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RESEARCH

Targeting brain health in subjective cognitive decline: insights from a multidomain randomized controlled trial

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Abstract

Background Multidomain lifestyle interventions are a promising approach to prevent cognitive decline, but their effects in subjective cognitive decline (SCD) remain controversial. We investigated the effects of lifestyle interventions on cognition and brain integrity in these at-risk individuals.

Methods One-hundred twenty-eight older adults with SCD were randomly assigned to either Active Control Intervention (ACI), i.e. health education; Partial Intervention (PI), i.e. tramiprosate supplementation (100 mg/die) and dietary advice; or Multilevel Intervention (MI), i.e. PI *plus* computerized cognitive training and physical exercise, for one year. Neuropsychological assessment and MRI were performed at baseline and at 1-year follow-up. Analyses of covariance were used to measure the effects of interventions on predefined outcomes.

Results The MI group significantly improved in attention-executive functioning ($p = 0.003$) compared to ACI (Cohen's d: 0.47, 95% CI 0.13–0.79). In addition, depressive symptoms (Cohen's d: – 0.48, 95% C.I. – 0.81 to – 0.14) and memory concerns (Cohen's d: – 0.77, 95% C.I. – 1.12 to – 0.41) decreased in the MI and PI respectively, relative to the ACI. The MI group also showed increased resting-state (i.e., intrinsic) brain activity in the right fronto-parietal executive network. No significant intervention effects on brain structural or vascular outcomes were found.

Conclusion The study shows that a multidomain lifestyle intervention can enhance attention-executive function, ameliorate depressive symptoms and increase functional connectivity in SCD. These findings support the role of lifestyle interventions in public health strategies to mitigate cognitive decline risk.

Trial registration The trial has been registered at the United States National Library of Medicine at the National Institutes of Health Registry of Clinical Trials under the code NCT04744922 on December 9th, 2017 (https://www.clinicaltrials.gov/ct2/show/NCT03382353).

Keywords Dementia prevention · Lifestyle · Multidomain interventions · fMRI · Subjective cognitive decline

Introduction

The prevention of late-life cognitive decline is one of the global public health priorities [1]. Indeed, the number of people living with dementia is expected to exponentially increase worldwide in the next decades, due to increased life expectancy. It was estimated that up to 45% of dementia cases could be potentially prevented by acting on modifiable vascular and lifestyle-related risk factors over the life span [2, 3]. Consistent with this perspective, observational studies have shown the benefits of healthy lifestyle habits such as regular physical exercise, cognitive and social stimulation and adherence to healthy dietary patterns, e.g., the Mediterranean or Nordic diets, in reducing cognitive decline and dementia incidence [4–6]. Such studies led to hypothesize that the major benefits of lifestyle interventions might arise from multidomain interventions, possibly counteracting the multifactorial etiology of AD and dementia [5, 7]. However, the evidence from multidomain lifestyle randomized controlled trials (RCT) is still controversial [8, 9]

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The FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) was the first large-scale RCT showing the efficacy of a high-intensity 2-year multi-domain lifestyle intervention on cognitive functions in older adults at risk for cognitive decline, compared to general health advice [10]. This trial represented a novel and pragmatic model for multidomain interventions that has been adapted and implemented in different settings and populations within the World-Wide Fingers global consortium [11]. Notwithstanding, a recent systematic review on multidomain prevention trials for cognitive decline and dementia showed that only 4 out of 18 RCTs found a beneficial effect on pre-specified cognitive outcomes, with wide heterogeneity in clinical endpoints and intervention designs across studies [12].

Furthermore, the use of biomarkers as a surrogate outcome was recently recommended to overcome the limitations of clinical endpoints (e.g., low sensitivity, lengthy and expensive follow-up periods) and to provide information about the pathophysiologic mechanisms underlying the effects of an intervention [12]. To date, only a few preventive multidomain trials included surrogate biomarkers (e.g., neuroimaging markers) in their design [13]. As a further shortcoming, it is still unclear the dose–response function [14]; in particular, an additive effect of multidomain interventions over single treatment and/or active control in older adults at risk for cognitive decline has not been demonstrated yet [15, 16]. It is worth noting that multidomain interventions were more strongly associated with improved cognitive functioning than single interventions in older adults with mild cognitive impairment, supporting the hypothesis of a synergistic effect [17].

To overcome the aforementioned shortcomings in the field, we designed a 3-arm RCT, the Efficacy of Multiple Nonpharmacological Interventions—E.Mu.N.I.—study, aimed at investigating the cognitive and brain imaging effects of lifestyle interventions delivered at increasing level of intensity, for 12 months, in individuals with subjective cognitive decline (SCD). These individuals can represent an ideal target for preventive strategies due to their increased risk for cognitive decline and dementia [18–20]. The effects of a Multilevel Intervention (MI), including physical exercise, computerized cognitive training, nutraceutical supplementation, and dietary guidance were compared to that of a Partial Intervention (PI), comprising nutraceutical supplementation and dietary guidance, and an Active Control Intervention (ACI), consisting of psychoeducation. We hypothesize a dose–response effect on cognitive function and brain imaging markers, with the MI showing the largest effect, and the PI showing an intermediate effect, relative to the ACI.

Methods

Study design

The E.Mu.N.I. study is a multi-center, randomized, controlled trial (registration number: NCT03382353). Enrolling sites were two research memory clinics located in Northern Italy: the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (Brescia) and the San Raffaele Hospital (Milan). SCD participants were recruited between February 2016 and June 2017 among individuals presenting at the above memory clinics for cognitive complaints or from the community through public advertisements. The enrolled participants underwent clinical and neuropsychological assessment and 3Tesla MRI scan at baseline and 12-month follow-up. The randomization was performed using a 2-blocks of 3-group sequence per site, generated using R software. Study personnel was blind to the allocation sequence until the conclusion of the enrollment. Further details on the randomization procedures and baseline features of the enrolled sample are available in the study protocol [21].

