visual memory involved in both encoding and retrieval tasks, and EMCI individuals showed lower performance than the control group in the 3-min task, but not in the 30-min task. This discrepancy in RCFT was likely a result of task difficulty. The degree of task difficulty for cognitive dysfunction subjects (e.g. MCI or AD patients) affects neuropsychological performance, and overly difficult tasks are not useful for assessing these disorders.[34] Digit span performance also differed between tasks in the current study. The DSF and DSB tests evaluate executive function, including attention, and the DSB further requires working memory.[25] These differences might have played a role in the differing results between the two digit span tests.

Verbal fluency assessed the ability to express language and executive function.[25,27,28] The present results were also consistent with the decline of both letter and category fluency, which were observed in LMCI.[32] In addition, the decline of letter fluency occurred in EMCI individuals, whereas category fluency did not differ between control and EMCI subjects, but was different between EMCI and LMCI subjects. These letter fluency and category fluency results show a discrepancy in verbal fluency ability. This discrepancy might be based on the differences of the neuronal requirements of these tasks. Letter fluency is thought to rely on a neural network involving the left prefrontal and inferior parietal cortex, whereas category fluency involves the frontal and temporal regions.[35] Although it is unclear which tasks of letter fluency and category fluency are most useful for detection of MCI, the present results indicate that both letter fluency and category fluency might depend on the severity of memory impairment in aMCI. Although category fluency is generally more frequently impaired in AD, worse letter fluency has also been reported.[35] The present results indicate that impairments of letter fluency may be a characteristic of EMCI. However, the sample size or study design of the present study might have limited the generalizability of these findings. The etiological data confirmed that the decline of cognitive function in aMCI, but not memory, was also a risk for conversion to AD.[10–12] The present results indicate that screening for EMCI should not only involve a verbal memory test, but also measurements of other domains.

The correlation analysis shows characteristics of cognitive function in EMCI. A variety of executive functions, including verbal fluency and DSB performance, were associated with logical memory in the EMCI group. However, there was no significant relationship in the LMCI group. These results remained after controlling for age and sex. Many neuroimaging studies have shown that memory impairment in aMCI and AD is induced by structural and functional changes in the MTL region.[6,8,9] Activation in the MTL region during MCI transforms from hyperactivation to hypoactivation according to the severity of cognitive function during the progression of MCI to AD, and hyperactivation in the MTL confirms a functional compensatory mechanism in very early MCI.[5,6] This compensation might occur as a result of an abnormal functional connectivity or network within the brain.[13–16] Activation of the MTL alone is not sufficient for successful memory function, and the MTL region shows strong connectivity with the cingulate cortex and frontal lobe within the memory network, which is decreased in aMCI and AD.[13,17,36] DSB performance has been found to activate the frontal lobe,[37] whereas verbal fluency tests activate in the prefrontal lobe, parietal lobe, frontal lobe and temporal lobe.[38,39] Additionally, the frontal lobe is a key region involved in human memory processing. Large cortico-cortical direct reciprocal connections exist between the frontal lobe and the MTL.[40] The characteristic relationship between logical memory and a part of executive function in EMCI patients might be caused by a functional abnormality in the brain network. Further studies should be carried out to confirm this hypothesis, using neuroimaging methods, such as functional magnetic resonance imaging.

Several limitations of the current study must be considered. First, the sample size was relatively small, introducing potential difficulties in avoiding heterogeneity in the MCI subjects. Second, the study was cross-sectional. The association between memory function and other cognitive domains should be investigated in prospective and neuroimaging studies. MCI is a reversible state in the spectrum of normal aging-MCI-AD. Clarifying the characteristics of cognitive function in EMCI during conversion to AD is important, and requires a longitudinal study. Finally, the present study did not include data involving apolipoprotein E ε4, amyloid status and cerebrospinal fluid biomarkers. These limitations should be taken into consideration when interpreting the current findings.

In conclusion, elderly adults with MCI showed deterioration not only in memory, but also in executive function, and the memory decline corresponded with poorer performance in executive function. The present preliminary results show that comprehensive assessments that include memory and executive functions might be required to distinguish elderly adults with MCI from cognitively normal elderly adults. Future research is required to determine appropriate neuropsychological tests for predicting the conversion of EMCI and LMCI to AD.

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Disclosure statement

The authors have no financial or any other kinds of conflicts with this paper.

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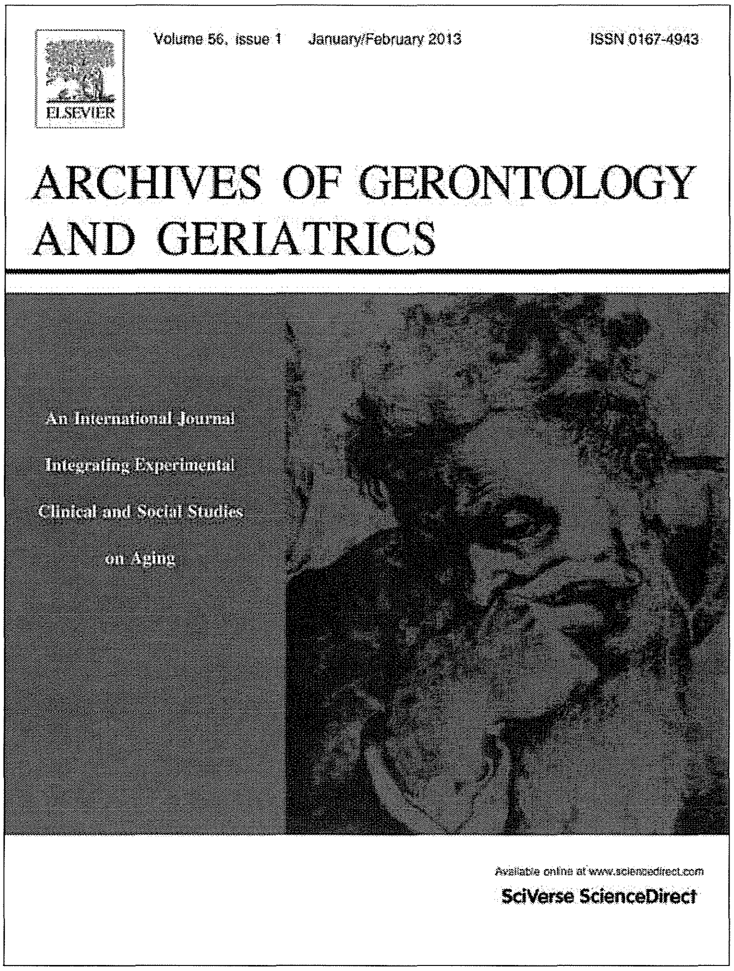
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Effects of multicomponent exercise on spatial–temporal gait parameters among the elderly with amnestic mild cognitive impairment (aMCI): Preliminary results from a randomized controlled trial (RCT)☆

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ABSTRACT

Exercise training has been shown to increase physical function in the elderly. However, the effects of exercise on elderly individuals with amnestic aMCI are unclear. The aim of this RCT was to investigate the effect of multicomponent exercise on gait in the elderly. Fifty elderly individuals with aMCI (age: 65–92 years) participated in the study and were randomly allocated to a multicomponent exercise or control group. Multicomponent exercise training was performed for 90 min, twice a week over six months. Gait was analyzed at baseline and after the six month intervention. Gait analysis was performed on an eleven meter walkway at each subject's comfortable walking speed. A miniature tri-axial accelerometer was attached to the L3 spinous process and was used to analyze gait speed, stride length, stride time, and the harmonic ratio (HR) (representing the smoothness of trunk movement). There were no differences in the participant characteristics or gait parameters between the groups at baseline. After adjustment for covariates the multicomponent exercise program had a significant ($p < 0.05$) effect on gait speed, stride length, and the vertical HR. Through improving gait, multicomponent exercise training improves the physical health of the elderly with aMCI.

