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Original Study

Effects of Combined Physical and Cognitive Exercises on Cognition and Mobility in Patients With Mild Cognitive Impairment: A Randomized Clinical Trial

Hiroyuki Shimada PhD [a,*], Hyuma Makizako PhD [a], Takehiko Doi PhD [a], Hyuntae Park PhD [b], Kota Tsutsumimoto PhD [a], Joe Verghese PhD [c], Takao Suzuki PhD [d]

[a] Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Japan
[b] Department of Medicinal Biotechnology, College of Natural Resources and Life Science, Dong-A University, Busan, Republic of Korea
[c] Department of Neurology, Albert Einstein College of Medicine, New York, NY
[d] Department of Gerontology, J. F. Oberlin University, Machida, Japan

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A B S T R A C T

Importance: Although participation in physical and cognitive activities is encouraged to reduce the risk of dementia, the preventive efficacy of these activities for patients with mild cognitive impairment is unestablished.
Objective: To compare the cognitive and mobility effects of a 40-week program of combined cognitive and physical activity with those of a health education program.
Design: A randomized, parallel, single-blind controlled trial.
Setting: A population-based study of participants recruited from Obu, a residential suburb of Nagoya, Japan.
Participants: Between August 2011 and February 2012, we evaluated 945 adults 65 years or older with mild cognitive impairment, enrolled 308, and randomly assigned them to the combined activity group (n = 154) or the health education control group (n = 154).
Interventions: The combined activity program involved weekly 90-minute sessions for 40 weeks focused on physical and cognitive activities. The control group attended 90-minute health promotion classes thrice during the 40-week trial period.
Measurement: The outcome measures were assessed at the study's beginning and end by personnel blinded to mild cognitive impairment subtype and group. The primary endpoints were postintervention changes in scores on (1) the Mini-Mental State Examination as a measure of general cognitive status and memory, (2) the Wechsler Memory Scale-Revised—Logical Memory II, and (3) the Rey Auditory Verbal Learning Test. We applied mobility assessments and assessed brain atrophy with magnetic resonance imaging.
Results: Compared with the control group, the combined activity group showed significantly greater scores on the Mini-Mental State Examination (difference = 0.8 points, $P = .012$) and Wechsler Memory Scale-Revised—Logical Memory II (difference = 1.0, $P = .004$), significant improvements in mobility and the nonmemory domains and reduced left medial temporal lobe atrophy in amnestic mild cognitive impairment (Z-score difference = −31.3, $P < .05$).
Conclusion: Combined physical and cognitive activity improves or maintains cognitive and physical performance in older adults with mild cognitive impairment, especially the amnestic type.

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* Address correspondence to Hiroyuki Shimada, PhD, Section for Health Promotion, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 430 Morioka-cho, Obu, Aichi 474-8511, Japan.
E-mail address: shimada@ncgg.go.jp (H. Shimada).

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Mild cognitive impairment (MCI) represents a clinical prodrome to neurodegenerative dementias such as Alzheimer disease (AD).[1,2] It is estimated that 10% to 15% of individuals with MCI develop dementia annually compared with 1% to 2% of unaffected older adults.[3] Earlier treatment of mild to moderate AD is associated with better clinical responses,[1,2] so treating MCI may be effective in delaying progression to dementia.

Epidemiologic data suggest that moderate exercise and cognitive activities are associated with a lower risk of dementia[4] and with various cognitive benefits.[5,6] A randomized study of adults with memory impairments suggested that physical activity may moderately improve cognition,[7] but other studies have been inconclusive about whether physical or cognitive activity improve cognition or prevent dementia in older adults.[8–13] We previously reported that a multicomponent intervention combining cognitive stimulation and physical exercise slightly improved global cognitive function in persons with MCI.[14,15] A systematic review concluded that in older adults, combined cognitive and exercise training may improve their cognitive and functional status, but little evidence was provided for this approach in those with cognitive impairments,[16] and the feasibility of such complex training for them remains unproven.

We designed a single-blinded, randomized controlled trial to determine if there were cognitive benefits of a combined cognitive and physical activity program in patients with MCI. Patients with MCI exhibit an elevated prevalence of mobility limitations[17] and mobility degeneration,[18,19] so we also examined the intervention's effects on mobility endpoints. We hypothesized that the combined cognitive and physical activity program would be beneficial to individuals with MCI.

Methods

Study Design

Our trial protocol was approved by the Ethics Committee of the Japanese National Center for Geriatrics and Gerontology (approval number 602) and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000007749; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000009121&language=J). All participants provided written informed consent before participating, in accordance with the principles of the Declaration of Helsinki.

