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Efficacies of Cognitive Interventions in the Elderly with Subjective Cognitive Decline: A Prospective, Three-Arm, Controlled Trial

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Background and Purpose A cognitive intervention (CI) is thought to improve cognition and delay cognitive decline via neuronal plasticity and cognitive resilience. Subjective cognitive decline (SCD) might be the first symptomatic stage of Alzheimer's disease, but few studies have examined the beneficial effect of CIs in SCD. We aimed to determine the efficacy of a 12-week, small-group-based, multidomain CI in elderly patients with SCD.

Methods Participants diagnosed with SCD (aged 55–75 years) were consecutively allocated to three groups: group 1, which received group-based CI implementation with lifestyle modifications; group 2, which received home-based lifestyle modifications without CI; and group 3, in which no action was taken. The primary outcome variables were the scores on computerized tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). The secondary outcomes included scores on tests evaluating general cognition, memory, visuospatial, and executive functions, as well as scores for the quality of life (QoL), anxiety, depression, and degree of subjective complaints. Changes in scores during the study period were compared between groups.

Results The study was completed by 56 SCD participants. The baseline characteristics did not differ among the groups. The primary outcomes (CANTAB scores) did not differ among the groups. However, the outcomes for phonemic word fluency, verbal memory, QoL, and mood were better for group 1 than for the other two groups. Improvements in verbal memory function and executive function were related to the baseline cognitive scores and group differences.

Conclusions CI in SCD seems to be partially beneficial for executive function, memory, QoL, and mood, suggesting that CI is a useful nonpharmacological treatment option in this population.

Key Words subjective cognitive decline, cognitive intervention, lifestyle modification, cognitive resilience, cognitive benefit, Alzheimer's disease.

INTRODUCTION

Subjective cognitive decline (SCD) is defined as a self-reported cognitive decline occurring in the absence of objective cognitive impairment in standard neuropsychological tests.[1,2] Despite its heterogeneity and uncertainty, SCD is attracting increasing research interest because it is a common condition in the elderly population and most disease-modifying interventions fail in the prodromal or later stage of Alzheimer's disease (AD).[3] SCD has recently been considered the first symptomatic stage of AD, based on previous biomarker studies.[1,2,4] In later periods of preclinical AD, rapid cognitive decline and compensations for the decline lead affected individuals to perceive cognitive worsening, even though objective im-

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pairments are not yet evident.[1] This situation means that SCD might be the most-appropriate target for the secondary prevention of the AD continuum.[3]

A cognitive intervention (CI) is thought to be a promising nonpharmacological therapy for improving cognition and delaying clinical progression, possibly via brain plasticity and increased cognitive reserve.[5] Because synaptic structures in the brain are modifiable even in old age, consistent and vigorous cognitive activities such as participating in CI programs should enhance cognition via optimization for more-efficient and flexible brain connectivity.[5,6] However, evidence is currently lacking for supporting the application of CIs to SCD.[3,7] Previous trials of SCD have produced conflicting results[8-13] due to ambiguous definitions of SCD, differences in study designs and methodological qualities, focusing only on memory function, small samples, and short study durations.[3,7]

In this study we hypothesized that nonpharmacological CIs would show cognitive benefits in subjects with SCD. In addition, implementing multidomain CI programs combined with lifestyle modifications was expected to be more beneficial than self-directed, home-based lifestyle modifications only. To examine the efficacy of CI programs, an active control group conducting home-based lifestyle modifications was included in this study. We aimed to determine the efficacy of a 12-week, small-group-based, multidomain CI in the elderly with SCD.

METHODS

Study design

This 12-week, prospective, single-center, rater-blinded, parallel-design, and controlled trial was conducted from April 2014 to February 2016 in the memory disorder clinic of a university-affiliated medical center. Participants were allocated at a 1:1:1 ratio into three groups with even distributions of age and education level. They were consecutively allocated to groups at the baseline visit based on an age- and education-stratified block allocation table. The three groups were as follows: group 1, in which CI was implemented twice weekly for 12 weeks combined with lifestyle modifications; group 2, in which only lifestyle modifications were applied for 12 weeks (active control group); and group 3, which was a nonactive control group in which no action was taken. The concomitant use of cognitive enhancers was permitted, but these were maintained at a stable dose throughout the study period. Participants were required to keep taking any medications that can potentially influence cognitive function (including anxiolytics, sedatives, hypnotics, antipsychotics, and antidepressants) at a same dose throughout the study.

The effects of the group-based CI and lifestyle modifications on cognitive performance were assessed. Outcome variables were evaluated by the same rater (S.H.N.) who was blinded to the group allocation. Efficacy measurements were conducted at baseline (week 0) and the end of the study (week 12). A 4-week-long visit window was permitted. Six lifestyle characteristics related to the risk of dementia (sedentary lifestyle, low intakes of fish, nuts, vegetables, and fruits, a low level of brain activity, no regular exercise, alcohol dependency or heavy drinking, and no social activity), comorbidities, and concomitant medications including cognitive enhancers, anxiolytics, sedatives, hypnotics, antipsychotics, and antidepressants were assessed at each visit. Vital signs, waist circumference, and body mass index (BMI) were also measured at each visit.