1. Introduction

Worldwide, AD is one of the most important health issues and is therefore the focus of numerous research projects investigating the impact of interventions for preventing the progression of the disease (Ballard et al., 2011). MCI is considered a prodromal AD (Petersen, 2004; Winblad et al., 2004) and aMCI, in particular, is likely to convert to AD (Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006). Early detection of MCI and treatment interventions are important components of an AD prevention strategy (Albert et al., 2011). The decline of cognitive function is a dominant characteristic in MCI, while cognitive function is associated with physical activity or performance. Epidemiological studies demonstrated that reduced physical activity, including walking, was a risk factor for cognitive decline and dementia (Abbott et al., 2004; Weuve et al., 2004), and that motor dysfunction among people with MCI was a risk for progression to AD (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2006). In addition, poor gait performances were a feature among older adults with MCI (Gillain et al., 2009; Muir et al., 2012), aMCI (Beauchet et al., 2011; Verghese et al., 2008) and AD (Allan, Ballard, Burn, & Kenny, 2005; Nadkarni, Mawji, McIlroy, & Black, 2009), and a risk factor for cognitive decline (Buracchio, Dodge, Howieson, Wasserman, & Kaye, 2010; Deshpande, Metter, Bandinelli, Guralnik, & Ferrucci, 2009; Verghese, Wang, Lipton, Holtzer, & Xue, 2007).

Exercise training is an intervention that enhances physical function among the elderly. A systematic review revealed that exercise training enhances physical function, including gait, among the elderly (Howe, Rochester, Jackson, Banks, & Blair, 2007). The positive effect of exercise training on physical performances among elderly individuals, even with cognitive impairments was confirmed in a meta-analysis (P. Heyn, Abreu, & Ottenbacher, 2004; P.C. Heyn, Johnson, & Kramer, 2008). However, the meta-analysis indicated limitations in previous

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research. These included the examination of various degrees of cognitive impairment in the same study, for example, mild, moderate, and severe impairment, as well as the use of several designs of study, for example, RCT or no-RCT. Another review concluded that exercise interventions had a limited effect on physical performance (Hauer, Becker, Lindemann, & Beyer, 2006). A recent exercise training RCT reported improvements in gait among elderly individuals with dementia (Hauer et al., 2012), but limited effects on mobility among individuals with MCI (Varela, Ayan, Cancela, & Martin, 2011). Whether exercise training has positive effects on physical performances, particularly gait, among MCI is unclear. Maintenance of gait ability was shown to have beneficial effects on several health conditions as well as survival rate among the elderly (Studenski et al., 2011). In addition, walking was the dominant activity performed by the elderly and gait ability was directly related with level of physical activity (Eyler, Brownson, Bacak, & Housemann, 2003). Lower physical activity was a major risk factor for cognitive decline (Sofi et al., 2011), as well as lower gait ability (Buracchio et al., 2010; Deshpande et al., 2009; Verghese et al., 2007). Improving gait ability may play an important role in the promotion of health in elderly individuals with MCI.

The aim of this RCT was to investigate the effects of multicomponent exercise on gait in the elderly with aMCI. The reason for examining this elderly group was because longitudinal studies have suggested that patients with aMCI are more likely to progress to AD compared with patients who have non-amnestic MCI (Yaffe et al., 2006). The multicomponent exercise program included aerobic exercise, muscle strength training, walking training, and postural balance retraining, because previous reviews have suggested that multiple exercise interventions improve mobility among older adults (Howe, Rochester, Neil, Skelton, & Ballinger, 2011). Gait ability was assessed using trunk acceleration data that was acquired from miniature sensors that are feasible for use in a clinical setting (Kavanagh & Menz, 2008).

2. Materials and methods

2.1. Participants and study design

The study was a RCT conducted over six months. Participants were allocated to a multicomponent exercise intervention group (MEG; $n = 25$) or a control group (CG; $n = 25$). The allocation occurred after completion of all baseline testing. The study protocol was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All subjects gave written, informed consent before participating in the study.

An initial 1543 subjects were recruited for the study from two volunteer databases using either random sampling or when they attended a medical check-up in Obu, Japan. The flow of the study is shown in Fig. 1. Assessments to determine eligibility for the study included cognitive and physical performances tests. Inclusion criteria for the study were that the participant was 65 years and older, had sufficient hearing and visual acuity to participate in the examinations, and met the conditions of aMCI. The criterion of aMCI, using the most international consensus criteria (Petersen, 2004), are summarized as follows; living independently in the community (i.e., no impairment of activities of daily living), to be intact in general cognitive function, Mini-Mental State Examination (MMSE) scores between 24 and 30 (Folstein, Folstein, & McHugh, 1975), and having memory impairment (assessed via education-adjusted scores on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II) (Wechsler, 1987). Exclusion criteria included a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses. After eligibility assessments, 68 subjects did not meet the criteria (29 subjects were non-aMCI, 21 subjects did not complete all the assessments of eligibility 2, and 18 subjects did not meet the inclusion criteria other than the type of MCI), five subjects had medical problems that did not allow them to participate in the study, and 12 subjects refused to participate. Finally, 50 participants (age: 65–92 years, women: $n = 23$, 46%)

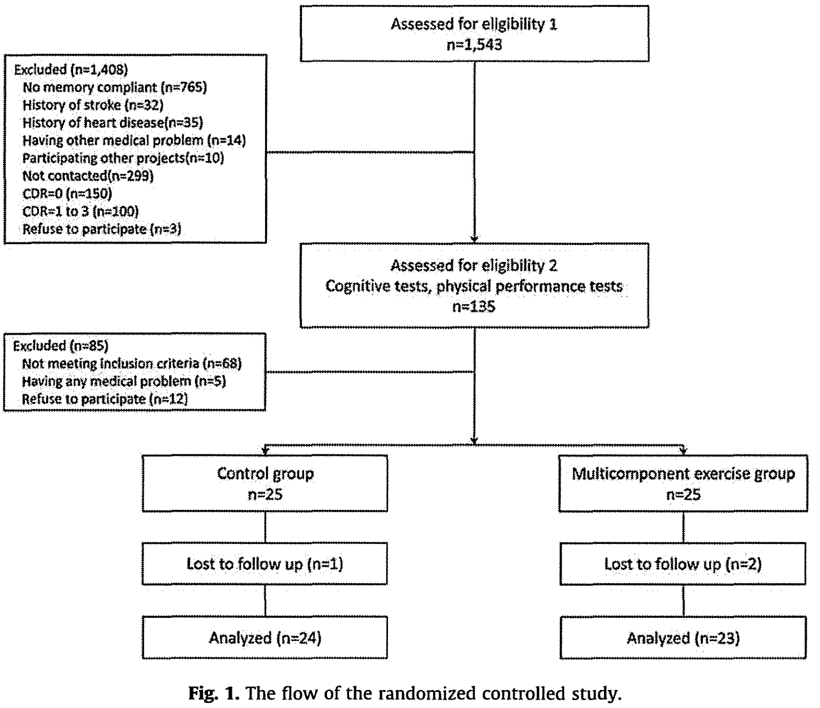

Fig. 1. The flow of the randomized controlled study.

satisfied the inclusion criteria and were allocated to either the MEG or CG.

2.2. Intervention

The six-month, multicomponent exercise program, consisted of 90-min sessions performed twice a week. The sessions included combinations of aerobic exercise, endurance walking, muscle strength training, postural balance retraining, and gait training. The average intensity of the aerobic exercise was 60% of aged-predicted maximal heart rate. Heart rate was monitored during the aerobic sessions using portable heart rate monitors (Pulse Plus, TRYTECH Co. Ltd., Tokyo, Japan). Eleven of the 40 classes during the six month intervention period included 20–30 min of consecutive outdoor walking. Postural balance exercises, such as tandem walking and side walking on balance boards, were also included in the sessions. Gait training was conducted at the same intensity as the aerobic exercise and included dual-task walking, e.g., walking whilst conducting a conversation or creating a poem. For the ladder training exercise, subjects learned to step into consecutive square segments, and were instructed to step as quickly and accurately as possible. In addition, participants performed combined exercises, e.g., circuit training including stair stepping, ladder training and endurance walking. The exercise program also included a focus on promoting exercise and behavior change. Two trained physiotherapists, with geriatric rehabilitation experience, supervised and conducted the sessions.

