formed to assess the association between a history of falling and combined status determined by SDA. The crude and adjusted OR and 95% CIs were calculated adjusting for important potentially confounding variables including age, sex, body mass index (BMI), medication, severe visual or auditory disturbance, and frequency of going out. Data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and p-values less than 0.05 were considered significant.

3. Results

3.1. Demographic characteristics of the sample

Of the 4481 participants who met our requirements, 645 (14.4%) participants reported falling at least once in the past year. Table 1 summarizes the characteristics of the faller and non-faller groups. The faller group had a statistically significantly higher age, number of medications, frequency of going out, female and osteoporosis population, and lower education level compared with the non-faller group ($p < 0.05$). In addition, the faller group exhibited statistically significant lower GS ($p < 0.001$), CST ($p < 0.001$) and TUG ($p < 0.001$) performance, and MMSE score ($p = 0.020$) and higher GDS score ($p < 0.001$) compared with the non-faller group. There were no statistically significant between-group differences in BMI ($p = 0.240$) and the proportion of severe visual or auditory disturbance ($p = 0.536$).

3.2. Sample divided into subgroups associated with a history of falling

Participants were categorized into four subgroups whose fall rate varied 11.7–36.4% by SDA (Fig. 1). Group-I had the lowest fall rate at 11.7%. This group consisted of participants who did not have symptoms of clinical depression (GDS < 6 points) and exhibited better chair stand performance (CST < 11.1 s). Group-II had the next lowest fall rate at 18.8%. Participants in Group-II did not have symptoms of clinical depression (GDS < 6 points), but exhibited poor chair stand performance (CST ≥ 11.1 s). Group-III had a fall rate of 21.6%. Group-III was characterized by reported symptoms of clinical depression (GDS ≥ 6 points) and better mobility performance (TUG < 11.6 s). The highest fall rate of 36.4% was confirmed in Group-IV. Group-IV consisted of participants who had symptoms of clinical depression (GDS ≥ 6 points) and exhibited poor mobility performance (TUG ≥ 11.6 s).

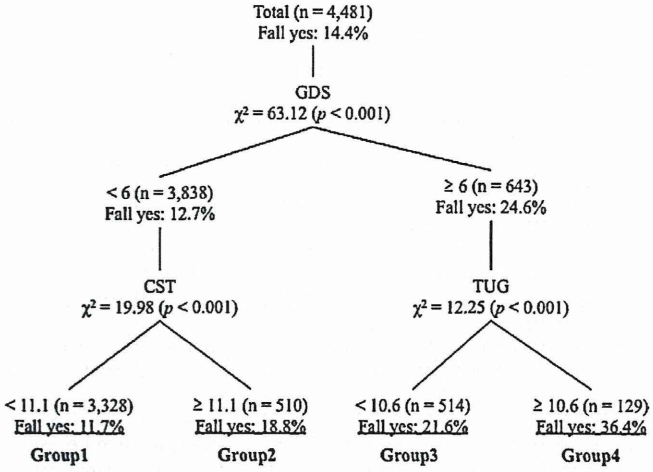

Fig. 1. Results of SDA for the participants' performance on the following measures: GDS; CST; TUG test.

3.3. Relationship between a history of falling and combined status determined by SDA

In the logistic regression analyses, compared with Group-I (the lowest fall rate group), the other three groups had significantly higher ORs after adjusting for age, sex, BMI, medication (number per day), severe visual or auditory disturbance, frequency of going out (days per week), GS, and MMSE score. In model 3 adjusting for these confounding variables, ORs (95% CI, p-value) of Group-II, Group-III, and Group-IV were 1.47 (1.14–1.91, $p = 0.003$), 1.92 (1.51–2.45, $p < 0.001$), and 3.12 (2.08–4.68, $p < 0.001$), respectively (Table 2).