Participants and procedures

The inclusion criteria were: (i) age between 60 and 80 years, and (ii) self-reported subjective cognitive decline, based on the research criteria proposed by the SCD-I working group [20] and the presence of memory complaints as rated by the Everyday Memory Questionnaire (EMQ) scale [22]. The exclusion criteria were: (i) objective cognitive impairment, based on the Italian age- and education-adjusted norms for neuropsychological tests (see cognitive outcome section); (ii) depressive or anxious symptoms, as indicated by scores > 8 on the 15-item Geriatric Depression Scale (GDS) [23], and > 53 on the trait scale of the State-Trait Anxiety Inventory (S.T.A.I. Form Y-2) [24]; (iii) major psychiatric disorders, (iv) chronic diseases or acute unstable illness that would interfere with the aims of the study protocol; and (v) contraindications to MRI exam.

Phone screening was conducted with participants to determine their preliminary eligibility, i.e., the willingness to participate in the study, the presence of SCD, and the absence of MRI contraindications. Specifically, SCD was investigated with four yes/no questions featuring the SCD *plus* criteria [20], i.e., the presence of a subjective decline in memory, rather than other domains of cognition, feeling of worse performance than others of the same age group, onset of SCD within the last 5 years, and worries associated with SCD.

Upon a successful phone screening, participants were invited to undergo in-person assessment. The study physician collected medical history and concomitant medications supported by medical records. Dietary habits were collected through questions on food consumption, which were taken from the multipurpose "Aspect of Daily Life" survey of the Italian National Institute of Statistics. We computed a MeDi score with higher values indicating increased adherence to the Mediterranean diet (range 0–137). The level of physical activity was assessed by the International Physical Activity Questionnaire (IPAQ), long version [25], with the score representing metabolic equivalent of task (MET) related to moderate or high intensity activities, or walking, during the last week, expressed in minutes. The neuropsychologist administered a cognitive battery (see [21] for details) and the scales for depression, anxiety, and memory complaints. The study eligibility was confirmed by a consensus between the study personnel performing the screening visit and the principal investigators at each site (E.C. for Brescia and C.C. for Milan). SCD was operationalized to include at least 3 out of 4 SCD *plus* features and/or a score ≥ 61 in the EMQ.

The enrolled subjects underwent pre- and post-intervention MRI scans acquired on 3 T scanners (Siemens MAGNETOM Skyra and Philips Ingenia CX) using an ADNI-compliant acquisition protocol [21, 26, 27]. MRI scanning sessions lasted approximately 40 min and included the following sequences: (i) high-resolution 3D T1-weighted; (ii) axial fluid attenuation inversion recovery (FLAIR); (iii) axial T2*; (iv) diffusion-weighted (DTI); (v) resting state functional MRI (rs- fMRI; 195 echo-planar-imaging (EPI) volumes with TR = 2.7 s, in-plane resolution = 1.875×1.875 mm, slice thickness = 4 mm). To ensure harmonization between scanners, quality control measures were conducted on the first two enrolled participants. Specifically, contrast-to-noise ratios were compared between the structural MRI scanners at the two centers, and cortical and subcortical segmentation reproducibility was assessed using CAT12. For functional MRI, 50 resting-state components were calculated and compared. For DTI, quality control was performed using DTIprep to assess consistency across scanners. Additionally, all acquired data underwent visual inspection for quality assurance before analysis. This included checks for gross partial brain coverage errors, major artifacts (e.g., motion, wraparound, radio frequency interference), and inconsistencies in signal intensity or contrast homogeneity.

Interventions

The ACI included psychoeducation, consisting of 16 group classes (two sessions per week for 8 consecutive weeks) led by a psychologist. The educational intervention included talks on ageing, brain, and cognitive functioning (10 sessions), alternated with documentary watching followed by group discussion (6 sessions). The adherence was measured based on session attendance.

The PI included the administration of tramiprosate 100 mg daily for one year *plus* attending a course on the Mediterranean diet (MeDi), consisting of four group classes (one session fortnightly) led by a nutritionist. The tramiprosate is a chemically synthesized formulation of homotaurine, which is a small natural aminosulfonate compound identified in different species of marine red algae. It is marketed as a nutraceutical for the promotion of memory, cognition, and healthy aging. The tramiprosate adherence was computed by subtracting the count of the number of pills remaining from the total number of pills dispensed. The adherence to the PI was computed as the average percentage of the MeDi course sessions' attendance and the tramiprosate adherence.

The MI included the same interventions as the PI, *plus* physical exercise and computerized cognitive training (CCT) for one year. The physical exercise training consisted of two sessions of moderate-intensity strength and aerobic exercises per week with a maximum of 80 sessions in a year, supervised by an exercise specialist. The CCT was a brain plasticity-based program [28], consisting of two sessions per week for 8 consecutive weeks supervised by trained psychologists. Each session comprised 4 tasks targeting memory functions and cognitive skills that usually decline during aging, i.e., sustained attention, processing speed and executive functions. The overall adherence to the MI was computed as the average percentage of the MeDi course, physical exercise, and CCT sessions' attendance, and the tramiprosate adherence.

The choice of the interventions included in the E.Mu.N.I. study was based on the available literature, as previously discussed [8, 21]. Further details on intervention procedures can be found in the study protocol [21].