Participants

Sixty-five people who had visited a hospital due to memory decline and had been diagnosed as SCD were consecutively recruited between April 2014 and August 2015. The inclusion criteria were as follows: 1) aged 55−75 years, 2) presence of self-reported cognitive complaints, 3) score within the normal range (no worse than 1.5 SDs below the mean norm) on the Korean version of the Mini Mental State Examination (K-MMSE),[14] 4) Clinical Dementia Rating score of 0,[15] 5) performance within the normal range (no worse than 1.0 SD below the mean norms) on all subtests of detailed neuropsychological tests battery named Seoul Neuropsychological Screening Battery,[16] 6) capable of reading and writing, with at least 3 years of formal education, 7) agreeing to participate in the study, and 8) able to visit a hospital regularly to participate in the CI program and for the study evaluations. The exclusion criteria were as follows: 1) any other neurodegenerative or major psychiatric disorders (a former history of depression was permitted), 2) any severe or unstable medical diseases (i.e., unstable or severe asthma or cardiovascular disease, active gastric ulcer, or severe hepatic or renal disease), or 3) fulfilling the criteria for mild cognitive impairment (MCI)[17] or dementia.[18]

To characterize the self-reported cognitive complaints, detailed questions about the perceived cognitive decline were asked at baseline according to an expert research guideline reported in 2014.[1] Written informed consent was obtained from all subjects before initiating the study. The study protocol and informed consent form were reviewed and approved by the Institutional Review Board of the center of the Asan Medical Center (approval number 2014-0050). The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. This trial is registered at clinicaltrials.gov as NCT02555774.

Cognitive intervention

We adopted a multidomain CI combining cognitive training with physical exercise and lifestyle modifications. The CI program was conducted in small groups (five to seven subjects per group) using a pencil-and-paper method to stimulate multiple cognitive functions including memory, executive, attention, visuospatial, and language functions. At the start of every session, 10 minutes of physical exercise was performed (called 'health gymnastics') comprising balance training, stretching, and walking; this was shown on a video at each session. After the exercise, participants wrote a diary about their previous 2–3 days and talked about the events in the diary for about 10 minutes. The cognitive tasks performed (covering 60 minutes) differed from session to session, were scheduled to be conducted using printed books, and were not the same as the neuropsychological tests assessed for efficacy measurements. During the cognitive training, participants received individual and group feedback on their performance.

The various programs and activities used in the sessions are described in Table 1. The CI programs were performed twice a week, with 90 minutes per session. Participants in group 1 received 24 sessions conducted by the same experienced psychometrician (E.J.C.) throughout the study period. Participants were encouraged to complete at least 19 sessions (80% of all the sessions).

Lifestyle modifications

After performing the group allocation, the participants in groups 1 and 2 received 1 hour of education about risk factors and prevention skills for dementia, and lifestyle modifications before participating in the study sessions. A printed brochure with instructions on lifestyle modifications [regular exercise, stopping smoking, low alcohol consumption, increasing social activities, increasing cognitive activities (with examples), consuming a good diet for brain function, and controlling hypertension and hyperlipidemia] was given out to the participants so that they could use it as a handy reference in their homes. A research coordinator made a regular, 5-minute phone call once a week to remind and guide the participants who belonged to groups 1 and 2 about the lifestyle modifications during the study. No further group activi-

Table 1. Detailed protocol of each cognitive training session

Category	Activities	Duration, minutes
Start exercise	'Health gymnastics' composed of balance training, stretching, and walking, as shown on a video	10
Diary writing and talking	Writing about the events during the past 2–3 days, including the foods consumed, the people that the subject met, and their feelings	10
Cognitive training	Memory training	
	1) Visual memory training: remembering locations, sequences, figures, and graphics	20
	2) Verbal memory training: remembering stories, words, phrases, and poems	
	Language training	10
	1) Grab on behinds-naming items shown (e.g., flowers and animals)	
	2) Finding other words with similar meanings	
	3) Initial quiz	
	4) Creative writing	
	Visuospatial training	10
	1) Finding differences between pictures	
	2) Completing incomplete figures	
	3) Drawing various figures using a few lines	
	Frontal executive function training	10
	1) Thinking and combining different things within a short time	
	2) Identifying differences between similar things	
	3) Identifying similarities among different things	
	4) Digit symbol coding	
	5) Generating names for foods, animals, and other items	
	Calculations and mathematics	10
	1) Calculations	
	2) Finding odd and even numbers	
	3) Finding a common multiple	
Finishing	Freely talking about the day's cognitive training	10

ties or CI programs were applied to group 2.