Screening and Randomization

We assessed 5104 individuals aged 65 years or older who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE).[20] Each individual was recruited from Obu, a residential suburb of Nagoya, Japan, between August 2011 and February 2012. Figure 1 outlines the study flow. A total of 945 potential participants with MCI were identified from the parent OSHPE study after review of available clinical, neuropsychological, and laboratory tests at meetings involving study neurologists, geriatricians, and neuropsychologists, as previously described.[20] In brief, the participants were independently recruited using the National Center for Geriatrics and Gerontology Functional Assessment Tool (NCGG-FAT), which has 8 task components that are reliable and valid in community-dwelling older adults.[21] In this study, we used 2 memory tasks, attention and executive function tasks, a processing speed task, and a visuospatial task. Using established criteria,[2] we diagnosed MCI in individuals who reported subjective memory complaints on questionnaires and exhibited cognitive impairment (age-adjusted scores at least 1.5 SD below the mean on any cognitive test; see later in this article) but were functionally independent in basic daily life activities. Based on NCGG-FAT–measured cognitive deficits, participants were assigned to the amnestic MCI (aMCI) (n = 159) or nonamnestic MCI (naMCI) (n = 149) subgroup. We excluded individuals with a history of stroke, Parkinson disease, or depression; past or present participants in other intervention studies; and individuals who met the *Diagnostic and Statistical Manual of Mental Disorders-IV* dementia criteria. We identified 308 eligible individuals with MCI (Figure 1) and assigned them to either the combined activity group (n = 154; aMCI subgroup = 80, naMCI subgroup = 74) or the health education group (n = 154; aMCI subgroup = 79, naMCI subgroup = 75) using a computerized 1:1 randomization scheme operated by a researcher blinded to study aims.

Combined Activity Program

The combined activity program involved 40 weekly 90-minute sessions focused on physical and cognitive activities. Sixteen to 32 individuals participated in each session conducted by 2 geriatric physiotherapists and 5 instructors at a fitness facility. The program included aerobic exercise, muscle strength training, postural balance retraining, and dual-task training. The exercises combined physical and cognitive tasks into what we called "cognicize." For example, participants played word games while doing stepping exercises. Each session featured, in order, 10 minutes of warm-up and stretching exercises, 20 minutes of muscle strength exercise and postural balance training, 25 minutes of dual-task "cognicize" training,[22] 5 minutes of rest, 25 minutes of aerobic exercise, and 5 minutes of cooling down. The aerobic exercises included stair stepping, endurance walking, and walking on balance boards. The mean aerobic exercise intensity was 60% to 80% of maximum heart rate (HR), consistent with previous studies.[6] HR was self-assessed immediately after the aerobic exercise based on pulse rate using an HR monitor (F-RUN Heart Meter; Fast Running Co. Ltd., Tokyo). The maximum HR was estimated as $207 - 0.7 \times$ age. The participants also performed daily home-based muscle strengthening exercises and walking, which were self-monitored using booklets and pedometers. To promote healthy behaviors, physiotherapists lectured the participants on cognitive health, the risks of dementia, how exercise affects dementia, exercise methods, and self-monitoring of regular physical activities.

Health Education Control

Participants in the control group attended 90-minute health promotion classes thrice over the 40-week trial period. The instructors taught participants about aging, nutrition, oral care, frailty, and urinary incontinence. The topics were chosen from those used in previous intervention studies[13] and those that experts considered unlikely to influence study outcomes. The group was mailed pamphlets about the topics thrice over the study period but did not receive specific information or recommendations regarding exercise, physical activity, or cognitive health. The instructors placed 10-minute telephone calls to the participants approximately 2 to 3 times over the study period to promote retention and adherence to the education program.

Outcomes

Functional outcomes

The outcome measures were assessed at the start and end of the interventions by study personnel blinded to MCI subtype and assignment group. The primary endpoints were postintervention score changes on (1) the Mini-Mental State Examination (MMSE), (2) the Wechsler Memory Scale-Revised—Logical Memory II (WMS-LM II), and (3) the Rey Auditory Verbal Learning Test (RAVLT). The MMSE measures general cognitive status and memory function. It takes approximately 10 minutes and consists of 30 questions that assess cognitive function in the areas of orientation, memory, attention and calculation, language, and visual construction. The score is the sum of correct responses, and a score of 24 or above is considered normal. The WMS-LM II assesses