Primary endpoints

The effect of the interventions was primarily tested on one-year change in cognitive functions based on pre-post evaluation. Specifically, we used the Rey Auditory Verbal Learning Test (RAVLT) and z-standardized composite measures of memory (RAVLT delayed and immediate recall, logical memory), attention-executive (digit span forward and backward, Trail Making Test A and B, letter and category fluency), and visuo-spatial functions (Clock Drawing Test, Rey-Osterrieth Complex Figure copy and recall). Details on the composite score computation were available in the study protocol [21].

Secondary endpoints

The effect of the interventions was secondarily tested on one-year change in brain structural (i.e. hippocampal and lateral ventricles volumes) and cerebral vascular (i.e. white matter hyperintensities) MRI measures.

Structural markers. 3D T1-weighted images were automatically processed with FreeSurfer (version 6, http://surfer.nmr.mgh.harvard.edu) to obtain hippocampal and lateral ventricular volumes as measures of AD-like atrophy. First, all time points were cross-sectionally processed with the default workflow launched on CBRAIN platform [29]. Then, an unbiased within-subject template from the two time points was created and longitudinal processing was performed on all timepoints following the FreeSurfer longitudinal pipeline [30]. To assure proper alignment and good segmentation, within-subject template and longitudinal outputs were visually inspected and manual edits were performed when appropriate. One subject was excluded by the analysis due to major segmentation errors of subcortical volumes. Hippocampal and lateral ventricles volumes were adjusted to the total intracranial volume (TIV) using residuals from linear regression models between raw volumes and TIV [31].

Vascular markers. White matter hyperintensities (WMH) were segmented by the lesion prediction algorithm as implemented in the Lesion Segmentation Toolbox (LST) version 3.0.0 (www.statistical-modelling.de/lst.html) for SPM12. Both FLAIR and 3D-T1 images were used for the cross-sectional analysis. For each subject, baseline and follow-up WMH segmentations were compared using the longitudinal pipeline implemented in the LST toolbox [32]. WMH volumes and number of lesions were extracted, and the volumes were proportionally adjusted to the total white matter volume.

Exploratory endpoints

Psychological features and memory complaints. As exploratory outcomes, we further tested changes on depressive and anxiety symptoms, as rated by the GDS and the S.T.A.I Form Y-2 scales, respectively, and self-reported memory complaints, as rated by the EMQ.

Functional connectivity. Longitudinal changes in resting-state functional connectivity were also tested as exploratory outcome. We used SPM12 (http://www.fil.ion.ucl.ac.uk/spm) to perform a standard pre-processing of fMRI data, including slice-timing, spatial realignment to the first volume and unwarping, spatial normalization to the Montreal Neurological Institute (MNI) space [33] and resampling in $2 \times 2x2$ mm^3 voxels, and spatial smoothing using 8 mm gaussian isotropic kernel.

We then performed a spatial group independent component analysis (gICA), using the Infomax algorithm as implemented in GIFT (https://trendscenter.org/software/gift/) [34, 35], to extract 75 maximally independent and temporally coherent spatial sources, i.e. functional networks or "spatial maps", from resting-state time courses of the whole sample. Following Allen et al.'s selection criteria [34], reliable RSNs were distinguished from physiological artifacts via visual inspection (to reject components clearly involving tissues and structures other than grey matter), spectral characteristics of IC time courses (to retain components dominated by low frequency fluctuations), and an Iq index reflecting the consistency of component extraction through 250 gICA rounds. This procedure led to retain 56 resting-state components [36–38], which were anatomically labelled based on a template including the main RSNs [34].

Statistical analysis

Baseline characteristics of subjects included in the E.Mu.N.I. study were described using mean and standard deviation (SD) for continuous variables, and number (percentage) for categorical variables. Differences in baseline characteristics among the three groups (MI, PI, ACI) were analyzed using the ANOVA test for continuous normally distributed variables, the non-parametric Wilcoxon signed-rank test for continuous skewed variables, and Chi-squared test for categorical variables.

Analysis of covariance (complete-case ANCOVA) was used to analyze the effect of interventions on primary and secondary outcomes, using the post-intervention measure as dependent variable. The 114 individuals included in the analyses had no missing post-test data. Analyses were adjusted for age, sex and education. To consider the individual differences in pre-treatment levels of the variables of interest, baseline measures were added to the statistical models as covariates. In the case of a significant effect of interventions on the variable of interest (baseline measure x group), multiple pairwise comparisons of the estimated means from ANCOVA were performed with Student's t-test, using a Bonferroni adjusted alpha level. The same analyses were carried out with the exploratory outcomes (i.e., psychological and memory concern measures) as variables of interest. All these analyses were performed using JMP Pro 14.

When an outcome showed a significant change from baseline to 12 months after Bonferroni correction, the effect size (ES) was also calculated using Cohen's d. Values of 0.20, 0.50, and 0.80 were indicative of small, medium, and large effect sizes, respectively. A post-hoc power analysis based on the observed effect sizes was also computed by using G*Power.

Finally, we aimed to isolate the effect of distinct treatment conditions on the intensity of intrinsic brain activity, reflecting connectivity and degree of coactivation within a network [34]. To this purpose, for all the retained resting-state independent components we modelled a 3 × 2 factorial design with group (MI, PI, ACI) and timepoint (baseline; follow-up) as between and within-group factors, respectively. A backward multivariate model selection strategy—as implemented in the GIFT toolbox—was used to reduce the total number of statistical tests performed [34]. This procedure employs a multivariate analysis of covariance (MANCOVAN) to select the factors/components explaining variability in the outcome measures, followed by univariate tests corrected for multiple comparisons on a reduced design matrix (thus decreasing the number of statistical tests performed), to highlight the direction and strength of the relationship between these factors and outcome variables. Data were thresholded at $p < 0.05$, and False Discovery Rate (FDR) was used to correct for multiple comparisons (i.e. number of voxels in spatial maps).