Outcome measures

The primary outcome variables were the changes in the mean scores on the four subtests (totally 30 minutes for the tests) from the Cambridge Neuropsychological Test Automated Battery (CANTAB): two visual memory tests of pattern recognition memory (PRM) and paired associates learning (PAL), one working memory/executive function test of spatial working memory (SWM), and one attention test of rapid visual information processing (RVP). The tests are described in detail on the website for the battery, at http://www.cambridgecognition.com/academic/cantabsuite/tests. In brief, SWM evaluates visual working memory function to retain spatial information and to manipulate the remembered items. SWM scores represent errors when the subject incorrectly clicks a box in which a token has not been seen, and a lower score is better. PRM evaluates visual recognition memory by assessing the ability to remember visual patterns that were shown previously. PAL evaluates visual memory function by assessing the ability to remember the location of the patterns that were shown previously. The PAL score reports the total number of errors, with a lower score being better. RVP evaluates attentional function by assessing the ability to remember target sequences of digits (e.g., 2-4-6 or 3-5-7), pressing the pad if a target sequence occurs on the screen. CANTAB is a validated battery of nonverbal computerized cognitive tests composed of various subtests evaluating multiple cognitive functions. We selected this test for the primary outcome variables because it is well validated, easy to administer, and more challenging for a study population with normal cognition, and might prevent practice effects through the inclusion of automatic stimuli randomization.

The secondary outcome variables were scores on the logical memory test of the fourth edition of the Wechsler Memory Scale,[19] self-rated Cognitive Failure Questionnaire (CFQ),[20] K-MMSE,[14] Quality of Life-Alzheimer's Disease (QOL-AD),[21,22] Seoul Instrumental Activities of Daily Living (S-IADL),[16] Rey Complex Figure Test (RCFT), copying,[16] Seoul Verbal Learning Test (SVLT),[16] Controlled Oral Word Association Test (COWAT),[16] Hospital Anxiety and Depression Scale (HADS),[23,24] BMI, and waist circumference. Body scores (BMI and waist circumference) were assessed because the CI program included physical exercise in each session and we provided 1 hour of education to groups 1 and 2 about risk factors and prevention skills for dementia that included regular exercise. Increases in scores represent cognitive improvement for the CANTAB PRM and RVP subtests, logical memory test, K-MMSE, QOL-AD, RCFT, SVLT, and COWAT, and cognitive worsening for the CANTAB SWM and PAL subtests, HADS, S-IADL, and self-rated CFQ.

Outcome variables were evaluated by a blinded neuropsychologist (S.H.N.) at baseline and within 4 weeks after the completion of the programs. CANTAB, RCFT, and COWAT scores were used as standard scores adjusted for age, sex, and education.

Statistical analyses

We conducted a pilot trial, and so did not calculate the required sample size considering the lack of evidence on CI in SCD and that the few previous trials adopted different interventions and outcome measures. We consecutively enrolled SCD participants during the study period. The group allocation table comprised the following four strata considering even distributions of age and education level: stratum 1 was for poorly educated (≤6 years) younger (age 55–65 years) participants, stratum 2 was for highly educated (>6 years) younger participants, stratum 3 was for poorly educated older (age 65–75 years) participants, and stratum 4 was for highly educated older participants. The block size in each stratum was 3 or 6. If a subject agreed to participate in the study, then an investigator consecutively identified the stratum number according to the participant's age and education level and assigned them to a group based on the allocation table.

The intention-to-treat (ITT) population was defined as all allocated participants who underwent a baseline evaluation and at least one post-baseline assessment. The per-protocol (PP) population was defined as patients who completed the study without any major protocol violations. No major protocol violation occurred during the study period and post-baseline assessments were performed once at the endpoint, which meant that the ITT population was the same as the PP population.

Demographic and clinical characteristics were compared using analysis of variance or Kruskal-Wallis tests for continuous variables, and chi-square tests for categorical variables. Group comparisons of changes were performed using analysis of covariance adjusted by the baseline scores and post-hoc analysis (Bonferroni correction). Relationships between changes in cognitive score and baseline characteristics were assessed using univariate multiple linear regression models, including age, sex, education level, baseline cognitive complaints, baseline cognitive scores, and treatment group factors. Each baseline factor was analyzed separately in model 1 to measure the relationship, whereas all baseline factors were analyzed together in model 2 to compare the relationships between baseline factors and cognitive changes. The cutoff for significance in all tests was set at α=0.05 (two-tailed). All statistical analyses were performed using SPSS (version 19.0, IBM Corp., Armonk, NY, USA).