Each session began with a 10 min warm-up period that included dynamic and static stretching, followed by 20 min of strength training and then combinations of aerobic exercise, gait training, postural balance training for an additional 60 min. The participants were provided with an exercise and physical activity logbook and were required to perform and record daily home-based exercises and walking. To promote exercise and behavior change, the subjects were required to self-monitor their own physical activity levels using a pedometer. Participants in the CG attended two education classes about health promotion during the six month study period. The class provided information regarding healthy diet, oral care, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

2.3. Outcome measures

Participants were checked before each gait assessment to ensure that they were wearing appropriate size shoes. The assessment required the subjects to walk at their preferred speed on an 11-m smooth, horizontal walkway. The walkway had a two meter space at either end that allowed for acceleration and deceleration. The mid five meter walking time was measured, and gait speed was expressed in meters per second. A tri-axial accelerometer (sampling rate: 200 Hz; MVP-RF8, MicroStone, Nagano, Japan) was attached to the L3 spinous process using a belt and surgical tape. This apparatus set-up was described in detail in a previous study (Doi et al., 2012). Before measurement proceeded, the accelerometer was calibrated statically against gravity. After analog to digital transformation, signals were immediately transferred to a laptop PC (Let's Note CF-W5, Panasonic, Osaka, Japan) via a Bluetooth Personal Area Network. The working range of the accelerometer to the PC was approximately 50 m. Signal processing was performed using commercially available software (MATLAB, Release 2008b, The MathWorks Japan, Tokyo, Japan). The person processing the acceleration data was blinded to any other results. Before analysis, all acceleration data were low pass filtered (dual pass zero lag Butterworth filtered) with a cutoff frequency of 20 Hz. Stride time was recorded as the interval from an initial contact event to the next ipsilateral event. The mean stride time was calculated from five consecutive stride times. This method of determining stride time was validated previously (Zijlstra, 2004). The average stride length was determined by multiplying gait speed by mean stride duration. The HR was used to evaluate the smoothness and stability of trunk movement during gait, and the procedure for calculating HR was reported elsewhere (Menz, Lord, & Fitzpatrick, 2003; Yack & Berger, 1993). Higher HR values indicated greater stability during walking. HR was computed separately in each direction (vertical direction: VT, mediolateral direction: ML and anteroposterior direction: AP) using digital Fourier transformations.

2.4. Statistical analysis

All analyses were performed using commercially available software, IBM SPSS statistics software (Version 19; SPSS Inc., Chicago, IL, USA). The spatial–temporal gait parameters data were found to be normally distributed. The baseline spatial–temporal gait parameters for each group were compared using *t*-tests. A multivariate repeated measure analysis of variance was used to determine between group differences relating to the intervention effect, for each gait parameter, adjusting for sex and gait speed, thought to be potential confounders for the majority of the spatial–temporal gait parameters. However, for gait speed, only sex was the factor adjusted in the analysis. Statistical significance was set at $p < 0.05$ a priori.

3. Results

Of the 50 individuals enrolled in the study, 47 (94%) completed the six month follow-up and complete assessment after the intervention (24 in the MEG (96%) and 23 in the CG group (92%)). Mean adherence to the exercise program in the MEG, for the 24 participants, was 86.9%, and 19 participants displayed a greater than 80% adherence to the exercise program.

There were no significant differences ($p > 0.05$) in subject characteristics between the two groups at baseline (Table 1). Table 2 shows the results of the gait analyses at baseline and after the intervention. There were no significant differences in the gait variables between the two groups at baseline. Gait speed and stride length were increased, and stride time was shortened in both groups, after the intervention period (gait speed: $p < 0.001$, stride time: $p < 0.001$ stride length: $p < 0.001$). HR in VT was significantly improved in the MEG (VT: $p < 0.01$), while there were no significant

Table 1
Characteristics of the control and exercise groups.

	Mean (SD)	
	CG (n = 25)	MEG (n = 25)
Age, years	76.8 (6.8)	75.3 (7.5)
Men, No. (%)	14 (56.0)	13 (52.0)
Educational level, years	10.8 (2.7)	11.1 (2.4)
Diagnosis, No. (%)		
Hypertension	11 (46)	13 (52)
Heart disease	0 (0)	2 (8)
Diabetes Mellitus	3 (12)	5 (20)
Medication, 3 and over	11 (46)	10 (40)
IADL subscale of TMIG index, score	4.9 (0.3)	5.0 (0.2)
Cognitive functions		
MMSE, score	26.6 (1.6)	26.8 (1.8)
Logical Memory IIA, score	3.3 (2.7)	4.0 (2.6)

Values are numbers (proportion). IADL subscale of TMIG index = instrumental activities of daily living subscale of Tokyo Metropolitan Institute of Gerontology index.

Table 2
Effects of intervention on spatial–temporal gait parameters.

Gait parameters	Mean (SD)				Mean differences (95% CI)		Group × Time[a]	
	Baseline		After intervention		Change after intervention			
	CG	MEG	CG	MEG	CG	MEG	F	p
Gait speed	1.10 (0.20)	1.10 (0.32)	1.26 (0.21)	1.38 (0.32)	0.16 (0.10, 0.22)	0.28 (0.18, 0.38)	4.629	0.037[b]
Stride time	1.02 (0.10)	1.04 (0.11)	0.96 (0.08)	0.96 (0.09)	−0.06 (−0.08, −0.04)	−0.08 (−0.11, −0.04)	1.262	0.268
Stride length	1.12 (0.15)	1.13 (0.31)	1.20 (0.17)	1.31 (0.28)	0.09 (0.04, 0.13)	0.18 (0.11, 0.24)	7.085	0.011
HR-VT	3.04 (0.65)	2.63 (0.88)	3.05 (0.64)	3.15 (0.88)	0.01 (−0.30, 0.33)	0.52 (0.19, 0.84)	5.272	0.027
HR-ML	2.06 (0.60)	2.11 (0.67)	2.21 (0.61)	2.32 (0.79)	0.15 (−0.05, 0.36)	0.20 (−0.05, 0.46)	0.110	0.741
HR-AP	3.32 (0.83)	2.89 (1.03)	3.43 (0.71)	3.34 (1.03)	0.12 (−0.35, 0.58)	0.45 (−0.004, 0.90)	1.163	0.287

CI, confidential interval.
[a] This is the interaction effect (group × condition) using a multivariate repeated measure analysis of variance. The value of the gait variables were analyzed at baseline and after intervention using a multivariate repeated measure analysis of variance, adjusting for sex and gait speed as covariances.
[b] Adjustment for sex as a covariance against gait speed.

changes in HR in the CG in all directions. In a multivariate repeated measure analysis of variance, multicomponent exercise was associated with significant group differences in gait speed and stride length, but not stride time (gait speed: $F = 4.629$, $p = 0.037$; stride length: $F = 7.085$, $p = 0.011$), and HR in VT ($F = 5.272$, $p = 0.027$).

4. Discussion

The primary finding of our study was that a multicomponent exercise program improved gait ability among elderly individuals with aMCI. Multicomponent exercise improved gait speed, stride length, and trunk smoothness during gait, but not stride time.

This is the first study to demonstrate that an exercise program improves gait ability among elderly individuals with aMCI. Previously, age-related changes and physical functional decline were shown to decrease gait ability (Menz et al., 2003). The maintenance of gait ability was beneficial for several health conditions among the elderly (Studenski et al., 2011). In addition, lower gait ability was a risk factor for cognitive decline or dementia (Buracchio et al., 2010; Deshpande et al., 2009; Verghese et al., 2007), and a feature among older adults with aMCI (Beauchet et al., 2011; Verghese et al., 2008) and AD (Allan et al., 2005; Nadkarni et al., 2009), although the characteristic gait variables most likely to be affected in cognitively impaired individuals remains unclear. The improvement of gait ability in individuals with aMCI may have a crucial role not only for functional improvements, but also for decreasing the risk of progression to AD. Furthermore, multicomponent exercise could improve trunk smoothness during gait. Trunk movement control during gait has a crucial role for successful locomotion among the elderly. Age-related deficits or having increased fall risk was associated with decreased trunk smoothness during walking (Menz et al., 2003; Yack & Berger, 1993). Additionally, cognitive impairment was one of the major fall risks and falling incidents are a serious health problem among older adults with or without cognitive impairment (Ganz, Bao, Shekelle, & Rubenstein, 2007). Therefore, enhanced trunk smoothness may contribute to successful locomotion and be important for the elderly with aMCI.