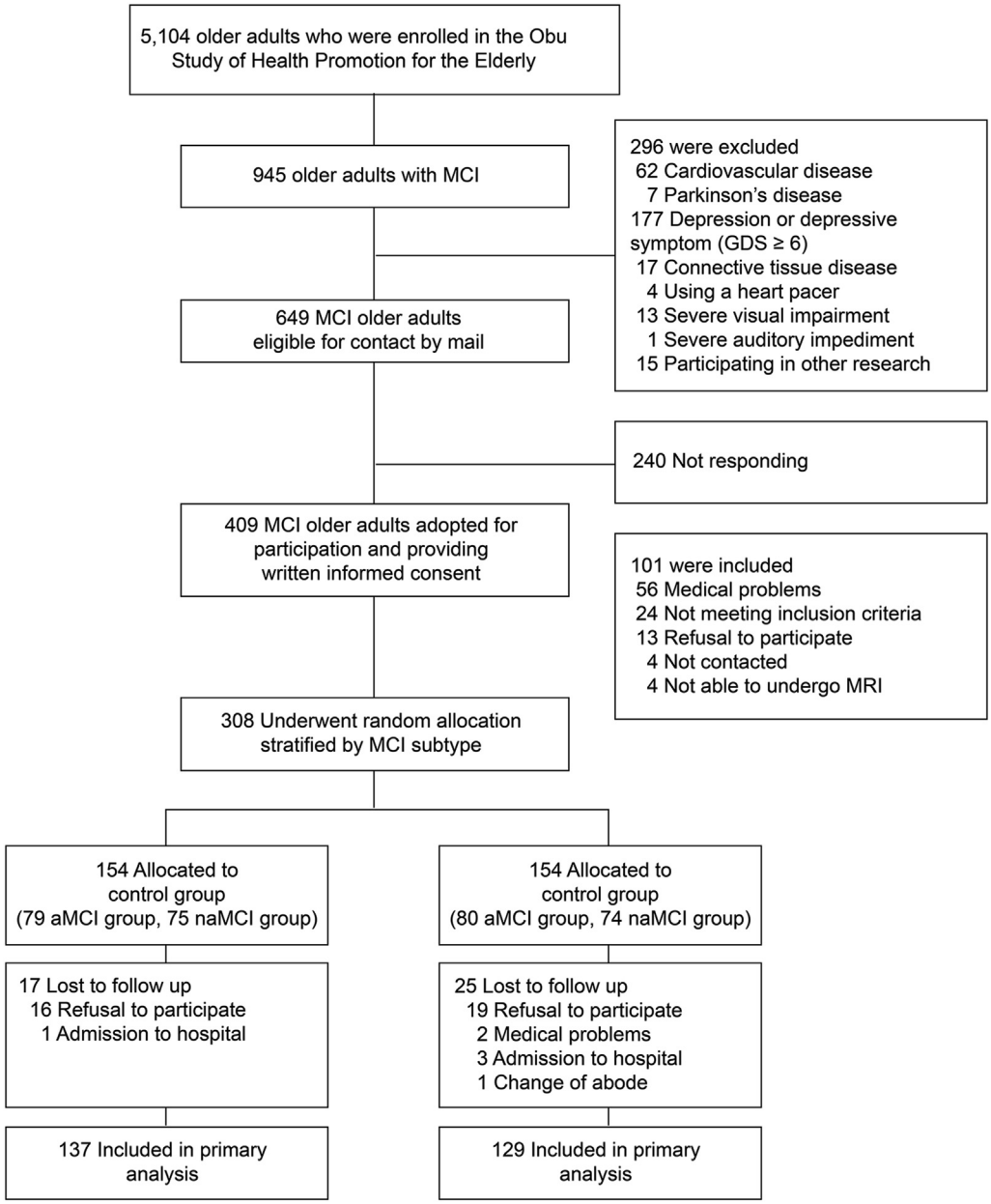

Fig. 1. Screening and randomization.

logical memory function and involves a short story being read aloud to the participants who are then asked to recall details of the stories after 30 minutes (Logical Memory II). We summed correct responses for the story to generate a score. The RAVLT assesses verbal memory, and in this test, 15 nouns ("list A") are read aloud 5 times to the participants who must recall them each time. The examiner then reads a second list of 15 new words that the participants must recall. Thirty minutes later, the participants are asked to recall list A again, and the number of correct recall responses is the score.

The secondary outcomes were scores on cognitive tests assessing nonmemory domains, such as the verbal fluency letter test (VFT-letter), the verbal fluency categorical test (VFT-category), and the trail-making test (TMT).[6] The VFT-letter and VFT-category tests are considered indices of frontal and temporal lobe function, respectively.[23] The completion rate difference between the TMT's 2 parts was used to measure executive function. Physical activity over a fortnight was measured with triaxial accelerometers (Active Style Pro HJA-350IT; Omron Healthcare, Kyoto, Japan) that recorded mean daily steps and mean duration (min/d) of moderate-to-vigorous intensity physical activity (MVPA), defined as 3 or more daily metabolic equivalents.[24]

Structural outcomes

Atrophy of the hippocampus and medial temporal lobe is characteristic of AD[25] and may be amenable to physical or cognitive interventions.[26,27] We therefore measured brain atrophy changes in medial temporal areas (MTAs), including the entorhinal cortex (ERC) at the study's start and end using magnetic resonance imaging (MRI). MRI was performed as described previously[28] using a 3-tesla system (TIM Trio; Siemens, Munich, Germany) for 3-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence (inversion time (TI) = 800 ms; echo time (TE)/repetition time (TR) = 1.98 ms/1800 ms; 1.1-mm slice thickness). Then axial T2-weighted spin-echo images (TR = 4200 ms; TE = 89.0 ms; 5-mm slice thickness) and axial fluid-attenuated inversion recovery imaging (TR = 9000 ms; TE = 100 ms;