RESULTS

Among 77 screened subjects, 65 SCD participants were found to be eligible for inclusion in this study and so were allocated to groups 1 (n=24), 2 (n=21), and 3 (n=20). Three of the allocated participants withdrew their consent before study initiation, and another six discontinued the study without endpoint evaluations. Therefore, 56 SCD participants (23 in group 1, 15 in group 2, and 18 in group 3, 91%) completed the study (Fig. 1). All participants in group 1 completed at least 19 sessions (80%) of the CI program.

The baseline demographics and clinical characteristics (in the PP population) did not differ among the three groups [p> 0.05; Table 2, with more data provided in Supplementary Tables 1, 2, and 3 (in the online-only Data Supplement)]. Table 2 and Supplementary Table 1 in the online-only Data Supplement list the baseline characteristics in the PP and ITT populations, respectively.

Primary outcomes

The efficacy outcomes in each group are presented in Table 3. The primary outcomes-the changes in CANTAB scores from

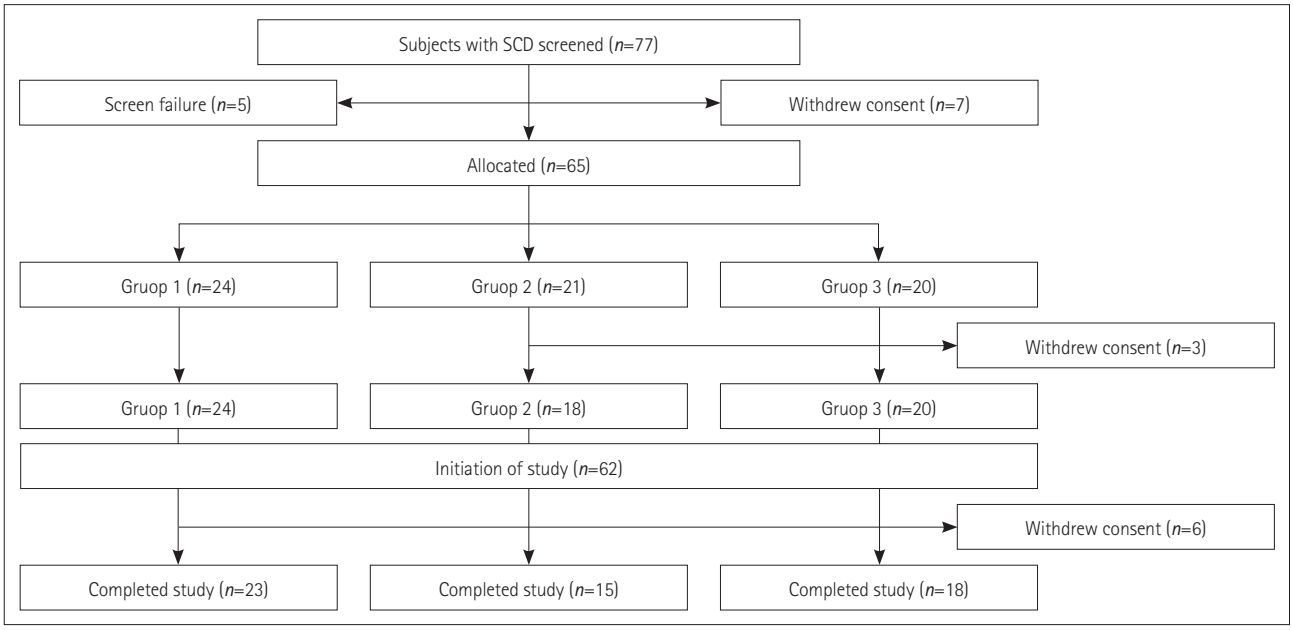

Fig. 1. Study flowchart. SCD: subjective cognitive decline.

Table 2. Baseline demographics and clinical characteristics (in the per-protocol population)

Variable	Group 1 (n=23)	Group 2 (n=15)	Group 3 (n=18)	p	Post-hoc
Age, years	66.22±5.73	65.40±4.82	65.83±4.89	0.895	1=2=3
Education, years	10.43±3.72	11.20±3.97	12.72±3.05	0.135	1=2=3
Sex, female	17/23 (73.9)	14/15 (93.3)	12/18 (66.7)	0.177	n/a
Systolic BP, mm Hg	124.91±14.65	125.69±11.00	127.94±12.44	0.767	1=2=3
BMI, kg/m^2	22.84±2.45	23.23±2.90	23.80±2.35	0.497	1=2=3
Waist circumference, cm	81.73±7.53	80.73±8.35	84.00±6.22	0.436	1=2=3
Symptom duration, years	3.29±2.21	2.25±1.28	2.83±2.79	0.387	1=2=3
Cognitive enhancer medication	1 (4.3)	3 (20.0)	2 (11.1)	0.353	n/a
CFQ score	39.96±14.78	36.53±15.82	29.59±14.33	0.103	1=2=3
QOL-AD score	29.05±5.16	30.00±4.94	31.78±5.95	0.283	1=2=3
GDepS (short form) score	6.37±4.01	6.00±3.53	4.61±3.96	0.340	1=2=3
BAI score	12.48±9.44	10.36±6.90	9.47±8.32	0.520	1=2=3
HADS, anxiety score	7.00±4.18	5.60±2.47	3.82±3.88	0.034	2=1>3=2
HADS, depression score	9.43±3.94	9.27±5.76	7.00±4.40	0.224	1=2=3

Data are mean±SD or n (%) values.
BAI: Beck Anxiety Inventory, BMI: body mass index, BP: blood pressure, CFQ: Cognitive Failure Questionnaire, GDepS: Geriatric Depression Scale, HADS: Hospital Anxiety and Depression Scale, QOL-AD: Quality of Life–Alzheimer's Disease.