Exercise training was shown to improve physical performances among cognitively impaired elderly individuals (P. Heyn et al., 2004; P.C. Heyn et al., 2008). However, there were several limitations of these studies, including the study sample or design of the RCT. These may have masked the benefits of exercise in for the cognitive impaired study populations (Hauer et al., 2006). Varela et al. (2011) performed a RCT study on MCI subjects and showed that aerobic exercise at different intensities did not have a significant effect on physical performance, compared to recreational therapy. In contrast, the training in the present study consisted of numerous modes of exercise in addition to aerobic exercise. In a RCT, Hauer et al. (2012) reported beneficial effects of combined physical training on motor performances, including gait ability, among individuals with dementia. The intervention was a combination of several types of training, including resistance and functional motor training as well as walking. Our results therefore support the findings of previous studies that reported positive effects of combined exercise training on physical performance, suggesting that multicomponent exercise training could improve gait ability among individuals with aMCI.

A systematic review concluded that multidimensional exercise interventions had beneficial effects on physical function such as gait ability (Howe et al., 2007). However, the content of programs and the exercise modality used varied across studies. The multicomponent exercise program developed in the present study also included gait training that may have played an important role in improving physical function, in particular the gait ability of the subjects. In addition, exercise training or enhanced physical activity has been shown to have several neuroprotective effects (Kaliman et al., 2011), and engaging in physical exercise is associated with reduced biomarkers of AD pathology, i.e., low level of Pittsburgh compound-B and cerebrospinal fluid Aβ42 (Liang et al., 2010). Therefore, a multicomponent exercise program may be a useful intervention for promoting health among elderly individuals with MCI.

There was a high level of adherence to the exercise program in the present study (mean adherence was 86.9%). This value is comparable to, as well as better than, previous exercise intervention studies on elderly individuals with MCI (Baker et al., 2010; Lautenschlager et al., 2008) or AD (Hauer et al., 2006, 2012). Only a few participants (three out of 50 participants) dropped out due to individual medical problems or refusal to participate. The exercise program was shown to be safe and no injuries were reported. Therefore the exercise program is feasible and can be supervised by physiotherapists. It is also associated with a low drop-out rate and is safe.

Our study had several limitations. First, this is a preliminary study and no follow-up data was collected after the initial post-intervention testing was performed. Second, the participants were limited to aMCI to avoid heterogeneity. To generalize the effects of multicomponent exercise among elderly with cognitive impairments, the investigation among other types of MCI, i.e., non-aMCI, or AD should be investigated further. A previous study reported that different intensities of aerobic exercise had no significant effects on individuals with MCI (Varela et al., 2011). Future research should investigate the effects of different combinations of duration and/or intensity of exercise interventions to determine the most beneficial exercise training for elderly individuals with aMCI. Additionally, methodology used in gait analysis using an accelerometer is variable in previous studies, with variations in the length of walkway, amount of data, and/or sampling rate used. Further study is required to determine the optimal methodology to evaluate the effects of intervention on gait. Finally, outcomes other than gait ability, such as the health benefits of increasing physical activity, should be investigated among elderly individuals with MCI.

5. Conclusions

In conclusion, a multicomponent exercise program had positive effects on gait ability, including trunk smoothness during walking, among elderly individuals with aMCI. Additional studies are required to clarify the effects of exercise training on gait ability including the control of trunk movement.

Conflicts of interest

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

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Clinical Interventions in Aging

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ORIGINAL RESEARCH

Cognitive function affects trainability for physical performance in exercise intervention among older adults with mild cognitive impairment

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Background: Although much evidence supports the hypothesis that cognitive function and physical function are interrelated, it is unclear whether cognitive decline with mild cognitive impairment influences trainability of physical performance in exercise intervention. The purpose of this study was to examine the association between cognitive function at baseline and change in physical performance after exercise intervention in older adults with mild cognitive impairment.

Methods: Forty-four older adults diagnosed with mild cognitive impairment based on the Peterson criteria (mean age 74.8 years) consented to and completed a 6-month twice weekly exercise intervention. The Timed Up and Go (TUG) test was used as a measure of physical performance. The Mini-Mental State Examination (MMSE), Trail Making Test Part B, Geriatric Depression Scale, baseline muscle strength of knee extension, and attendance rate of intervention, were measured as factors for predicting trainability.

Results: In the correlation analysis, the change in TUG showed modest correlations with attendance rate in the exercise program ($r = -0.354$, $P = 0.027$) and MMSE at baseline ($r = -0.321$, $P = 0.034$). A multiple regression analysis revealed that change in TUG was independently associated with attendance rate ($\beta = -0.322$, $P = 0.026$) and MMSE score ($\beta = -0.295$, $P = 0.041$), controlling for age and gender.

Conclusion: General cognitive function was associated with improvements in physical performance after exercise intervention in subjects with mild cognitive impairment. Further research is needed to examine the effects of exercise programs designed to address cognitive obstacles in older adults with mild cognitive impairment.

Keywords: exercise, mobility, rehabilitation, Timed Up and Go test

Introduction

Mild cognitive impairment is widely regarded as a transitional syndrome between normal cognitive ageing and clinical dementia.[1] Deterioration in episodic learning and memory functions constitute the core characteristics of mild cognitive impairment and Alzheimer's disease. Older adults with mild cognitive impairment demonstrate decreased physical performance, which in turn is related to the risk of Alzheimer's disease.[2] Reduced physical function leads to restricted life space mobility,[3] which is associated with increased risk of Alzheimer's disease and cognitive decline among older persons.[4] Improved usual gait speed over a 12-month period predicts a substantial reduction in mortality.[5] Maintaining and improving physical function may be beneficial for preventing conversion to Alzheimer's disease in older adults with mild cognitive impairment.

A better understanding of the modifiable factors independently associated with improved physical performance is needed.[6] This would ensure effective intervention

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based on a valid theoretical framework for increasing physical performance. Possible modifiable factors include cognitive function, mental status, and physiological function, such as muscular strength. Logsdon et al[7] found that older adults with mild cognitive impairment may benefit significantly from an exercise program specifically designed to address their cognitive needs (ie, memory aids and easy to follow instructions). They suggest that cognitive impairment may prevent successful engagement in exercise. Several studies support the hypothesis that cognitive and physical function are interrelated,[2,8] although it is not clear whether older adults with mild cognitive impairment have decreased trainability for improving physical performance.

The purpose of this study was to examine the association between cognitive function at baseline and trainability of physical performance using a 6-month exercise intervention in older adults with mild cognitive impairment. We used the Timed Up and Go test (TUG) as an assessment of physical performance.[9] This test has frequently been used to assess lower extremity function, mobility, and risk of falls in older adults. Recent research has revealed that TUG is associated with executive function[8] and periventricular leukoaraiosis[10] in older adults with mild cognitive impairment. Changes in TUG before and after intervention were measured as the dependent variable. In the present study, we defined trainability as the ability to be trained and this was expressed by rate of improvement between before and after intervention.[11] By means of correlation and regression analysis, we examined how cognitive function at baseline influenced change in TUG. Other factors including depression, attendance rate, and physiological function (such as muscle strength) were also investigated. Similar to the relationship between physical and cognitive function,[2,8] it is also possible that improvements in physical performance are associated with cognitive function, where cognitive impairment may prevent successful engagement in exercise.

We hypothesized that reduced cognitive functioning affects trainability of physical performance by exercise intervention in older adults with mild cognitive impairment. This investigation is critical for the exploration of the modifiable factors associated with trainability in order to plan future rehabilitation programs that prevent deterioration of physical and cognitive function.