Results

Hereby, we report the results of pre-post changes on the predefined primary, secondary, and exploratory outcomes.

Participants

Figure 1 shows the flowchart of the study. A total of 134 participants were randomly assigned to receive the MI (n = 48), the PI (n = 45) or the ACI (n = 41). Six participants did not receive the allocated interventions. In addition, 14 participants discontinued the intervention and were lost at follow-up, resulting in a total sample of 114 individuals (MI, n = 39; PI, n = 40; ACI, n = 35) analyzed in the present study. The mean attrition rate was 11%. Participants who completed the study and those who dropped-out did not differ for socio-demographics and global cognition at baseline (see Supplementary Table 1, Online Resource 1). Baseline sociodemographic, clinical, and brain features were similar among the three intervention groups (Table 1). At the baseline, the participants reported good adherence to the MeDi and vigorous intensity level of physical activity, with no differences among the groups (103.6 ± 5.6 vs 105.3 ± 5.6 vs 103.9 ± 6.3 on the MeDi score, p = 0.411; 3829.6 ± 3298.6 vs 5349.3 ± 4863.8 vs 4143.2 ± 4469.1 MET minutes a week, p = 0.267, respectively). The adherence rate to the three interventions was 80% for the ACI, 87% for the PI, and 85% for the MI.

Effect of interventions on primary endpoints

A significant intervention effect was found on the attention-executive composite score (effect size: 0.12, 95% CI: 0.02–0.23; p = 0.003), with both the MI and PI groups significantly improving relative to the ACI (p = 0.0007 and 0.031 on post-hoc comparison, see Fig. 2). After Bonferroni correction, only the difference between MI and ACI groups survived (p = 0.002). The effect size of attention-executive change in the MI group was medium (Cohen's d: 0.47, 95 C.I. 0.13–0.79; post-hoc power: 0.95). No significant intervention effects were found for the other cognitive outcomes, namely RAVLT score, memory and visuo-spatial composite scores (Supplementary Fig. 1, Online Resource 1).

Effect of interventions on secondary endpoints

No significant treatment effect was found on structural MRI markers (i.e., right hippocampus p = 0.227; left hippocampus p = 0.526, right ventricle volume p = 0.518; left ventricle volume p = 0.484) as well as on white matter lesions load (p = 0.845). The inclusion of the MRI scanner as a covariate did not change the results (Supplementary results, Online Resource 1).

Effect of interventions on exploratory endpoints

Psychological features and memory complaints. A significant effect of treatment was found on depressive symptoms as measured by the GDS (effect size: 0.06, 95% CI: 0.00–0.15; p = 0.032), with the MI group showing a significant reduction of depressive symptoms compared with the ACI (p = 0.011 on post-hoc comparison, see Fig. 3). Furthermore, a significant effect was found on the EMQ score (effect size: 0.08, 95% CI: 0.00–0.18; p = 0.013), with PI participants showing a significant reduction of memory complaints compared with ACI (post-hoc comparisons, p = 0.003, Fig. 3). Both p values were below the threshold set for multiple comparisons with Bonferroni correction ($p < 0.0167$). The effect sizes were medium for the GDS change in the MI group (Cohen's d: – 0.48, 95% C.I. – 0.81 to – 0.14; post-hoc power: 0.96), and large for the EMQ change in the PI group (Cohen's d: – 0.77, 95% C.I. – 1.12 to – 0.41; post-hoc power: 0.99). No significant effect of interventions was found on anxiety (p = 0.170).

Functional connectivity. A significant group X timepoint interaction in rs-fMRI was found in the right middle-superior frontal sector of the fronto-parietal executive network (xyz: 7,22,48; Fig. 4). Namely, functional connectivity in these regions was significantly increased in the MI group, compared to both PI and ACI groups, after one year. To confirm that this result was not due to baseline rs-fMRI