Table 3. Changes in the primary outcome variables after 12 weeks among the groups (in the per-protocol population)

Test domain	CI (group 1, *n*=23)		Active control (group 2, *n*=15)		Control (group 3, *n*=18)		*p** (group)	Post-hoc
	Before	After	Before	After	Before	After		
Memory function								
CANTAB PAL	25.35±13.16	19.61±8.55	38.07±28.66	26.40±17.67	22.94±8.50	23.78±9.99	0.378	1=2=3
CANTAB PRM	82.79±10.68	83.88±9.67	86.39±9.25	85.83±11.87	84.26±11.03	83.57±8.63	0.900	1=2=3
Attention								
CANTAB RVP	0.87±0.04	0.88±0.05	0.85±0.05	0.84±0.06	0.89±0.04	0.89±0.04	0.298	1=2=3
Executive function								
CANTAB SWM	48.35±16.48	44.74±17.68	43.73±11.34	46.67±15.35	45.94±16.37	47.83±16.32	0.575	1=2=3

Data are mean±SD values.
*Analysis of covariance adjusted by the baseline scores.
CANTAB: Cambridge Neuropsychological Test Automated Battery, CI: cognitive intervention, PAL: paired associates learning, PRM: pattern recognition memory, RVP: rapid visual information processing, SWM: spatial working memory.

baseline to the end of the study-did not differ significantly among the groups (p>0.05, Table 3). While the CANTAB scores (PRM and SWM tests) showed numerical differences, with more improvements in group 1 than in the other groups, these difference did not reach statistical significance (Table 3, Fig. 2).

Secondary outcomes

Group 1 showed better outcomes than the other two groups in a few secondary outcomes, in terms of the changes in the scores for COWAT, phonemic total (p=0.010), verbal memory delayed recall (p=0.025), quality of life (QoL, p=0.016), anxiety (HADS, anxiety; p=0.015), and depression (HADS, depression; p=0.038) (Table 4, Fig. 2). Additionally, the changes in K-MMSE scores indicated trends of benefit in the group 1 (0.05<p<0.10) (Table 4, Fig. 2). Digit symbol test scores also showed numerical differences (greater benefit in group 1) that did not reach statistical significance (Table 4, Fig. 2).

Associations between baseline factors and cognitive changes

Using regression models, changes in the SVLT delayed recall scores were negatively correlated with baseline SVLT delayed recall scores and treatment-group allocations (Table 5). Changes in the COWAT phonemic total scores also showed negative correlations with baseline COWAT phonemic total scores and treatment-group allocations (Table 5). In other words, participants with lower cognitive scores at baseline and who underwent CIs (group 1 better than group 2, and group 2 better than group 3) showed more cognitive improvements in both verbal memory function and frontal executive function tests at the end of the study.

DISCUSSION

This study investigated the efficacy of a 12-week, group-based multidomain CI in elderly with SCD. Applying the CI in SCD showed cognitive benefits in verbal memory and frontal executive function as well as better outcomes in anxiety, depression, and QoL. Although the changes were not statistically significant, the CI program also showed a trend toward providing cognitive benefits in general cognitive measures represented by K-MMSE. Significant associations between cognitive changes and treatment-group allocations in the regression analyses also support these findings.

Recent dementia-prevention trials have increasingly focused on targeting individuals without dementia because intervening prior to widespread neuronal loss could maximize the therapeutic potential. However, for any therapy to be considered a preventive measure for dementia, especially in the cognitively normal elderly, it should exhibit cost-effectiveness, safety during long-term therapies, and tolerability. These considerations have resulted in nonpharmacological interventions receiving close attention as viable options to mitigate neurodegeneration and prevent cognitive decline. Nonpharmacological CIs have been shown to attenuate the risk of dementia in both healthy older people at risk[25-27] and patients with MCI.[28,29] The efficacies of a CI might be attributable to enhancements of cognitive reserve and neuronal plasticity.[5,6] The cognitive reserve hypothesis suggests that people have varying susceptibilities to pathological changes[5] that are attributable to different efficiencies and flexibilities in recruiting brain networks.[30] Cognitive reserve might be affected by multiple factors such as the education level, occupation, leisure activities, and social activities, and it is modifiable even in old age due to neuronal plasticity.[31] Sustained cognitive activities might stimulate neural structures to increase the efficient brain connections and enhance cognitive reserve.[32] In addition, cognitive training has been found to increase the volume of the gray matter in both the healthy elderly and subjects with SCD.[33,34] Considering that subjects with SCD have an increased likelihood of developing AD and they might be