Table 1
Baseline Characteristics of Participants

Characteristic	Combined Activity Group (n = 154)	Control Group (n = 154)	*P*
aMCI, n	80	79	
naMCI, n	74	75	
Age, y	71.6 ± 5.0	71.6 ± 4.9	.963
No. of men (%)	77 (50.0)	77 (50.0)	1.000
Educational level, y	10.9 ± 2.6	10.8 ± 2.2	.694
Body mass index, kg/m^2	23.3 ± 2.8	23.5 ± 2.9	.462
Illness incidences (%)			
Hypertension	62 (40.3)	59 (38.6)	.761
Heart disease	15 (9.7)	22 (14.3)	.220
Diabetes mellitus	19 (12.3)	12 (7.8)	.191
Arthritis	22 (14.3)	26 (16.9)	.530
No. taking ≥3 medications (%)	53 (34.4)	60 (39.0)	.408
Blood tests			
Total cholesterol, mg/dL	206.6 ± 34.6	205.6 ± 34.6	.795
Triglyceride, mg/dL	159.9 ± 105.8	161.0 ± 97.2	.924
HbA1c, %	5.54 ± 0.67	5.60 ± 0.67	.409
No. of ApoE4 carriers (%)	31 (20.7)	28 (18.5)	.643
TMIG index score	12.5 ± 0.9	12.3 ± 1.3	.256
GDS score	2.2 ± 1.6	2.3 ± 1.6	.431
Physical performance			
Maximum walking speed, m/s	1.79 ± 0.30	1.76 ± 0.31	.427
Grip strength, kg	27.9 ± 7.7	27.0 ± 7.1	.277
Primary outcomes, baseline values			
MMSE score	26.6 ± 1.8	26.8 ± 1.8	.532
WMS-LM II score	5.7 ± 3.9	5.6 ± 3.7	.799
RAVLT score	7.5 ± 3.2	7.2 ± 3.7	.438
Secondary outcomes: cognitive, baseline values			
VFT-letter score	19.9 ± 7.4	19.0 ± 6.9	.251
VFT-category score	35.2 ± 7.8	34.9 ± 7.4	.725
TMT, s/n	1.8 ± 2.7	1.5 ± 1.3	.266
MTA-ERC atrophy, right	0.63 ± 0.47	0.72 ± 0.66	.154
MTA-ERC atrophy, left	0.64 ± 0.50	0.63 ± 0.45	.909
Secondary outcomes: mobility, baseline values			
Total daily steps	7237.0 ± 3684.6	6383.7 ± 3021.6	.046
MVPA, min/d	24.5 ± 23.4	18.7 ± 18.1	.028

Values are mean ± SD unless otherwise noted. The body mass index is weight in kilograms divided by the square of height in meters. The TMIG index is a self-administered, 13-item questionnaire that assesses the concepts of instrumental activity of daily living, intellectual activity, and social role. GDS scores range from 0 to 15, with higher scores indicating more dysphoria. The maximum walking speed measures the speed at which participants walked a distance of 5 m at their maximum gait as an objective assessment of mobility. The grip strength measures maximum isometric strength of the hand and forearm muscles. HbA1c, hemoglobin A1c; TMIG index, Tokyo Metropolitan Institute of Gerontology index.

TI = 2500 ms; 5-mm slice thickness) were obtained. The mean and SD of each patient's gray matter volumes were compared with those of healthy individuals using voxel-by-voxel *Z*-score analysis. The data for healthy individuals were calculated using brain templates of healthy individuals. We used the voxel-based specific regional analysis system for AD in which higher *Z*-scores indicate greater MTA-ERC atrophy.[29]

Statistical Analysis

All analyses were conducted using SPSS version 20.0 (IBM, Armonk, NY). The primary analysis was conducted according to the intention-to-treat principle to determine whether participants in the combined program exhibited significantly smaller declines in primary and

Table 2
Comparison of Outcomes Between Groups

Outcomes	Overall					aMCI	
	Combined Activity Mean Change	Control Mean Change	Between-Group Difference	*P*	Adjusted R^2	Combined Activity Mean Change	Control Mean Change
Primary outcomes							
MMSE	0.0 (−0.4 to 0.4)	−0.8 (−1.2 to −0.4)	0.8 (0.2 to 1.4)	.012	0.222	−0.1 (−0.7 to 0.5)	−0.9 (−1.5 to −0.2)
WMS-LM II	1.2 (0.7 to 1.8)	0.3 (−0.3 to 0.8)	1.0 (0.2 to 1.7)	.004	0.246	1.6 (0.8 to 2.4)	0.4 (−0.3 to 1.2)
RAVLT	0.8 (0.3 to 1.3)	0.6 (0.2 to 1.1)	0.2 (−0.5 to 0.8)	.352	0.22	0.9 (0.2 to 1.5)	0.6 (−0.5 to 1.2)
Secondary outcomes							
Cognitive							
TMT	−0.3 (−0.7 to 0.1)	0.0 (−0.2 to 0.3)	−0.4 (−0.8 to 0.1)	.350	0.533	−0.4 (−1.1 to 0.3)	−0.1 (−0.4 to 0.2)
VFT-letter	4.3 (3.2 to 5.4)	0.7 (−0.3 to 1.6)	3.6 (2.2 to 5.1)	<.001	0.235	4.6 (2.9 to 6.2)	0.2 (−1.0 to 1.5)
VFT-category	3.3 (2.2 to 4.4)	1.1 (0.1 to 2.1)	2.2 (0.8 to 3.6)	.002	0.065	3.8 (2.2 to 5.4)	1.6 (0.2 to 2.9)
Mobility							
Total steps (steps/d)	1817.2 (1125.1 to 2509.3)	163.1 (−362.3 to 688.5)	1654.1 (840.7 to 2467.5)	<.001	0.148	2405.4 (1380.2 to 3430.6)	538.8 (−71.0 to 1148.5)
MVPA (min/d)	14.3 (9.5 to 19.0)	2.0 (−1.3 to 5.2)	12.3 (6.6 to 18.1)	<.001	0.104	18.7 (11.4 to 25.9)	2.6 (−1.8 to 7.0)
Imaging (brain atrophy)							
Atrophy of right MTA-ERC (*Z*-score × 10^3)	−0.5 (−21.2 to 20.2)	0.5 (−20.0 to 21.0)	−1.1 (−30.1 to 28.0)	.893	0.016	0.3 (−26.9 to 27.4)	5.1 (−24.7 to 34.9)
Atrophy of left MTA-ERC (*Z*-score × 10^3)	2.6 (−15.3 to 20.6)	20.2 (3.0 to 37.4)	−17.6 (−42.1 to 0.7)	.123	0.078	−9.1 (−34.8 to 16.6)	22.8 (0.9 to 44.6)