4. Discussion

The results of this study including 4481 community-dwelling older adults indicated that the combination of GDS (≥6 points) and TUG (≥10.6 s) was the highest (36.4%), and GDS (<6 points) and CST (<11.1 s) was the lowest in term of fall rate (11.7%). Groups with a combined status of GDS, TUG, and CST had statistically significantly higher ORs compared with the lowest fall rate group (Group-I: GDS < 6 points and CST < 11.1 s), after adjusting for age, sex, BMI, medication (number per day), severe visual or auditory disturbance, frequency of going out, GS, and MMSE score.

Table 1
Demographic details and characteristics for the non-fallers and fallers.

Variables	All ($n = 4481$)	Non-fallers ($n = 3836$)	Fallers ($n = 645$)	p-Value
Age, years	72.0 ± 5.5	71.8 ± 5.4	73.2 ± 6.1	<0.001
Female, n (%)	2320 (51.8)	1926 (50.2)	394 (61.1)	<0.001
BMI, kg/m^2	23.2 ± 3.7	23.2 ± 3.6	23.4 ± 3.9	0.240
Education, years	11.4 ± 2.5	11.4 ± 2.5	11.0 ± 2.5	0.001
Medical history (self-reported), n (%)				
Cardiac disease	723 (16.1)	610 (15.9)	113 (1735)	0.303
Diabetes	578 (12.9)	487 (12.7)	91 (14.1)	0.322
Osteoporosis	483 (10.8)	377 (9.8)	1.6 (16.4)	<0.001
Cancer	437 (9.8)	368 (9.6)	69 (10.7)	0.383
Medication, number/day	2.0 ± 2.1	1.9 ± 2.0	2.4 ± 2.4	<0.001
Severe visual or auditory disturbance, n (%)	15 (0.3)	12 (0.3)	3 (0.5)	0.536
Frequency of going out, days/week	5.8 ± 1.7	5.8 ± 1.7	5.7 ± 1.8	0.014
GS, kg	26.8 ± 8.0	27.2 ± 8.0	24.8 ± 7.5	<0.001
CST, s	8.7 ± 2.9	8.6 ± 2.8	9.3 ± 3.4	<0.001
TUG test, s	8.4 ± 1.9	8.3 ± 1.8	8.9 ± 2.5	<0.001
GDS, score	2.8 ± 2.6	2.7 ± 2.5	3.7 ± 3.0	<0.001
MMSE, score	26.2 ± 2.7	26.3 ± 2.7	26.0 ± 3.0	0.020

Note: Data are presented as mean ± SD, unless otherwise indicated.

Table 2
Logistic regression summary for participants groups classified by the SDA on falls.

Variable	Fallers, no. (%)	Crude		Model 1		Model 2		Model 3	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Group I: GDS < 6 and CST < 11.1 (n = 3328)	391 (11.7)	1.00 [Reference]	–	1.00 [Reference]	–	1.00 [Reference]	–	1.00 [Reference]	–
Group II: GDS < 6 and CST ≥ 11.1 (n = 510)	96 (18.8)	1.74 (1.36–2.23)	<0.001	1.55 (1.20–2.00)	0.001	1.52 (1.17–1.96)	0.002	1.47 (1.14–1.91)	0.003
Group III: GDS ≥ 6 and TUG < 10.6 (n = 514)	111 (21.6)	2.07 (1.64–2.62)	<0.001	2.02 (1.59–2.56)	<0.001	1.96 (1.54–2.48)	<0.001	1.92 (1.51–2.45)	<0.001
Group IV: GDS ≥ 6 and TUG ≥ 10.6 (n = 129)	47 (36.4)	4.31 (2.96–6.26)	<0.001	3.60 (2.43–5.33)	<0.001	3.30 (2.21–4.91)	<0.001	3.12 (2.08–4.68)	<0.001

Model 1: adjusted for age, sex, and BMI.
Model 2: adjusted for Model 1 plus medication (number/day), and severe visual or auditory disturbance.
Model 3: adjusted for Model 2 plus frequency of going out (days/week), GS, and MMSE.