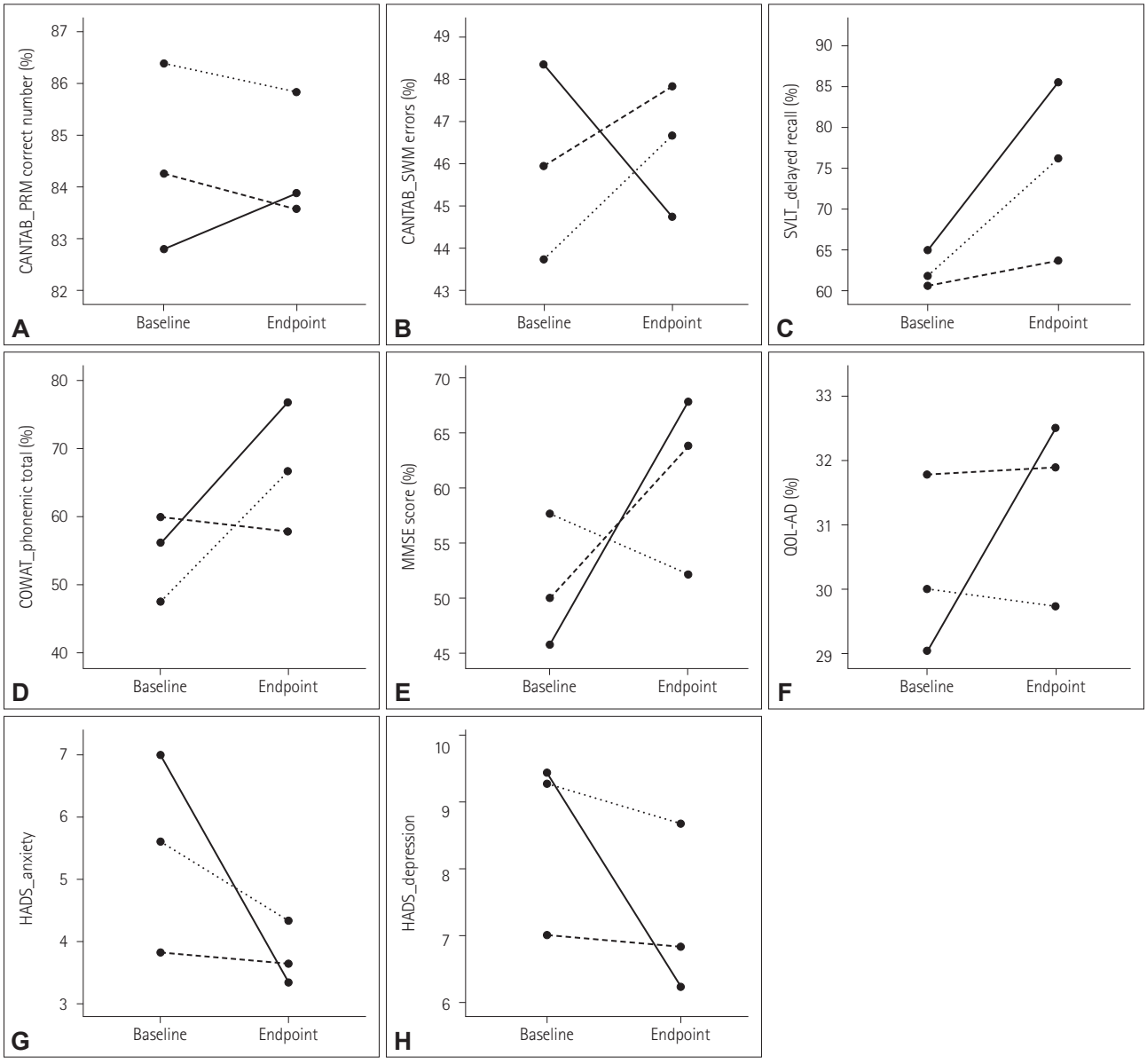

Fig. 2. Changes after 12 weeks among the groups (in the per-protocol population). Solid line, group 1 (cognitive intervention); thin dotted line, group 2 (active control); thick dotted line, group 3 (control). A and B : Primary outcomes. C–H : Secondary outcome variables. CANTAB: Cambridge Neuropsychological Test Automated Battery, COWAT: Controlled Oral Word Association Test, HADS: Hospital Anxiety and Depression Scale, MMSE: Mini Mental State Examination, PRM: pattern recognition memory, QOL-AD: Quality of Life–Alzheimer's Disease, SVLT: Seoul Verbal Learning Test, SWM: spatial working memory.

at the earliest symptomatic stage of AD, a CI would induce a larger response in SCD compared to later stages with objective cognitive impairments and more-advanced neurodegenerative changes.