Values represent differences between pre- and postintervention measurements based on data after multiple imputations.

secondary outcome measures than those in the control group. The *Z*-scores for MRI-measured left MTA-ERC atrophy were logarithmically transformed in all analyses to correct for right-skewed distributions. Based on our previous study,[14] we estimated that this study needed 292 participants to have a 95% power to detect a significant between-group difference in WMS-LM II score changes with an effect size of 0.15. We performed multiple imputation analyses to account for possible bias introduced by participants without 40 weeks of data. Using the Markov chain Monte Carlo approach that assumes multivariate normality and is appropriate for our measurement outcomes, we generated 50 imputed data sets based on age, sex, education history, apolipoprotein E ε4 (ApoE4) carrier status, geriatric depression scale (GDS) score, MCI subtype, and prior observations of the outcome variables. These variables were corrected at baseline assessment in the study. We used a multiple linear regression model and repeated-measures calculations to examine outcome measurement changes between the study's start and end. Within the multivariate models, these outcome changes were dependent variables, the group assignment was the independent variable, and the covariates included age, sex, educational level, GDS score,[30] ApoE4 genotype carrier status, and MCI subtype. Because we hypothesized that the cognitive deficits associated with aMCI and naMCI might differentially influence the intervention's effects, we repeated the analyses separately in the subgroups. All statistical tests were 2-sided with an alpha level of 0.05.

Results

Baseline Characteristics and Completion Rates

The control and combined activity groups did not significantly differ in demographic variables, medical variables, or baseline primary outcome measures (Table 1). Among the secondary outcomes, the groups did significantly differ in baseline mobility measures (total daily steps and MVPA) (Table 1). No participants were taking dementia medications.

A total of 266 participants (129 and 137 in the combined activity and control groups, respectively) completed the 40-week study (Figure 1). Twelve individuals assigned to the combined activity group withdrew before the program's start but were included in the analyses. If the 12 nonparticipants are included, the mean adherence to the exercise program was 84.5%, and this rises to 92.3% if the nonparticipants are excluded.

Outcome Measures

The individual changes and between-group differences in primary and secondary outcomes for the pooled MCI sample and the MCI subtypes, amnestic or nonamnestic, are summarized in Table 2.

Primary outcome measures

Compared with the controls, the combined activity group exhibited significantly greater score changes on the MMSE (difference = 0.8, $P = .012$) and WMS-LM II (difference = 1.0, $P = .004$) but not the RAVLT (difference = 0.2, $P = .352$).

The analysis by MCI subtype showed that the pooled samples' significant between-group differences were explained by the aMCI subgroup (Table 2). The naMCI group exhibited no significant improvements on any of the 3 primary outcomes during the study period. Figure 2 graphically illustrates the MCI subtypes' scores at the study's start and end.

Secondary outcome measures

Among the nonmemory tasks, the combined activity group showed greater improvements than the control group on the VFT-letter (difference = 3.6, $P < .001$) and VFT-category (difference = 2.2, $P = .002$) tests but not the TMT (difference = −0.4, $P = .350$).

We obtained a fortnight of accelerometer data from 122 (94.5%) combined activity group participants and 127 (92.7%) controls. Compared with the control group, the combined activity group showed longer MVPA durations (difference = 12.3 min/d; $P < .001$) and higher daily step numbers (difference = 1654.1 steps/d; $P < .001$), even after adjusting for covariates and baseline values (Table 2; Figure 3). As the mobility measures were not balanced at baseline despite randomization, we adjusted all mobility-related analyses for baseline levels on mobility measures, as done in previous studies.[31] The aMCI and naMCI subgroups showed similar improvements in MVPA durations and daily step numbers during (Figure 3) and after the combined activity program (Table 2).