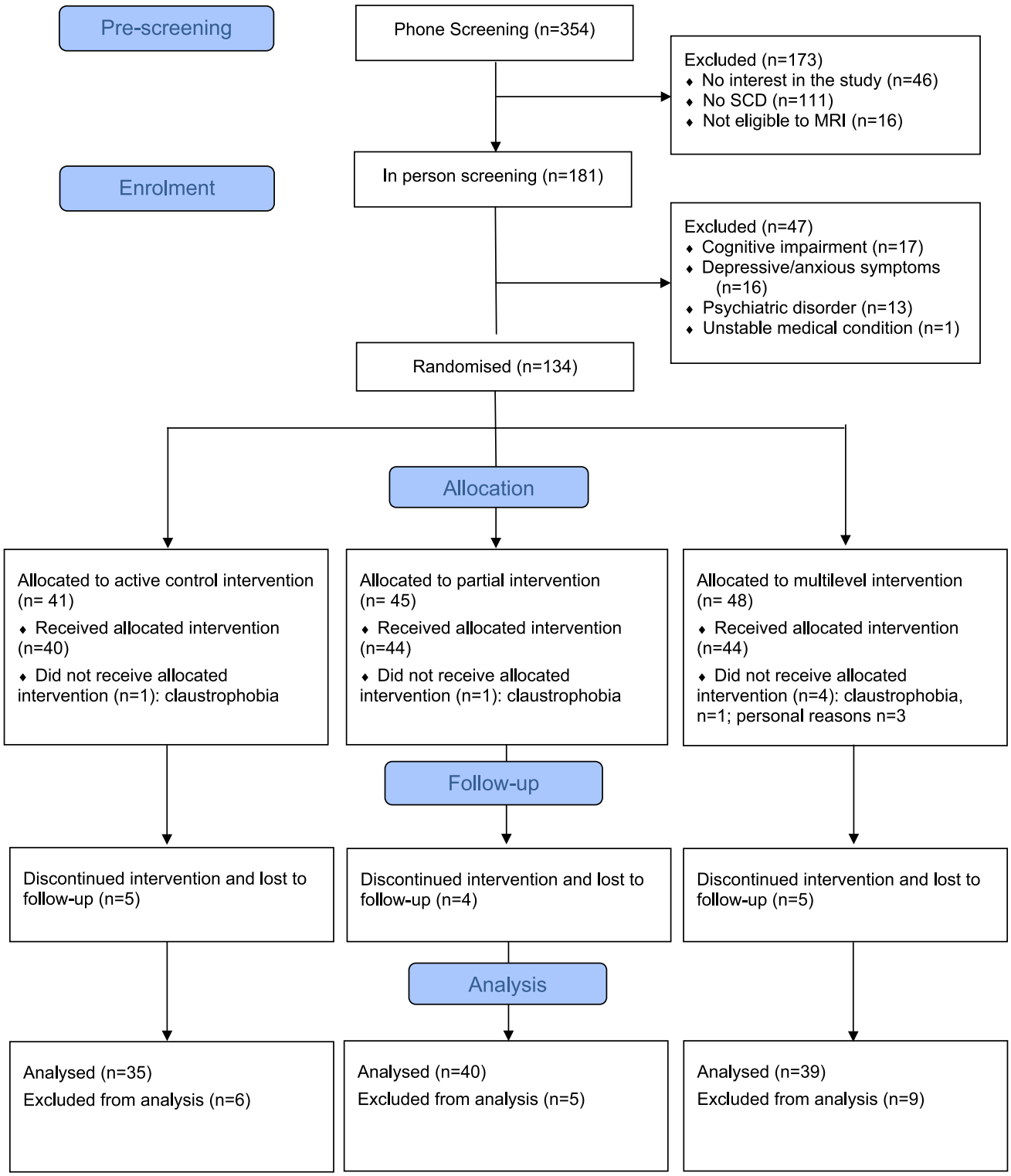


Fig. 1 CONSORT flowchart

connectivity differences in the fronto-parietal executive network, we performed a post-hoc analysis confirming the lack of significant baseline group differences in this network ($p = 0.303$).

Based on the observed pattern of results, a linear mixed effect model was used to assess the correlation between the longitudinal changes in fronto-parietal resting-state activity and attentional-executive composite score or depressive

Table 1 Baseline sociodemographic, clinical, and brain features of the participants with SCD included in the longitudinal analysis by intervention allocation

	All sample N = 114	ACI N = 35	PI N = 40	MI N = 39	p-value
Sociodemographics					
Age	67.8 ± 4.9	68.7 ± 5.3	68.1 ± 5.0	66.8 ± 4.2	0.298
Gender (F)	74 (65%)	25 (71%)	23 (58%)	26 (67%)	0.434
Education (years)	13.4 ± 4.2	14.0 ± 4.3	12.8 ± 3.6	13.6 ± 4.7	0.467
Psychological features and memory complaints					
Geriatric Depression Scale	2.2 ± 2.1	2.0 ± 1.9	2.3 ± 2.4	2.5 ± 1.9	0.453
State-Trait Anxiety Inventory—state	38.1 ± 9.2	36.1 ± 9.6	39.9 ± 9.1	38.2 ± 8.7	0.165
Everyday Memory Questionnaire	72.1 ± 21.9	71.8 ± 27.1	68.5 ± 16.1	76.2 ± 22.0	0.244
Cognitive features					
Mini Mental State Examination	29.0 ± 1.3	29.0 ± 1.1	28.9 ± 1.1	29.1 ± 1.1	0.590
RAVLT delayed recall	47.1 ± 9.3	46.6 ± 10.4	47.5 ± 8.7	47.2 ± 8.9	0.915
Memory composite score	− 0.01 ± 0.77	− 0.10 ± 0.7	− 0.02 ± 0.77	0.10 ± 0.78	0.504
Attentional-executive composite score	0.03 ± 0.66	0.08 ± 0.7	0.01 ± 0.62	0.01 ± 0.68	0.986
Visuospatial abilities composite score	− 0.08 ± 0.75	− 0.19 ± 0.73	− 0.04 ± 0.85	− 0.02 ± 0.67	0.519
Brain features					
Left hippocampal volume	3.6 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	3.5 ± 0.6	0.563
Right hippocampal volume	3.7 ± 0.6	3.7 ± 0.6	3.8 ± 0.6	3.7 ± 0.6	0.795
Left lateral ventricle	12.7 ± 5.6	11.8 ± 5.5	13.2 ± 5.7	12.9 ± 5.7	0.509
Right lateral ventricle	11.2 ± 4.6	10.6 ± 4.6	11.3 ± 4.7	11.5 ± 4.5	0.674
WMH volume	2.43 ± 3.7	2.9 ± 4.0	2.4 ± 4.1	2.1 ± 3.1	0.722
WMH% of total white matter	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.1	0.01 ± 0.01	0.612

Values denote mean ± SD or number (percentage)

ACI Active Control Intervention; *PI* partial intervention; *MI* multilevel intervention; *RAVLT* Rey Auditory Verbal Learning Test; *WMH* white matter hyperintensities