We adopted a multidomain CI program involving not only memory training but also stimulation in other cognitive domains, combined with physical activity and lifestyle modifications to facilitate training-driven brain plasticity and better outcomes. This approach was based on previous studies showing better transfer effects in multidomain CI.[3] Although we did not find statistically significant differences in the primary outcome variables, our results are consistent with previous studies targeting SCD and the normal elderly, in that the CI improved verbal memory function and executive function.[8,9,11,35,36] Moreover, social interactions and emotional activities during the CI program enhanced the QoL and mood status, which is consistent with previous evidence.[35,37,38] Ceiling effects in a population with objectively normal cognition might explain the lack of significance in the beneficial effects of the CI. It is intriguing that lower baseline scores were related to greater improvements in our study. This might be due to participants with higher baseline cognitive scores hav-

ing non-AD-related conditions such as anxiety or depression, with ceiling effects therefore resulting in minimal changes. Hence, considering that improvements in verbal memory function and executive function were affected by baseline cognitive scores (better outcomes in those with lower baseline scores) and treatment-group allocations (better outcomes

Table 4. Changes in the secondary outcome variables after 12 weeks among the groups (in the per-protocol population)

Test domain	CI (group 1, *n*=23)		Active control (group 2, *n*=15)		Control (group 3, *n*=18)		*p*† (group)	Post-hoc
	Before	After	Before	After	Before	After		
General cognition								
K-MMSE*	45.73±32.42	67.84±23.14	57.68±27.30	52.17±31.45	50.08±34.70	63.88±20.77	0.109	1=2=3
Memory function								
Logical memory, immediate recall	21.87±7.20	23.52±7.04	20.21±7.32	19.50±6.86	23.67±5.77	25.94±6.01	0.080	1=2=3
Logical memory, delayed recall	18.74±8.11	20.35±7.61	14.14±8.35	14.93±8.85	18.67±9.37	21.11±8.52	0.338	1=2=3
Logical memory, recognition	22.70±3.78	23.17±3.19	21.50±4.36	22.29±4.23	23.33±1.97	25.11±3.43	0.168	1=2=3
SVLT, immediate recall*	73.43±27.34	88.41±22.83	68.84±25.87	79.07±23.18	59.30±27.26	75.19±28.00	0.400	1=2=3
SVLT, delayed recall*	65.00±28.28	85.57±21.43	61.84±28.67	76.22±24.56	60.63±24.06	63.72±27.56	0.025	1>3=2
SVLT, recognition*	62.78±28.62	68.50±25.84	57.61±26.68	62.61±29.42	64.18±23.27	72.67±18.68	0.632	1=2=3
Visuospatial function								
RCFT, copying*	74.36±21.18	71.91±24.39	75.18±13.63	58.04±31.50	67.78±16.42	60.83±22.92	0.249	1=2=3
Executive function								
COWAT, phonemic*	56.25±31.30	76.78±29.06	47.55±29.39	66.68±24.12	59.95±29.70	57.90±33.10	0.010	1>3=2
Digit symbol	39.59±12.57	42.95±13.29	42.43±8.59	42.50±6.78	44.94±10.28	44.65±11.17	0.225	1=2=3
Other secondary outcomes								
BMI, kg/m2	22.84±2.45	22.89±2.46	23.21±3.01	23.51±3.17	23.80±2.35	23.76±2.01	0.560	1=2=3
Waist circumference, cm	82.19±7.38	82.02±7.15	80.31±8.75	80.15±8.48	84.00±6.22	84.21±5.80	0.650	1=2=3
CFQ	39.96±14.78	31.04±11.72	36.93±16.34	32.07±15.24	29.59±14.33	25.59±12.81	0.343	1=2=3
QOL-AD	29.05±5.16	32.50±4.64	30.00±4.94	29.73±3.58	31.78±5.95	31.89±7.22	0.016	1>2=3
GDepS (short form)	6.37±4.01	3.26±3.76	6.00±3.53	4.53±3.04	4.61±3.96	3.89±3.55	0.359	1=2=3
HADS, anxiety	7.00±4.18	3.35±3.04	5.60±2.47	4.33±2.99	3.82±3.88	3.65±3.50	0.015	1>3=2
HADS, depression	9.43±3.94	6.22±4.73	9.27±5.76	8.67±3.77	7.00±4.40	6.82±4.42	0.038	1=2=3

Data are mean±SD values.
*Percentile scores adjusted by age and education level. †Analysis of covariance adjusted by baseline scores.
BMI: body mass index, CFQ: Cognitive Failure Questionnaire, CI: cognitive intervention, COWAT: Controlled Oral Word Association Test, GDepS: Geriatric Depression Scale, HADS: Hospital Anxiety and Depression Scale, K-MMSE: Korean version of the Mini Mental State Examination, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, QOL-AD: Quality of Life–Alzheimer's Disease.