We obtained baseline and postintervention MRI data from 129 combined activity group participants and 135 controls. The pooled sample groups did not significantly differ in bilateral MTA-ERC region volumes (left hemisphere: *Z*-score difference = −17,600, $P = .123$; right hemisphere: *Z*-score difference = −1100, $P = .893$). Compared with the aMCI control subgroup, the aMCI combined activity subgroup showed significantly smaller MTA-ERC volume losses in the left hemisphere (*Z*-score difference = −31,900; $P = .032$) but not the right hemisphere (*Z*-score difference = −4900; $P = .629$). The naMCI subgroups did not exhibit significantly different MTA-ERC volume changes in either hemisphere (left hemisphere: *Z*-score difference = −2200, $P = .926$; right hemisphere = *Z*-score difference = 2900, $P = .773$).

Safety

During the study, 3 combined activity participants and 1 control participant were hospitalized for illnesses or injuries unrelated to the interventions. Falls in daily life occurred in 11 combined activity participants (8.4%) and 13 control participants (9.2%) with no significant

Table 2
Continued

aMCI			naMCI				
Between-Group Difference	*P*	Adjusted R^2	Combined Activity Mean Change	Control Mean Change	Between-Group Difference	*P*	Adjusted R^2
0.7 (−0.1 to 1.6)	.039	0.253	0.2 (−0.4 to 0.8)	−0.7 (−1.3 to −0.1)	0.9 (0.6 to 1.7)	.123	0.192
1.2 (0.1 to 2.2)	.022	0.259	0.8 (0.0 to 1.6)	0.1 (−0.7 to 0.9)	0.7 (−0.4 to 1.8)	.025	0.215
0.3 (−0.6 to 1.2)	.354	0.213	0.7 (0.1 to 1.4)	0.7 (0.1 to 1.3)	0.0 (−0.9 to 0.9)	.769	0.22
−0.3 (−1.0 to 0.4)	.966	0.762	−0.2 (−0.6 to 0.2)	0.2 (−0.2 to 0.6)	−0.5 (−1.0 to 0.1)	.186	0.113
4.4 (2.3 to 6.4)	<.001	0.278	4.0 (2.6 to 5.5)	1.2 (−0.3 to 2.6)	2.9 (0.8 to 4.9)	.002	0.185
2.3 (0.2 to 4.4)	.030	0.061	2.7 (1.3 to 4.1)	0.6 (−0.8 to 2.0)	2.1 (0.1 to 4.1)	.039	0.074
1866.7 (722.6 to 3010.7)	<.001	0.118	1209.0 (443.3 to 339.2)	−256.5 (−1088.0 to 575.0)	1465.5 (318.0 to 2613.0)	.019	0.16
16.1 (7.8 to 24.3)	<.001	0.124	9.8 (3.9 to 15.7)	1.3 (−3.4 to 6.0)	8.5 (1.1 to 15.9)	.034	0.072
−4.9 (−45.2 to 35.5)	.629	0.039	−1.4 (−32.6 to 29.8)	−4.3 (−32.1 to 23.5)	2.9 (−38.5 to 44.3)	.773	−0.013
−31.9 (−65.4 to 1.7)	.032	0.08	15.3 (−9.4 to 40.0)	17.5 (−8.9 to 44.0)	−2.2 (−38.6 to 34.2)	.926	0.077