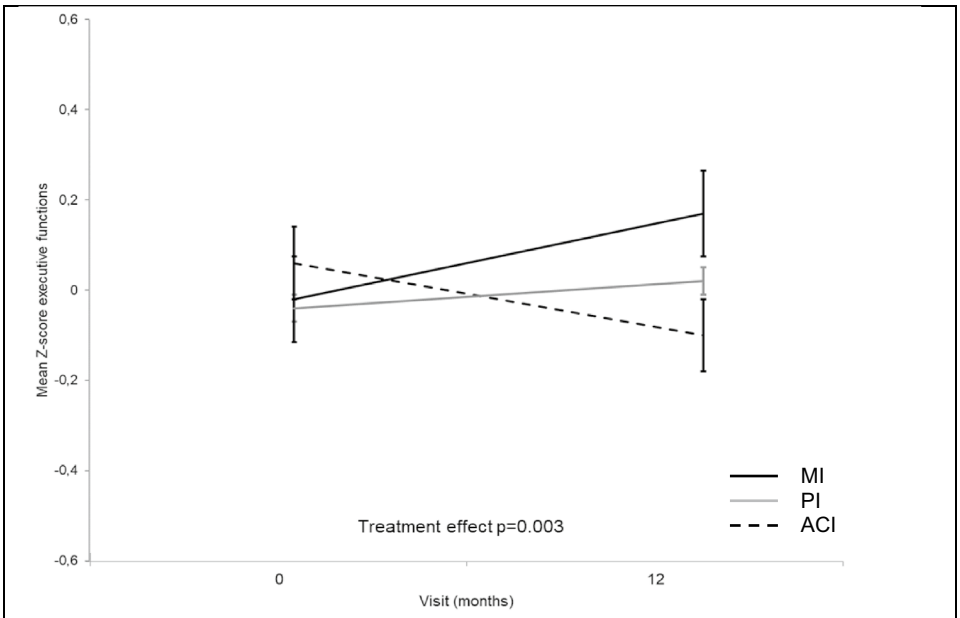
symptoms in MI subjects, with time, treatment allocation and interaction time x treatment allocation as fixed effects, and adjusting for age, sex and education. Statistical analysis did not reveal a significant association between functional connectivity and attention-executive or GDS changes over time (p = 0.143, and p = 0.113, respectively).

Discussion

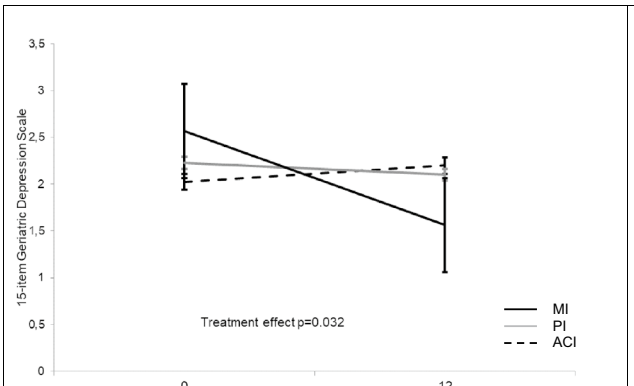
The E.Mu.N.I. study investigated the effects of lifestyle multilevel (i.e., physical exercise, CCT, nutraceutical supplementation, and dietary guidance), and partial (i.e., nutraceutical supplementation and dietary guidance) interventions delivered for one year on cognitive and brain outcomes in older adults experiencing SCD relative to psychoeducation. The findings indicated that SCD individuals undergoing the MI improved in attention-executive functions and depressive symptoms, while SCD individuals undergoing the PI improved in subjective memory, relative to active control group. Furthermore, the MI group showed increased functional connectivity in the fronto-parietal network relative to the PI and active control groups.

In our study, the cognitive benefit of the MI was present on attention-executive functions, with a medium effect size (Cohen's d: 0.47). The finding is in line with the large-scale FINGER trial, showing a positive effect of a 2-year multidomain lifestyle intervention, including dietary guidance, physical exercise, cognitive training, social activities, and management of metabolic and vascular risk factors, on executive functions and processing speed, compared to regular health advice [10]. The positive results observed in our study add a piece of evidence in favor of the concept that targeting a combination of modifiable dementia risk factors may represent the best strategy for dementia prevention [39].

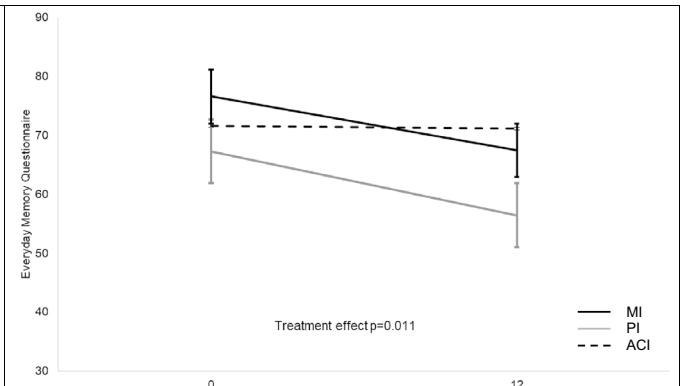
Whether a particular combination of lifestyle interventions might confer greater benefits on cognitive functions has not been established yet. This can be due to the limited number of longitudinal studies examining clustering of specific dementia risk factors and subsequent cognitive outcomes [39], as well as published and ongoing RCTs examining the effect of single-domain interventions compared to multi-domain ones [11]. In addition, the large heterogeneity of



	Estimated difference	95% CI	p	P Bonferroni
MI vs ACI	0.26	0.08;0.44	0.0007	0.002
PI vs ACI	0.16	-0.02;0.34	0.031	0.093