Materials and methods

Subjects

The participants were recruited from two volunteer databases (n = 1543), which included elderly participants aged 65 years and over who either attended a health check in Obu, Japan, or were selected by stratified random sampling. The strata used in our stratified random sampling were age and gender. Criteria for inclusion in this intervention study required that participants were 65 years or older, living independently in the community (ie, no impairment of activities of daily living), and Japanese-speaking, with sufficient hearing and visual acuity to participate in the examinations. In the first eligibility assessment for this study, 528 potential participants who had either a Clinical Dementia Rating of 0.5 or subjective memory complaints were screened. One hundred and thirty-five participants met the criteria for the second eligibility assessment. They also needed to meet the Peterson criteria for a diagnosis of mild cognitive impairment.[1] The final sample consisted of 44 older adults (mean age 74.8 years; 20 males; mean years of education, 11.1 years). These participants were exposed to an exercise intervention and they completed a randomized controlled trial that aimed to examine the effect of multicomponent exercise on cognitive function. The design and the primary results of the study have been reported elsewhere.[12]

Exclusion criteria included a history of major psychiatric illness (eg, schizophrenia or bipolar disorder) and other serious neurological or musculoskeletal diagnoses. This study was approved by the ethics committee of National Center for Geriatrics and Gerontology, Japan. Appropriate written informed consent was obtained for all participants.

Procedures

The 6-month exercise program involved biweekly 90-minute sessions with a combination of aerobic exercise, muscle strength training, and postural balance retraining. In addition, the exercise program focused on promoting exercise and behavior change. Two trained physiotherapists involved in geriatric rehabilitation conducted the interventions. Each supervised session began with a 10-minute warmup period and stretching exercise, followed by 20 minutes of muscle strength exercise. The participants then practiced aerobic exercise, postural balance retraining, and a combination of both activities over a period of 60 minutes.

Before and after each session of the program, physiotherapists conducted a health check of each participant. The physiotherapists and a well trained instructor implemented risk management for adverse events during the program. In the aerobic exercise, participants performed stair stepping and endurance walking. The intensity of the aerobic exercise was prescribed at approximately 40% of maximum heart rate during weeks 1–8. The intensity was then increased to 60% of maximum heart rate from week 9. Heart rate was measured before and after exercise at every training session for risk management and estimation of the strength of training. The strength of aerobic exercise was adjusted by the height of the stair in stair stepping, walking speed, or weights put on participants' feet in endurance walking. Eleven of the 40 classes during the 6-month intervention period included approximately 20–30 minutes of consecutive outdoor walking. Muscle strength training was mainly performed using subjects' own weight; training equipment was not used (eg, knee extension, calf raise, squat). Postural balance exercise (such as tandem walking and side walking on balance boards) was also included in the program. There were five different widths of balance boards (4, 6, 8, 10 and 12 cm), which were narrowed progressively. Further, participants performed a combination of exercises (eg, circuit training including stair-stepping, endurance walking, and walking on balance boards). They also performed concurrent cognitive tasks during exercise (eg, walking while inventing a poem) because effects of dual tasks on brain activation have been reported.[13] Between individual training sessions, participants were invited to sit and rest for about 5 minutes. Participants were required to perform daily home-based muscle strength exercises and walking. These were self-monitored using a booklet and pedometer based on the concept of promoting exercise and behavior change.

Physical performance test to assess trainability

The TUG was used to assess physical performance.[9] The TUG involves rising from a chair, walking 3 meters, turning around, walking back to the chair, and sitting down. Participants were instructed to complete the task at their usual walking pace. The score for this test represents the time (in seconds) that the participant needed to complete the assessment. Lower times indicate better physical performance. The recorded TUG score was the lesser of the times measured in the two trials in order to exclude immediate change by learning effects from the measured value.[14] Licensed and well-trained physical therapists assessed the physical performance tests. Interrater reliability of TUG is very high in community-dwelling older adults (intraclass coefficient of 0.98).[15] Changes in TUG were calculated as trainability using the following formula:

(Post score – pre score)/pre score.[11]

Thus, a higher negative value represents greater improvement by exercise intervention.

Potential correlates

All measurements were performed before the intervention commenced. Demographic data were recorded, including age, gender, number of medications, and educational history. Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).[16]

All neuropsychological testing was conducted by well trained speech therapists. Each score was rechecked by one therapist who was blinded to all other participant data. General cognitive function was assessed with the Japanese version of 30-item Mini-Mental State Examination (MMSE),[17] the most frequently used cognitive screening measure in cognitive aging research, with good test-retest reliability (intraclass coefficient = 0.827).[18,19] Executive function was assessed using the Trail Making Test Part B (TMT-B).[20] For this task, participants were required to navigate a series of alternating numbers and letters, and connect them in alternating sequential order. In the Japanese version of the TMT-B, letters from the Roman alphabet are exchanged for Kana characters.[21] The time required to complete each task was recorded, where a higher time indicates a poorer performance. The TMT-B has demonstrated adequate test-retest reliability for use in longitudinal studies.[21]

The participants' muscle strength of knee extension was measured twice using a dynamometer (MDKKS, Molten Co, Ltd, Tokyo, Japan). The recorded strength score was the higher of the strength measurements (Nm/kg) in the two trials.[22]

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences version 19.0 for Windows (SPSS Inc, Chicago, IL). A probability level of $P < 0.05$ was considered to be statistically significant. Data were expressed as mean values and standard deviations. TUG scores were compared before and after intervention using the paired Student's t-test. The relationships between change in TUG score and potential correlates (measurements at baseline and attendance rate for exercise intervention) were investigated using Pearson's correlation. A stepwise multivariate linear regression model was used to examine whether potential predictors were independently associated with the change in TUG. Age, gender, and other variables that were significantly correlated with change in TUG were entered as independent variables.

Results

Table 1 shows the demographic and baseline clinical characteristics and attendance rate of the study participants. Mean adherence to the exercise program was 88.2%. TUG showed significant ($P < 0.001$) improvement between before

Table 1 Demographic and clinical characteristics of study participants

Age (years)	74.8 ± 7.3 (65–93)
Education (years)	11.1 ± 2.9
Gender (males)	20 (48)
Medications (n)	2.6 ± 2.3
MMSE (points)	26.9 ± 2.3
GDS (points)	3.7 ± 2.9
TMT-B (seconds)	174.9 ± 75.3
Muscle strength of knee extension (Nm/kg)	1.19 ± 0.4
TUG (seconds)	8.6 ± 1.9
Attendance rate (%)	88.2 ± 19.2

Note: values presented are the mean ± standard deviation or n (%).
Abbreviations: MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; TMT-B, Trail Making Test Part B; TUG, Timed Up and Go test.

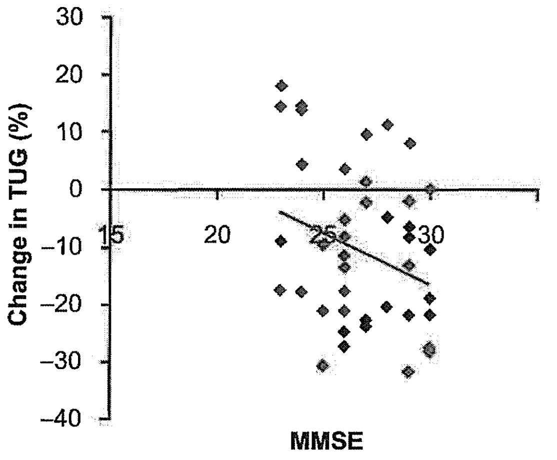

Figure 1 Scatter graph showing the relationship between change in Timed Up and Go test and Mini-Mental State Examination scores.
Abbreviations: MMSE, Mini-Mental State Examination; TUG, Timed Up and Go test.

and after intervention (8.6 ± 1.9 versus 7.6 ± 2.1 seconds, respectively). In the correlation analyses (Table 2), the change in TUG had significant negative correlations with attendance rate ($r = -0.354$, $P = 0.027$) and MMSE ($r = -0.321$, $P = 0.034$; Figure 1). The change in TUG was not correlated with age ($r = 0.146$, $P = 0.35$), TMT-B ($r = 0.202$, $P = 0.19$), GDS ($r = 0.03$, $P = 0.85$), or muscle strength of knee extension ($r = -0.236$, $P = 0.12$).