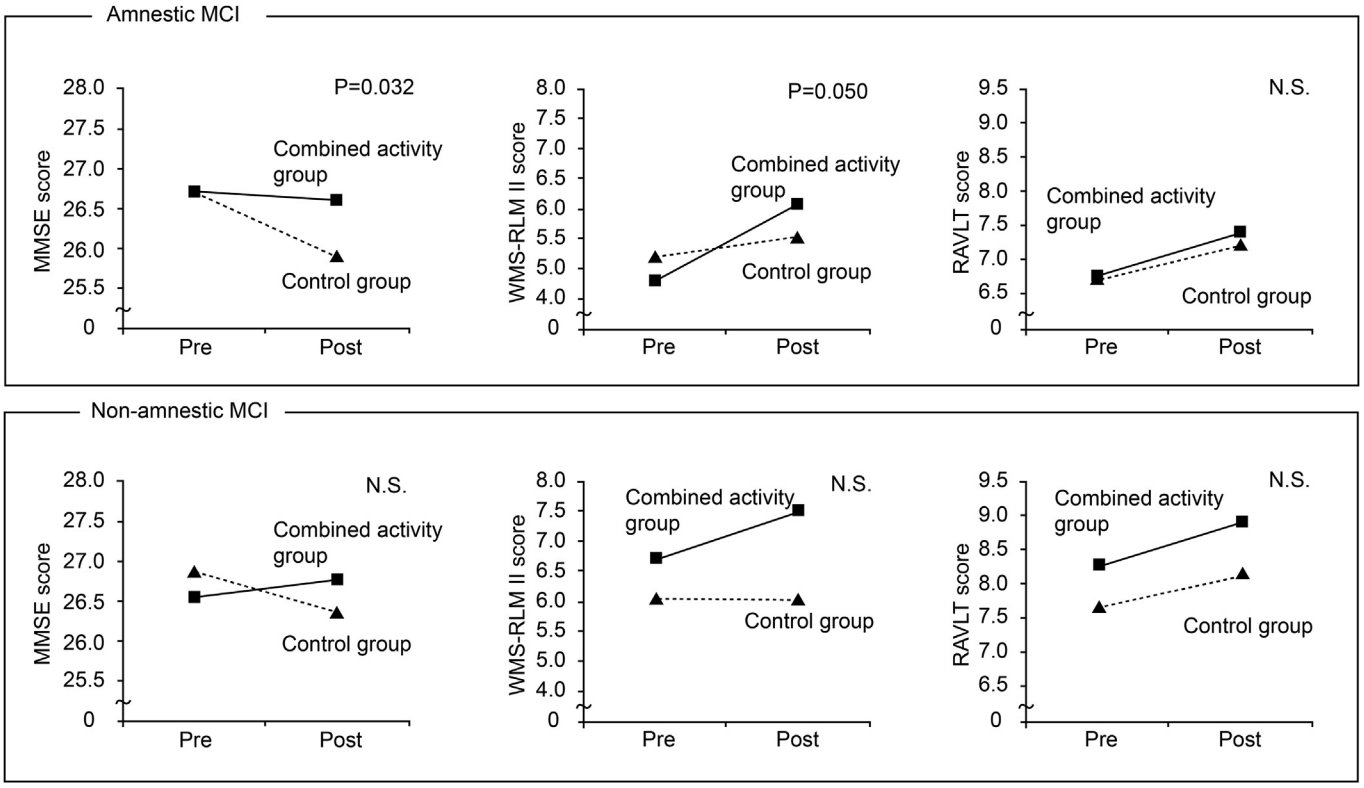

Fig. 2. Changes in cognition by MCI subtype. The *P* values for between-group differences were calculated with adjustments for age, sex, education history, GDS score, and ApoE4 carrier status.

between-group difference ($P = .811$). There were no other adverse events during the study period.

Discussion

In this study, we sought to determine whether a combined cognitive and physical exercise program would have any beneficial effects in older adults with MCI. Our results showed that a 40-week program of weekly combined cognitive and physical activity improved cognitive and physical performance in older adults with MCI and reduced left MTA-ERC atrophy in participants with aMCI.

The combined activity program significantly improved the MMSE and WMS-LM II scores in participants with aMCI, suggesting significant improvements in their cognitive abilities and logical memory. Interestingly, patients with naMCI who participated in the combined activity program exhibited nonsignificant improvements on the RAVLT, which assesses learning and memory. The program yielded significantly improved physical performance and daily physical activity in both MCI subgroups. These findings are consistent with those of our preliminary clinical trial involving a different set of 100 patients with MCI.[14] One systematic review found very limited evidence that exercise improves cognitive function in individuals with MCI,[32] but another review found that cognitive training produces moderate to large benefits in memory-related outcomes.[33] Our results suggest that a composite approach involving muscle strength training, combined aerobic and cognitive exercises, and health behavior education improves cognitive and motor function in older adults with MCI, possibly more than exercise alone does.

Moreover, verbal fluency tests, such as those used here, are among the cognition tests most commonly used in clinical and research settings and help distinguish individuals with normal cognition from those with MCI. They require lexical and semantic retrieval operations and could possibly measure these specific aspects of frontal lobe dysfunction in patients with MCI. Although they do not reliably differentiate MCI from AD,[34] lower scores predict progression from MCI to AD.[35] Here, the combined activity program improved verbal fluency test scores in older adults with MCI more than education alone did, which is consistent with reports in cognitively intact adults.[36] The combined activity program enhanced VFT-letter score gains in patients with either MCI subtype but enhanced VFT-category score gains only in patients with aMCI. We speculate that the discrepancy arose from the VFT-category's semantic memory requirements.

Patients with MCI are at elevated risk for both dementia and noncognitive deficits, including physical disabilities and related adverse health outcomes.[17–19] Improving mobility in seniors, including those with cognitive impairment, reportedly improves function and community ambulation, reduces disability, and increases survival,[37,38] making mobility an important clinically relevant outcome for interventions. Although the program's physical exercise components are well recognized to improve mobility, recent studies have suggested that cognitive enhancement approaches might also improve mobility.[39] Encouragingly, the combined activity program enhanced daily activity levels in patients with either MCI subtype.