Table 5. Results of the linear regression analysis between cognitive changes and baseline factors

Baseline variable	Changes in SVLT delayed recall					Changes in COWAT phonemic score				
	Model 1			Model 2		Model 1			Model 2	
	Beta	R^2 (adj)	*p*	Beta	*p*	Beta	R^2 (adj)	*p*	Beta	*p*
Age	0.082	-0.012	0.549	0.198	0.108	-0.160	0.007	0.246	-0.227	0.101
Sex	-0.048	-0.016	0.727	0.229	0.057	-0.073	-0.014	0.601	-0.151	0.256
Education level	-0.068	-0.014	0.621	0.034	0.764	0.137	0.000	0.324	0.190	0.137
Treatment groups 1, 2, and 3	-0.289	0.066	0.031	-0.350	0.003*	-0.374	0.124	0.005	-0.392	0.003*
K-MMSE	-0.363	0.115	0.007	-0.199	0.072	-0.109	-0.007	0.435	-0.035	0.777
CFQ	-0.128	-0.002	0.350	-0.156	0.160	0.200	0.021	0.151	0.190	0.129
SVLT, delayed recall	-0.569	0.312	<0.001	-0.686	<0.001*	-0.105	-0.008	0.451	0.031	0.826
COWAT, phonemic	0.060	-0.015	0.661	0.248	0.046	-0.430	0.169	0.001	-0.430	0.003*
Logical memory, delayed recall	-0.105	-0.008	0.444	0.060	0.668	-0.142	0.001	0.307	-0.077	0.622

In model 1, each baseline factor was analyzed separately to measure the relationship. In model 2, all baseline factors were analyzed together to compare the relationships between baseline factors and cognitive changes. Adjusted (adj) R^2 was 0.484 for changes in SVLT delayed recall and 0.349 for changes in COWAT phonemic scores. *Statistically significant. CFQ: Cognitive Failure Questionnaire, COWAT: Controlled Oral Word Association Test, K-MMSE: Korean version of the Mini Mental State Examination, SVLT: Seoul Verbal Learning Test.

in the CI group), future CI trials involving larger samples with lower baseline cognitive scores are expected to reveal better outcomes.

Assessing whether or not lifestyle modifications are effective is an important issue to address in future studies. Our study found no cognitive benefits in group 2, which only received lifestyle modification. We thought that adherence to the instructions about lifestyle modifications and the intensity of cognitive activities at home might have been responsible for the absence of any apparent benefit in group 2. In other words, whether the participants actually performed lifestyle modifications and vigorous cognitive activities at home could not be assessed in group 2. In addition, lifestyle modifications at home might not exert significant effects on mood and QoL.

This study has some limitations. First, the study period was relatively short and no follow-up evaluation was performed. Verifying whether the cognitive improvements could be maintained over time is another important issue, and this study can serve as a basis for relevant future investigations. Hence, further studies to clarify the sustained effects are warranted. Second, we consecutively recruited SCD subjects during the study period and did not calculate the required sample size before initiating the study since it was a pilot trial, which might also be a significant study limitation. An insufficient sample size could be another explanation for the small effect sizes found in the study. Third, the lack of randomized group allocations might also limit the generalizability of the study results. We attempted to minimize selection bias by using an age- and education-stratified block allocation table to consecutively assign the participants. The lack of biomarker-based diagnoses that may have resulted in heterogeneity of the participants' brain pathologies would be another limitation. In addition, CI trials have several inherent challenges. It is difficult to recruit participants for these studies since the participants do not have any need for a regular medical checkup or other help. Subjects who are willing to participate in a trial of this sort are more likely to have a higher education level and socioeconomic status and better overall health than those who experience SCD in the general population. A double-blind design and performing exact evaluations of lifestyle modifications are also difficult to implement. Considering that this population exhibits ceiling effects and practice effects in standard neuropsychological tests, future preventive trials need to adopt more-challenging outcome measures and focus on the decrease in dementia incidence based on biological findings of AD-related pathological changes.

Notwithstanding the above limitations, the present study also had particular strengths, in that we targeted people with SCD and assessed various outcome measures including objective and subjective cognitive functions, emotional status, QoL, and physical health. In addition, we adopted an extensive neuropsychological test battery to detect positive changes in cognition following a CI.

In conclusion, a multidomain CI combined with physical exercise and lifestyle modifications showed benefits in verbal memory recall function, frontal executive function, QoL, and mood status along with trends for an improvement in general cognitive function. In addition, group-based regular cognitive activities produced better outcomes than did home-based lifestyle modifications.

Supplementary Material

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.2.304.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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