Table 3 shows the factors that were significantly related to change in TUG in the stepwise multiple regression. The regression model explained 24% of the change in variance of TUG. The factors retained in the final model were attendance rate ($\beta = -0.322$, $P = 0.026$) and MMSE ($\beta = -0.295$, $P = 0.041$). Age and gender did not show a significant relationship with change in TUG.

Discussion

Exercise intervention was considered beneficial for older adults with mild cognitive impairment in the present study, and we showed a significant improvement in physical performance between before and after intervention. However, investigation of the association between physical performance and other variables revealed that improvement in physical performance after exercise intervention depended on general cognitive function, as assessed by the MMSE, in addition to attendance rate. Generally, it has been reported that exercise intervention in older adults improves physical performance, such as gait speed,[23] dynamic balance,[24] and cardiovascular fitness.[25] Previous studies targeting older adults with Alzheimer's disease or dementia have reported larger improvements in TUG (approximately 41%)[26–28] than those reported in the present study (8.6%); however, we targeted relatively healthy older adults with better physical function at baseline. This is the first study to focus on baseline cognitive function and the trainability of physical performance in older adults with mild cognitive impairment.

The results of the present study indicate that general cognitive function may be important for persons with mild cognitive impairment to gain benefit from an exercise intervention. Previous studies support the relationship between cognitive and physical function.[2,8] Therefore, general cognitive function may provide an important basis for improvement in physical performance, particularly in older adults with mild cognitive impairment. It is possible

Table 2 Correlation coefficients for potential correlates and change in TUG

Potential correlates	Change ratio in TUG Correlation coefficient	
	R	*P* value
Age	0.146	0.35
MMSE	−0.321	0.034
GDS	0.03	0.85
TMT-B	0.202	0.19
Muscle strength of knee extension	−0.236	0.12
Attendance rate	−0.354	0.027

Abbreviations: MMSE, Mini-Mental State Examination; TUG, Timed Up and Go test; GDS, Geriatric Depression Scale; TMT-B, Trail Making Test Part B.

Table 3 Factors associated with improved TUG in stepwise multiple regression

	Factors	β	*P* value	R^2
Change ratio in TUG	Attendance rate	−0.322	0.026	0.24
	MMSE	−0.295	0.041	

Abbreviations: TUG, Timed Up and Go test; MMSE, Mini-Mental State Examination.

that persons with mild cognitive impairment may experience several cognitive obstacles, such as difficulties in learning new exercises and remembering how to perform them correctly, even if they have previously participated in the same programs with similar adherence.

Our findings suggest that it is important for therapists and health care practitioners to assess general cognitive function in order to estimate training ability at baseline and adjust their approach to exercise. Logsdon et al[7] reported that older adults with mild cognitive impairment show significant benefit from an exercise program specifically designed to address their cognitive needs. The findings of the present study confirm that physical benefits vary based on the degree of general cognitive functioning. This indicates the necessity for older adults with mild cognitive impairment to engage in an exercise program specifically designed to address cognitive needs (ie, one that provides memory aids and easy to follow instructions). In addition, individually prescribed exercise is a more effective intervention strategy for the improvement of balance, gait performance, and reduction in risk of falling than group exercise in older adults.[29]

When an exercise program is prescribed for older adults in clinical practice, individual physical function is usually considered an important factor, by which strength and contents of exercise are regulated by therapists or practitioners. Our findings suggest that it is also important for therapists or practitioners to assess general cognitive function in order to estimate training ability at baseline and adjust their approach to exercise. Exercise programs designed to address cognitive obstacles should be developed and prescribed according to the level of cognitive functioning in older adults with mild cognitive impairment. For example, we recommend that complex exercise behaviors are broken into small steps and practiced repeatedly in class, and simple written materials are provided along with memory aids to support exercise outside of class.[7] These programs, tailor-made for level of cognitive function, would be effective and efficient for improving physical function in older adults.

Improvement in some aspects of cognitive function has been related to adherence to an exercise program in older adults with mild cognitive impairment.[30] This finding is in line with the present study which shows that attendance rate was associated with improvement in physical performance. Williams et al[31] reported that reduced muscle strength, slow reaction time, and psychoactive drug use explained most of the variance in adherence during an exercise trial. For interventions to be effective it may be important to maintain attendance rates by addressing associated factors.

Several limitations in this study need to be mentioned, such as the small sample size and lack of a control group. Additionally, there may be other compounding factors, such as motivation and self-efficacy, which should be included in future analysis. Only 24% of the change in TUG variance could be explained in the present study. Future research should include a broader range of cognitive impairment levels, more detailed neuropsychological testing, and more extensive physical assessments, particularly those that may have more or less of a cognitive demand than TUG. These areas should be addressed to evaluate the association between various cognitive functions and trainability of physical performance in detail and to determine the cutoff points for predicting improvement in physical performance. Further research is needed to clarify whether specific exercise programs designed to address cognitive obstacles could improve physical function effectively and lead to a potentially preventive effect for conversion to Alzheimer's disease. Our findings concerning the relationship between trainability and cognitive function are specific to older adults with mild cognitive impairment, and cannot be applied to persons with severe dementia.

In summary, despite some limitations, the present study examined the association between cognitive function at baseline and the effect of intervention on physical performance in older adults with mild cognitive impairment. Our results reveal that MMSE and attendance rate were independently associated with improvement in physical performance. A major implication of this study is that general cognitive function may be important for persons with mild cognitive impairment to gain benefit from an exercise intervention.

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Disclosure

The authors report no conflicts of interest in this work.

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RESEARCH ARTICLE Open Access

Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial

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Abstract

Background: To examine the effects of a multicomponent exercise program on the cognitive function of older adults with amnestic mild cognitive impairment (aMCI).

Methods: Design: Twelve months, randomized controlled trial; Setting: Community center in Japan; Participants: Fifty older adults (27 men) with aMCI ranging in age from 65 to 93 years (mean age, 75 years); Intervention: Subjects were randomized into either a multicomponent exercise (n = 25) or an education control group (n = 25). Subjects in the multicomponent exercise group exercised under the supervision of physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times over 12 months. The exercises included aerobic exercises, muscle strength training, and postural balance retraining, and were conducted using multiple conditions to stimulate cognitive functions. Subjects in the control group attended three education classes regarding health during the 12-month period. Measurements were administered before, after the 6-month, and after the 12-month intervention period; Measurements: The performance measures included the mini-mental state examination, logical memory subtest of the Wechsler memory scale-revised, digit symbol coding test, letter and categorical verbal fluency test, and the Stroop color word test.

Results: The mean adherence to the exercise program was 79.2%. Improvements of cognitive function following multicomponent exercise were superior at treatment end (group × time interactions for the mini-mental state examination (P = 0.04), logical memory of immediate recall (P = 0.03), and letter verbal fluency test (P = 0.02)). The logical memory of delayed recall, digit symbol coding, and Stroop color word test showed main effects of time, although there were no group × time interactions.

Conclusions: This study indicates that exercise improves or supports, at least partly, cognitive performance in older adults with aMCI.

Keywords: Aerobic exercise, MCI, Elderly, Alzheimer's disease, Prevention

Background

Population-based studies in older adults performed in North America, Europe, and Asia report a prevalence of mild cognitive impairment (MCI) ranging from 11% to 17% [1-5], and a prevalence of the amnestic MCI (aMCI) subtype between 3 and 5% [2,6]. Evidence from both neuropsychological and neuroimaging studies have suggested that MCI represents a clinical prodrome to degenerative dementias such as Alzheimer's dementia (AD) [7,8]. This is particularly the case with aMCI, which is likely to progress to AD [9]. Early treatment of mild to moderate AD is associated with better responses than later treatment [10], so it is conceivable that treating MCI may be particularly effective in delaying the progression to AD.

Clinical aspects have been widely examined as possible biomarkers for MCI to detect subjects at greater risk of conversion to dementia. Neuropsychological predictors of conversion include performance on specific cognitive

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tests, particularly those assessing delayed recall and executive functions [11-14]. Reducing or recovering from identified risk factors is important in the prevention of the conversion from MCI to AD or to delay the progression of the prodromal symptoms of dementia.