The combined activity group's improvements in general cognitive status and memory function are mostly explained by improvements in the patients with aMCI. Older adults with aMCI exhibit greater memory function losses than healthy older adults do.[1,2] Hence, enhancing cognitive function, especially memory, in patients with MCI may delay or prevent progression to AD. The maintenance of MTA-ERC brain volumes in the patients with aMCI who received the combined activity intervention may explain their strengthened memory functions. Hippocampal volume shrinks by 1% to 2% annually in older adults without dementia,[40] and this increases the risk of cognitive impairment.[41] A clinical trial of exercise training showed that hippocampal volume losses in late adulthood are avoidable and reversible with moderate-intensity exercise.[42] The mechanism by which

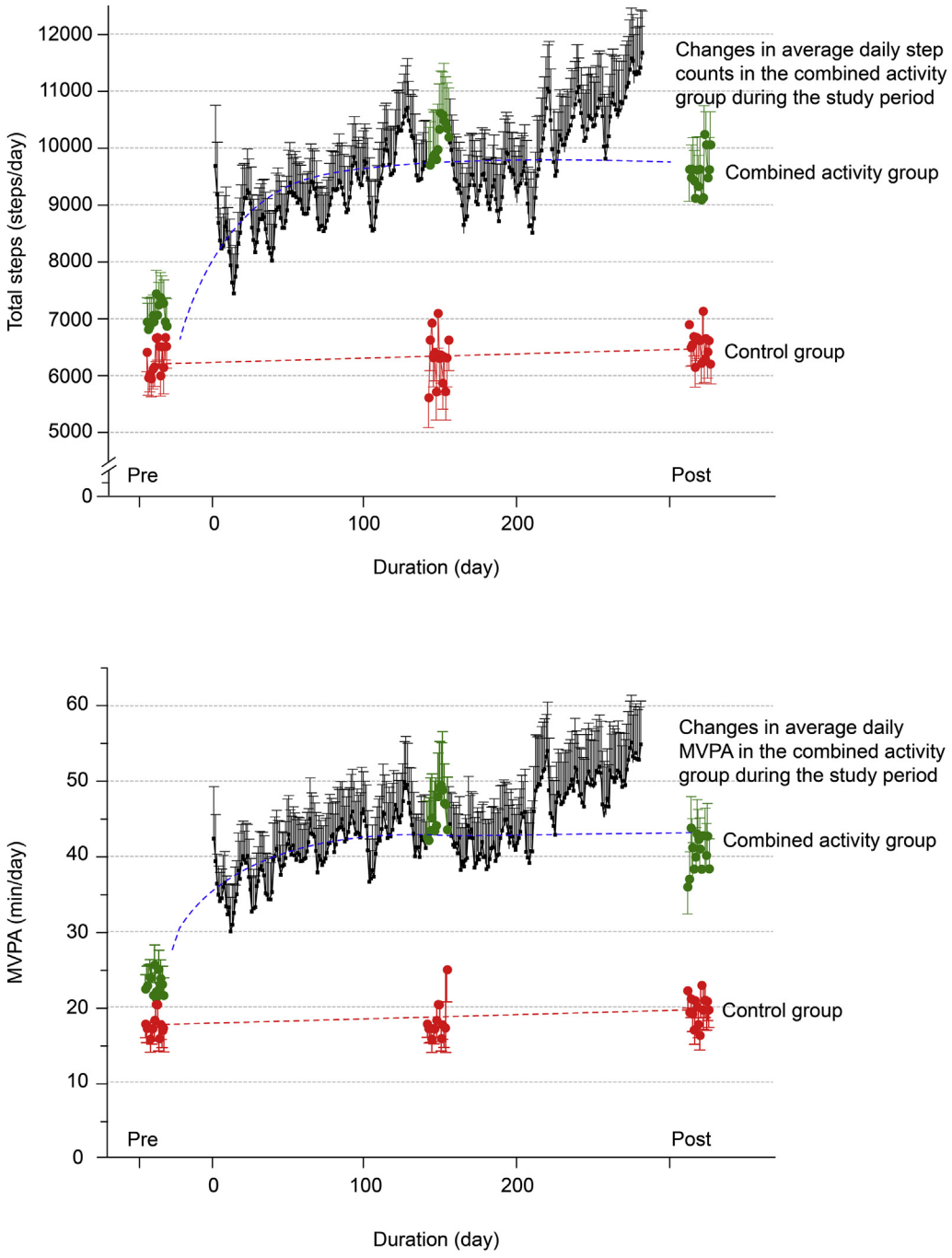

Fig. 3. Physical activity during the intervention period. Mean mobility measures for the combined activity and control groups are indicated in green and red, respectively. Black lines show values obtained from the combined activity group during study period monitoring. The combined activity group wore waist-mounted accelerometers during the intervention period, but the control group wore them only at baseline, midintervention, and postintervention. Error bars indicate SD.

physical and cognitive activities promote brain health is poorly understood, although biological mediators may modulate the effects on cognition. For instance, brain-derived neurotrophic factor[43] is expressed in various brain regions during exercise, most robustly in the hippocampus,[44] and enhances synaptic plasticity, hippocampal function, memory, and learning.[45]

A limitation of this study was that the control group had less interaction with the instructors than the intervention group did.

Conclusion

The results of our controlled trial highlight the beneficial effects of a combined cognitive and physical exercise program in older individuals with MCI especially of the amnestic type. However, a longer-term investigation is necessary to determine whether the combined activity effects are associated with prevention or delayed onset of AD in older adults with MCI.

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