Depressive symptoms have been related to incident falls in prospective studies (Eggermont, Penninx, Jones, & Leveille, 2012; Kwan et al., 2012) and cross-sectional studies with large samples (Halil et al., 2006; Lawlor, Patel, & Ebrahim, 2003). One of the problems associated with falling in older people is a post-fall psychological reaction. A prospective cohort-study reported that depression at 1 year post-injury due to falling was higher than at the pre-injury baseline (Scaf-Klomp, Sanderman, Ormel, & Kempen, 2003). Although the present study included community-dwelling older people with and without fall-related injury and differences between with them were not compared, depressive symptoms were identified as being strongly associated with a history of falling. A cut-off score of 6 or greater on the GDS was used to divide the first two groups. A score of 6 or more symptoms on the GDS has been reported as an optimal cut-off point with comparison to a structural clinical interview for depression (Friedman, Heisel, & Delavan, 2005). Thus, depressive symptoms were also thought to be associated with falls in our large sample study.

To screen for fall risk among older people, measures of lower extremity function, balance, and gait performance have been recommended (Rubenstein & Josephson, 2006; Scott et al., 2007; Shimada et al., 2009). The TUG has been recommended as a key test for detecting fall risk in community-dwelling older adults. Many retrospective studies have found a significant positive association between the time taken to perform the TUG and a history of falls (Beauchet et al., 2011). However, the cut-off time separating non-fallers and fallers was varied and inconsistent. For instance, Shumway-Cook et al. (2000) demonstrated that older adults who required 13.5 s or longer to perform the TUG were classified as fallers, with an overall prediction rate of 90%. In another prospective study, a cut-off score of 10 s on the TUG yielded high sensitivity (71%) and specificity (89%) to discriminate between older adult fallers and non-fallers (Rose, Jones, & Lucchese, 2002). The cut-off time established for separating non-fallers and fallers in a study including day hospital patients was considerably longer than 30.2 s (Thomas & Lane, 2005). The different cut-off values among these previous retrospective studies may be the results of a variation in participants' physical function characteristics. Additionally, cut-off values may related to different definitions of fallers (e.g., single and recurrent fallers, or only recurrent fallers). Furthermore, these studies that demonstrated cut-off times for TUG had limited findings with a relatively small cohort (less than 200 participants). Thus, a consensus for an accurate cut-off score for TUG has not yet been established. The results of our large cohort study with an aged population (n = 4481) demonstrate that older adults with the highest fall rate (36.4%) required more than 10.6 s to perform the TUG and had depressive symptoms (GDS ≥ 6 points). According to a combination fall risk assessment, renewed cut-off values are required and further prospective studies are needed to identify high-risk groups and the predictive value for future falls in community-dwelling older adults.

CST is a valid measure of lower extremity strength and function. Several studies have suggested that a slower CST performance is useful for the detection of older adults at higher risk for falls, independent of other prominent risk factors (Buatois et al., 2008; Tiedemann, Shimada, Sherrington, Murray, & Lord, 2008). In a previous prospective cohort study involving 362 subjects aged 74–98 years, a cut-off point of 12 s on the CST was associated with an increased fall risk, with 66% sensitivity and 55% specificity regarding the identification of multiple fallers (Tiedemann et al., 2008). Data from a prospective population-based study involving 1958 subjects aged 65 years and older found that the ideal cut-off time for performing the CST for use in predicting recurrent fallers was 15 s (sensitivity 55%, specificity 65%) (Buatois et al., 2008). The present data provide a cut-off point of 11.1 s on the CST for separating non-fallers and fallers among older adults without depressive symptoms (GDS < 6 points). Moreover, a combined status of a lower GDS score (<6 points) and better CST time (<11.1 s) demonstrated the lowest fall rate (11.7%). The results of this study, however, may indicate a shorter CST cut-off point compared with previous studies as we defined participants who had had at least one fall within the past year as fallers and we analyzed cross-sectional data.

One key finding was a strong association between a history of falls and combined status using the GDS, TUG, and CST in a large aged population sample. This is the first study to suggest the validity of a combined classification of both physical and psychological factors. Multi-dimensional measures may be important to assess fall risks. Additionally, studies including longitudinal data are needed to confirm whether these combined statuses of the GDS, TUG, and CST predict future falls in older people.