Epidemiological data suggests that moderate exercise and physical activity, such as walking, are associated with a lower risk of dementia [15]. According to these findings, epidemiological studies and randomized controlled trials examining the effects of exercise have proposed it is associated with various cognitive benefits [16-25], and a meta-analysis reported that physical activity or exercise is associated with improvements in attention, processing speed, and executive function in older adults with or without cognitive impairments [26-28]. RCT have been conducted to determine the effects of exercise or physical activity on cognitive functions in older adults with MCI. These studies identified the effects of exercise or physical activity on cognitive function including general cognitive function, executive function and glucometabolic and hypothalamic-pituitary-adrenal axis responses in older adults with MCI [16,19,22,23]. However, because the results of these studies differed largely due to differences in methodology, sufficient evidence has not been garnered regarding the relationship between exercise and cognitive function in aMCI.

We designed the present randomized trial to test whether 12 months of supervised multicomponent exercise improved cognitive function among older adults with aMCI. The multicomponent exercise included aerobic exercise, muscle strength training, and postural balance retraining. We adopted the multicomponent regimen because a previous review suggested that participants in combined aerobic and strength training regimens improved cognitive function to a reliably greater degree than those in aerobic training alone (0.59 vs. 0.41, SE = 0.043, n = 101, $p < 0.05$) [29].

Methods

Participants

In this 12-month randomized controlled trial, the subjects were divided into a multicomponent exercise or an education control group at the end of the baseline assessment. Study personnel involved in collection of outcome measures were unaware of each subject's assigned group. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The purpose, nature, and potential risks of the experiments were fully explained to the subjects, and all subjects gave written, informed consent before participating in the study.

Subjects in this study were recruited from our volunteer databases, which included elderly individuals (65 years and over). The inclusion criteria we used were dwelling in the community and being 65 years or age or older. 528 prospective subjects with a Clinical Dementia Rating (CDR) [30] of 0.5, or who complained of memory impairments, were recruited for the initial eligibility assessments. 135 subjects participated in the secondary eligibility assessments, including neuropsychological tests and magnetic resonance imaging. 35 of these 135 subjects were excluded and the remaining 100 subjects met the definition of MCI using the Petersen criteria [31]. The objective memory impairment was defined as having a lower memory in the Logical Memory II subtest of the Wechsler memory scale-revised (WMS-LM II) [32]. The cut-off score to define the aMCI was adjusted by educational history (0–9 years: <7 points, 10–15 years: <10 points, more than 16 years: <12 points) [33]. The exclusion criteria we used included having a CDR = 0, 1, 2, and 3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, loss of independence in basic activities of daily living (ADL), and current participation in other research projects. A diagram consistent with the Consolidated Standards of Reporting Trials (CONSORT) [34] that outlines the subject flow from first contact to study completion is shown in Figure 1. Fifty older adults (mean age 76.0 ± 7.1 years, range 65–92 years, male = 27 (54 %), mean education level 10.9 ± 2.5 years) with aMCI who had objective memory disabilities and who completed the neuroimaging assessments were selected as the subjects in the study.

Intervention

Subjects in the multicomponent exercise group exercised under the supervision of physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times over 12 months. Two physiotherapists involved in geriatric rehabilitation and three well-trained instructors conducted each intervention. The exercise class consisted of 16–17 participants, and each supervised session began with a 10-min warm-up period, followed by 20 min of muscle strength exercise. The subjects then practiced aerobic exercise, postural balance retraining, and dual-task training for 60 min. In the aerobic exercises and postural balance retraining, subjects completed circuit training including stair stepping, endurance walking, and walking on balance boards. The mean intensity of the aerobic exercises was approximately 60% of maximum heart rate. Heart rate was monitored after aerobic exercise each session to take their pulse. One out of every four classes during the intervention period included outdoor walking during approximately 20–30 minutes. These exercises or training were also conducted under multitask conditions. For example, the subjects in the exercise group were asked to invent their own poem while walking. In the ladder training, subjects memorized a step pattern in

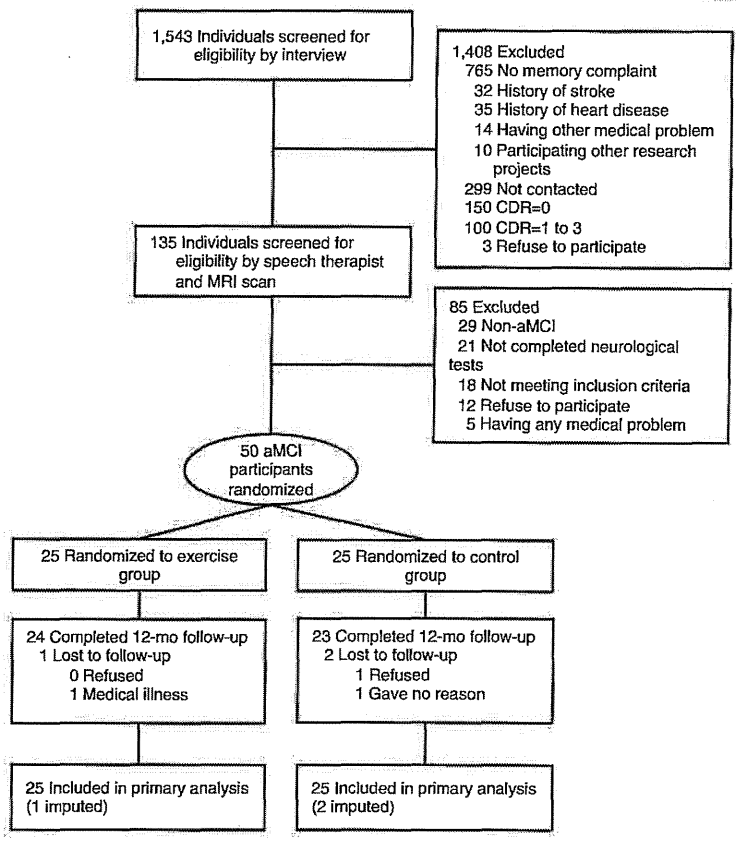

Figure 1 Subject flow diagram from the initial contact through the study completion.

consecutive square segments, and were instructed to step as quickly and accurately as possible. Before and after each session of the program, physiotherapists conducted a health check of each subject. The physiotherapists and well-trained instructors provided ongoing safety monitoring to prevent adverse accidents such as falling during the program. Daily home-based exercise in addition to structured program and outdoor walking was recommended to the exercise group. The subjects allocated the exercise group were asked to recording the amount of time spent on daily home-based exercise and the daily total steps for pedometer in a notebook. The subjects made graphs from the records of amount of time and steps to promote active lifestyle through a self-monitoring. Attendance at each session was recorded and a transportation service was provided for the participants, if necessary, to help the subjects maintain their participation in the program.

Subjects in the education control group attended three education classes regarding health promotion during the 12-month study period. The class provided information regarding aging, healthy diet, oral care, brain image diagnosis, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

Outcomes

The cognitive function before, after 6-month, and after 12-month intervention period was measured by speech therapists. Prior to the commencement of the study, all staff received training from the authors in the correct protocols for administering all of the assessment measures included in the study. The assessors introduced and demonstrated the assessments to facilitate understanding of the tests by the participants before they conducted the tests. A speech therapist calculated all of the results of the cognitive function tests.

The mini-mental state examination (MMSE) was measured as a general cognitive function [35]. The WMS-LM I and II [32] was used to assess logical memory function. In the WMS-LM, two short stories (story A and B) were read aloud to the subjects, who were then instructed to recall details of the stories immediately (WMS-LM I) and after 30 min (WMS-LM II) (total recall score = 50) [32]. The digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III was used to assess processing speed [36]. Verbal fluency

[37,38] was measured by the number of words generated across 60-second trials [37]. The subject's listed words began with a letter composed of Japanese characters for the three trials (letter verbal fluency test: LVFT) and that belonged to a semantic category (category verbal fluency test: CVFT). The total number of correct responses was used for the analysis. The Stroop Color and Word Test (SCWT) [39] was used to assess executive function. For the Stroop test, we used two conditions. First, the subjects were instructed to read out words printed in black ink (e.g., *blue*) (SCWT-I). Second, they were shown a page with color words printed in incongruent colored inks (e.g., the word *blue* printed in red ink). The subjects were asked to name the ink color in which the words were printed (while ignoring the word itself) (SCWT-III). There were 24 trials for each condition, and we recorded the time the participants took to read each condition.

