, outcomes and estimation	26	For each primary and secondary outcome, by group: ● the number of participants included in the analysis ● the number of participants with available data at the outcome time point ● result for each group, and the estimated effect size and its precision (such as 95% confidence interval) ● for binary outcomes, presentation of both absolute and relative effect size	10-12
Harms	27	All harms or unintended events in each group	8
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post hoc	11-12
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-15
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	14-15

Citation: Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025; 388:e081123. https://dx.doi.org/10.1136/bmj-2024-081123

*We strongly recommend reading this statement in conjunction with the CONSORT 2025 Explanation and Elaboration and/or the CONSORT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant CONSORT extensions. See www.consort-spirit.org.

Plain Language Summary

Impulsivity is the tendency to act quickly without careful thought. It is often linked to unhealthy behaviors, mental health problems, and a higher risk of disease. This study examined whether a 3-year healthy lifestyle program could reduce impulsivity in older adults at risk of cardiovascular disease.

Participants in the intervention group were encouraged to follow a calorie-reduced Mediterranean diet rich in fruits, vegetables, whole grains, and healthy fats. They also received guidance to increase physical activity and behavioral support to maintain these habits. In contrast, participants in the control group received general advice about following Mediterranean diet without calorie restriction or exercise recommendations.

After 3 years, participants in the intensive lifestyle program showed larger reductions in impulsivity compared with those in the control group. Although both groups lowered impulsivity, combining a healthy diet, regular physical activity, and behavioral support produced stronger effects.

These findings suggest that a multicomponent lifestyle intervention using counseling to promote balanced diets and physical activity, with continued behavioral support to adopt healthy lifestyle habits, may help lower impulsivity in older adults at risk of cardiovascular disease and improve their adherence to healthier lifestyles. Further studies are needed to confirm these results and to better understand how lifestyle modifications influence impulsivity.

Figure legend 1:

Figure 1. Graphical representation of linear predictions for the effect of the PREDIMED-Plus intervention on changes in impulsivity constructs

Description 1:

Abbreviations: CG, control group; IG, intervention group. Dash lines: CG; Dot lines: IG; Solid lines: difference between IG and CG. A graphical representation of the linear predictions of the linear mixed models is displayed in this figure. Linear mixed models were conducted to assess the effect of the PREDIMED-Plus intervention on Global, Trait, and Behavioral Impulsivity z-score changes. The term “difference” results from the comparison between IIG and CG. Models were adjusted for sex, age, educational level, marital status, smoking status, alcohol intake, 17-point Mediterranean diet, total energy intake, physical activity, obesity, hypercholesterolemia, hypertension, type 2 diabetes, diabetes medication use, and depressive symptomatology.