	Estimated difference	95% CI	p	P Bonferroni
MI vs ACI	-0.86	-1.65;-0.07	0.011	0.031
PI vs ACI	-0.28	-1.06;0.51	0.408	0.685



	Estimated difference	95% CI	p	P Bonferroni
MI vs ACI	-7.27	-17.44;2.90	0.085	0.255
PI vs ACI	-12.79	-22.93;-2.65	0.003	0.008

Fig. 2 Mean change and confidence interval (CI) in composite score of attention-executive functions from baseline to 12 months. Dark, grey, and dotted lines indicate Multiple Intervention (MI), Partial Intervention (PI), and Active Control Intervention (ACI), respectively

Fig. 3 Mean change and confidence interval (CI) in depressive symptoms and memory complaints from baseline to 12 months. Dark, grey, and dotted lines indicate Multiple Intervention (MI), Partial Intervention (PI), and Active Control Intervention (ACI), respectively

intervention designs, data analysis, and clinical endpoints make it difficult the comparison of results across studies. The 3-year MAPT study showed no significant effects on cognition of a multidomain lifestyle intervention including cognitive training, physical activity, and nutrition *plus* omega-3 supplementation, either alone or in combination, in a large sample of frail community-dwelling older adults [15]. On the contrary, combining a multidomain lifestyle intervention—similar to that of the MAPT study—with tramiprosate supplementation, we showed a moderate effect

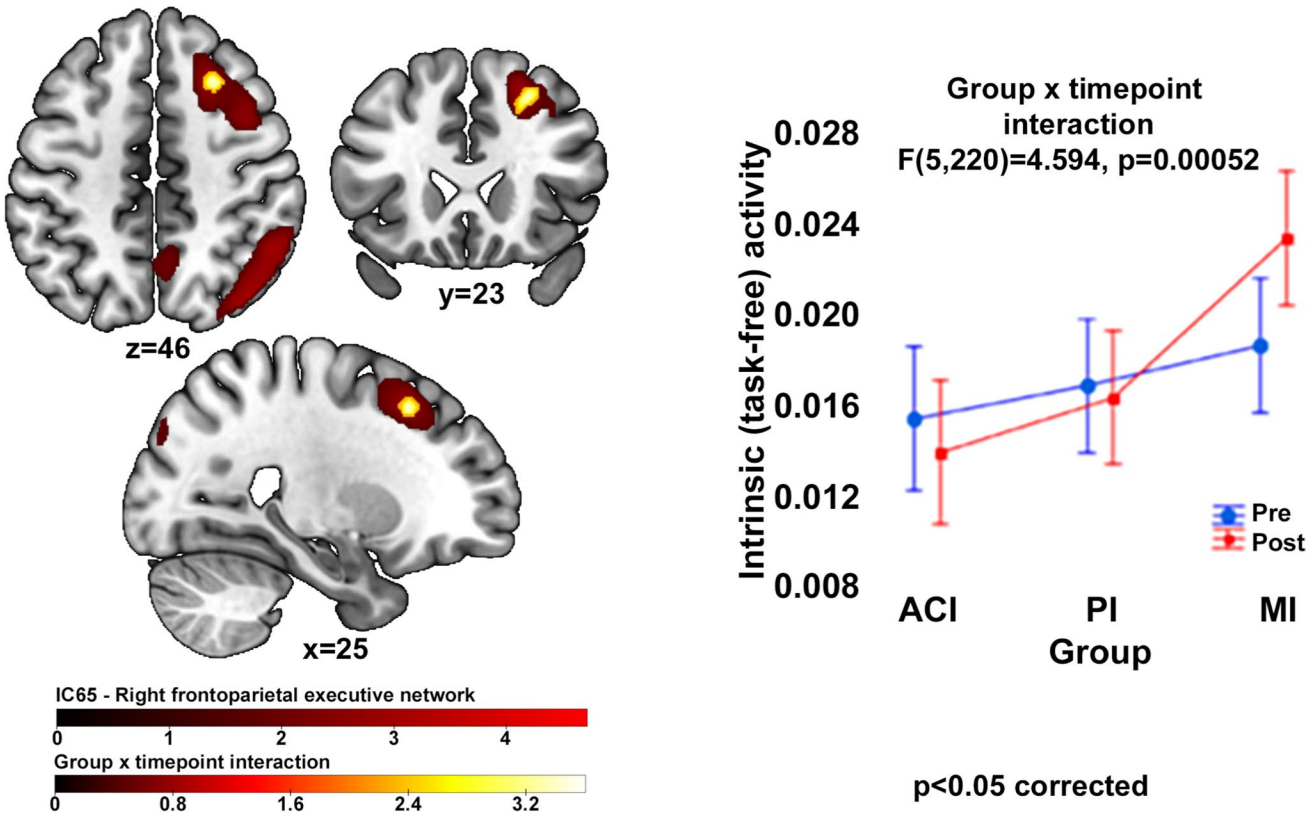


Fig. 4 Effect of the MI on the intensity of intrinsic brain activity in the middle-superior frontal sector of the right fronto-parietal executive network

on attention-executive functions in individuals at increased risk of cognitive decline. Furthermore, we found preliminary evidence of a dose–response of lifestyle interventions, since the PI group showed a positive, albeit non-significant, trend on attention-executive function improvement, relative to active control group.