Analysis
The statistical analyses were conducted using SPSS software (Version 20; SPSS Inc., Chicago, IL, USA). The independent samples *t*-test or Chi-square test was used to compare the basic characteristics between the exercise and education control group. The effect of intervention (exercise vs control) over time on the cognitive functions was investigated in intention-to-treat (ITT) analyses. Measurements were analyzed using linear mixed models; analyses assumed missing at random with missingness allowed to be driven by variables included in the analyses. All models included random intercepts to account for correlations between the repeated measures for each participant. The fixed components of the models included effects of group and time and a group × time interaction. To assess the presence of a group and time effect, where this may change over time, we first determined the existence of time, group, and group × time interactions. The post hoc analyses were made between times and groups using the Bonferroni method. All statistical significance tests were two-sided, and an alpha-level of 0.05 was considered statistically significant.

Results
Adherence to intervention
There were no significant differences in the baseline characteristics between the exercise and education control groups (Table 1). Figure 1 shows the flow of the participants from the time of screening to study completion at 12 months. 47 (exercise group, n = 24) subjects completed the 12-month follow-up. Two of the twenty-five subjects in the exercise group (1 man and 1 woman) did not attend a single session, but were included in the following analyses. The mean adherence to the exercise program, including these subjects, was 79.2%, and 17 subjects (68.0%) in the exercise group attended our intervention program with more than 80% adherence.

Table 1 Baseline characteristics of the subjects

Characteristic	Exercise (n=25)	Control (n=25)
Age, mean ± SD, y	75.3 ± 7.5	76.8 ± 6.8
Men, No. (%), n	13 (52.0)	14 (56.0)
Educational level, mean ± SD, y	11.1 ± 2.4	10.8 ± 2.7
Blood pressure, mean ± SD, mmHg		
Diastolic	77.3 ± 11.1	74.3 ± 10.1
Systolic	152.2 ± 21.0	143.7 ± 21.3
Diagnosis, No. (%), n		
Hyper tension (1*)	13 (52.0)	11 (44.0)
Heart disease (1*)	2 (8.0)	0 (0)
Diabetes Mellitus	5 (20.0)	3 (12.0)
Medication, 3 and over	10 (40.0)	11 (44.0)
Blood test, mean ± SD		
Total cholesterol, mg/dL	212.6 ± 36.9	202.8 ± 32.2
Triglyceride, mg/dL	146.8 ± 73.7	130.4 ± 112.3
Glucose, mg/dL	116.3 ± 27.1	110.4 ± 23.4
HA1c, %	5.6 ± 0.6	5.4 ± 0.5
Cognitive functions, mean ± SD		
MMSE, score	26.8 ± 1.8	26.6 ± 1.6
WMS-LM I, score	12.5 ± 5.9	12.0 ± 4.9
WMS-LM II, score	8.2 ± 5.4	6.9 ± 5.0
DSC, s	47.5 ± 15.4	44.3 ± 16.3
LVFT, score	16.0 ± 5.3	16.9 ± 6.0
CVFT, score	33.1 ± 6.9	31.2 ± 7.7
SCWT-I, s	22.6 ± 9.7	23.4 ± 11.1
SCWT-III, s	42.0 ± 13.7	41.5 ± 17.7
TMIG index, mean ± SD, score		
IADL	5.0 ± 0.2	4.9 ± 0.3
Intellectual activity	3.8 ± 0.4	3.8 ± 0.4
Social role	3.6 ± 0.9	3.6 ± 0.8
Total	12.3 ± 1.1	12.3 ± 0.9
GDS, mean ± SD, score	3.0 ± 2.1	2.6 ± 2.0

SD; standard deviation, MMSE; mini-mental state examination, WMS-LM II; Logical Memory II subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test, CVFT; category verbal fluency test, DSC; digit-symbol cording, SCWT; Stroop Color and Word Test, TMIG index; Tokyo Metropolitan Institute of Gerontology index, GDS; Geriatric Depression Scale. * missing value.

Changes in cognitive function
Table 2 shows changes in cognitive scores over the 12 months across the groups. On the MMSE, there was a group × time interaction ($P = 0.04$) indicated benefit of the exercise over time (Figure 2). Although there were no main effects of group or time, the control group showed significant decline in the MMSE score after 6

Table 2 Comparison of cognitive functions between exercise and control groups

	Mean difference (95% CI) between before and after 6 months		Mean difference (95% CI) between before and after 12 months		Time			Group			Group × time		
	Exercise (n=25)	Control (n=25)	Exercise (n=25)	Control (n=25)	df	F value	P value	df	F value	P value	df	F value	P value
MMSE	0.32 (−0.96–1.60)	−1.37 (−2.66–−0.07)	−0.47 (−1.75–0.81)	−0.44 (−1.74–0.86)	92.1	1.17	0.32 [d]	48.0	2.2	0.14 [g]	92.1	3.4	0.04
WMS-LM I	3.83 (1.40–6.25)	0.60 (−1.87–3.06)	4.62 (2.19–7.05)	5.00 (2.53–7.46)	90.9	23.0	<0.01 [a, b, e, f]	47.8	0.9	0.34 [g]	90.9	3.9	0.03
WMS-LM II	3.79 (1.49–6.10)	2.09 (−0.25–4.43)	5.13 (2.82–7.43)	6.20 (3.86–8.54)	91.1	35.4	<0.01 [a, b, e, f]	48.1	1.1	0.30	91.1	2.1	0.13
DSC	−0.19 (−4.20–3.81)	3.27 (−0.80–7.34)	3.64 (−0.36–7.64)	3.73 (−0.34–7.80)	90.4	5.0	<0.01	48.0	0.2	0.65	90.4	1.4	0.25
LVFT	2.87 (0.57–5.17)	−0.97 (−3.31–1.37)	2.99 (0.69–5.30)	1.61 (−0.73–3.95)	91.2	5.9	<0.01	48.3	0.3	0.59	91.2	4.1	0.02
CVFT	1.54 (−1.27–4.35)	−1.81 (−4.67–1.04)	1.33 (−1.48–4.14)	−1.61 (−4.46–1.25)	91.2	0.02	0.98	48.5	3.1	0.08	91.2	2.5	0.09
SCWT-I	−3.30 (−7.56–0.96)	−0.98 (−5.30–3.34)	−3.68 (−7.94–0.58)	−3.20 (−7.52–1.12)	91.5	3.9	0.02	47.7	0.73	0.40	91.5	0.5	0.62
SCWT-III	−4.70 (−12.72–3.33)	0.15 (−8.00–8.30)	−2.61 (−10.64–5.42)	−4.57 (−12.72–3.58)	92.0	1.2	0.31	48.8	0.009	0.92	92.0	1.1	0.34

MMSE; mini-mental state examination, WMS-LM; Logical Memory subtest of the Wechsler memory scale-revised, DSC; digit-symbol cording, LVFT; letter verbal fluency test, CVFT; category verbal fluency test, SCWT; Stroop Color and Word Test, TMIG; Tokyo Metropolitan Institute of Gerontology index.

[a] P < .05; significant differences between before and after 6 months in the exercise group, [b] P < .05; significant differences between before and after 12 months in the exercise group, [c] P < .05; significant differences between after 6 months and 12 months in the exercise group, [d] P < .05; significant differences between before and after 6 months in the control group, [e] P < .05; significant differences between before and after 12 months in the control group, [f] P < .05; significant differences between after 6 months and 12 months in the control group, [g] P < .05; significant differences between the exercise and control groups at after 6 months, [h] P < .01; significant differences between the exercise and control groups at after 12 months.