This positive result could be due to the specific characteristics of the E.Mu.N.I. study design, in terms of target population and interventions. SCD is a condition at higher risk for AD and dementia, thus representing an ideal enrichment strategy to detect a cognitive change even with medium-term follow-ups [11]. Although RCTs evaluating the effects of multidomain versus single-domain interventions in SCD are being developed [40], clinical trials were usually focused on single-domain interventions, showing mixed results on cognitive outcomes [41, 42], or compared a multidomain intervention with active control [43]. Thus, our design of a three-arm multidomain study is original, the results are promising and need to be replicated in larger samples of SCD individuals.

Evidence for the benefits of physical exercise and cognitive training on cognitive functions is increasingly provided in older adults with and without cognitive impairment, both as a single intervention [44, 45], and in combination [46]. In particular, a recent systematic review found significant improvement of attention and executive functions when the trainings were based on repeated practice of cognitive or physical training [46]. Notably, it has been suggested that mechanisms related to brain and cognitive reserve may underpin the protective role of physical and cognitive activities in dementia prevention, by preserving brain structural integrity and strengthening the plasticity of neural circuits, respectively [47]. In preclinical studies, the tramiprosate has shown a neuroprotective effect through anti-amyloid and GABA-dependent activity [48]. In clinical studies, the compound reduced beta-amyloid protein concentrations in the cerebrospinal fluid and hippocampal volume changes in mild AD patients, highlighting a disease-modifying potential [48, 49]. We hypothesize that tramiprosate supplementation might have a synergistic effect with physical exercise and cognitive training in supporting brain and cognitive reserve, and that increased brain and cognitive reserve might underly cognitive benefits observed in the MI.

Our finding of increasing functional brain connectivity in the fronto-parietal executive network in individuals randomized to the MI seems in accord with the above hypothesis. Indeed, increased activations in the prefrontal

cortex were involved in compensatory brain mechanisms of cognitive reserve, supporting brain functioning in the face of cognitive decline [47]. To the best of our knowledge, this is the first study investigating the impact of a multidomain intervention on functional brain connectivity in SCD. Significant functional alterations have been previously found in frontal regions in SCD both at rest [50–52], and during working memory and executive tasks [53], supporting the hypothesis that increases in resting-state functional connectivity at the early stages of AD might represent either upstream or downstream brain compensatory mechanisms in brain regions typically affected in AD [54]. In this regards, multiple lifestyle interventions may modulate altered functional connectivity characterizing this population [55]. The failure to find a significant correlation between increased fronto-parietal resting-state activity and attentional-executive improvement suggested that further brain plasticity processes (e.g., microvascular, metabolism) [56] might underlie the cognitive benefits observed in our population. More research is needed to determine the biological mechanisms underlying the clinical effects of multidomain interventions.

As regards neuroimaging markers, we did not find a significant longitudinal treatment effect on structural MRI markers and white matter lesions load. The finding aligns with a recent systematic review of 43 studies evaluating the effects of preventive interventions on imaging biomarkers for subjects at-risk to develop AD [13]. The review highlighted that interventions involving individuals without cognitive impairment usually did not show significant effects on structural, vascular, or metabolic neuroimaging markers, while positive effects were found for most neuroimaging modalities and type of interventions in participants with cognitive impairment [13]. Also functional imaging was more sensitive to lifestyle intervention-related changes, mostly in frontal areas, in cognitively impaired individuals [13].

Finally, the positive findings in two exploratory outcomes, i.e., depressive symptoms and memory concerns, deserve a comment. Our study revealed that SCD participants in the MI showed a reduction of depressive symptoms with a medium effect size (Cohen's d: -0.48). The finding is in line with studies examining multidomain interventions in subjects with frail older adults [56]. In particular, aerobic physical exercise reliably showed to be a "natural antidepressant" in older adults with clinical depression [57] and in MCI [58]. SCD and depressive symptoms often co-occur and both represent relevant modifiable risk factors to be targeted by dementia prevention initiatives [3]. As regards memory concerns, we found an improvement, with a quite large effect size, only in the PI, i.e., in individuals who attended the nutrition course and took tramiprosate supplementation. It has been suggested that people worried about their subjective memory complaints might be more sensitive to a placebo response, as taking nutritional supplements can be viewed as a relief to feel better [59]. We speculate that the administration of tramiprosate in the PI might have provided an improvement in subjective memory, but not objective cognition, as a main effect of placebo response, while the administration of tramiprosate in combination with physical exercise and cognitive training might have provided an objective cognitive improvement as a result of the synergistic effect of the three interventions on brain and cognitive reserve. In the MI, the placebo response might be smaller than in the PI, as suggested by the non-additive model of placebo research [60], due to high engagement in multiple activities.

The results of this study should be interpreted in the context of its limitations. First, this is a small-scale multidomain trial, thus the findings need confirmation in larger studies. Second, the lack of information regarding participants' genetic status or biological marker profile prevents us to characterize SCD subjects with preclinical AD, who might be more prone to benefit from this trial. Finally, the limited duration of the study (one year) hampered to examine the long-term effects of the multidomain intervention.

Conclusions

The present study adds evidence to the argument that lifestyle multidomain interventions can enhance executive functions in individuals experiencing SCD, and supports the concept that interventions targeting multiple lifestyle risk factors may have added benefit over single-domain strategies, possibly due to brain mechanisms related to increased cognitive reserve. The results need further confirmation in larger trials of biologically well-characterized SCD individuals.

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Availability of data and materials The dataset analysed during the current study is available in a publicly available repository (https://zenodo.org/records/15315692).

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate The study was performed in accordance with the guidelines of the Declaration of Helsinki. The study protocol was approved by the local ethics committees (Ethic Committee of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli and Ethic Committee of the San Raffaele hospital). Written informed consent was collected for all of the participants before screening evaluation. The principles of good clinical practice were observed in conducting the study.

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