Our study has several limitations. Our data were collected using a cross-sectional design. Participants who had had at least one fall in the past year were categorized as fallers in this study. A previous study has found that single fallers are more similar to non-fallers than to recurrent fallers on a range of medical, physical, and psychological risk factors (Lord, Ward, Williams, & Anstey, 1994). Other researchers define fallers as people who have had at least one injurious or two non-injurious falls (Delbaere et al., 2010; Zheng et al., 2012). In addition, one-year memory recall on falls may be long and the accuracy of self-reported falls for older adults, especially those with severe depression, may results over- or under-reported the number of falls. Therefore, future research with a longitudinal design and different definitions of fallers are needed to supplement the present results.

5. Conclusions

This study found that a combination of the GDS, TUG, and CST performance was strongly associated with a history of falling in community-dwelling elderly. In particular, the group with depressive symptoms (GDS ≥ 6 points) and lower mobility

function (TUG ≥ 10.6 s) had the highest fall rates. Multi-dimensional measures may be important to assess fall risks. Future studies including longitudinal data are needed to confirm whether the combination of using the GDS, TUG, and CST measures predicts future falls in older people.

Conflict of interest statement

None.

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Short Communication

Moderate-Intensity Physical Activity, Cognition and APOE Genotype in Older Adults with Mild Cognitive Impairment

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Abstract

Mild Cognitive Impairment (MCI) is associated with an elevated risk of developing Alzheimer's disease (AD). The presence of the *APOE* ε4 allele is one of established risk factors for AD, and physical activity has been reported to be effective for preventing cognitive decline in older people. The aim of this cross-sectional study was to investigate the association between moderate levels of physical activity and cognitive function among older subjects who had MCI and were *APOE* ε4 carriers or non-carriers. Comprehensive neurocognitive assessments were conducted for 317 participants with MCI aged 65 or more (mean age 71.3 years, 54.6% women), and their physical activity levels were assessed using portable triaxial accelerometers. The activity group included participants who performed weekly physical activity for ≥150 minutes at an intensity of ≥3 metabolic equivalents. Among subjects with MCI who were *APOE* ε4 carriers, compared to the inactive group, the active group exhibited significantly better visual memory performance-delayed retention (age-adjusted $P = .039$), Rey Auditory Verbal Learning Test-immediate score (age-adjusted $P = .024$), and verbal fluency test performance (age-adjusted $P = .022$). In contrast, among MCI subjects who were *APOE* ε4 non-carriers, the active and inactive groups showed no statistical difference in performance on cognitive function tests. These results indicate that recommended moderate physical activity might have a greater impact on cognitive function in older adults with MCI who are *APOE* ε4 carriers than in those who are *APOE* ε4 non-carriers.

ABBREVIATIONS

MCI: Mild Cognitive Impairment; AD: Alzheimer's disease; APOE: Apolipoprotein E; METs: Metabolic Equivalents; WMS-R: Wechsler Memory Scale-Revised; RAVLT: Rey Auditory Verbal Learning Test; VFT: Verbal Fluency Test

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and causes an immense burden on patients, caregivers, and society. The presence of the *APOE* ε4 allele is one of the few established risk factors for AD [1]. In addition to the *APOE* ε4 allele, which is one of the non-modifiable risk factor for dementia, several potential modifiable risk factors have been reported. For instance, physical activity is a modifiable risk factor for healthy aging and plays a role in AD prevention [2].

Recent systematic reviews and meta-analyses have suggested a significant and consistent effect of physical activity in preventing cognitive decline among older adults without dementia [3,4]. Although these previous findings are encouraging, majority of these studies were conducted on healthy subjects or did not define the cognitive status of subjects, such as whether they had Mild Cognitive Impairment (MCI). MCI is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia, and is associated with an elevated risk of developing AD [5].

Another key limitation of most previous studies is that they examined the effects of physical activity on cognition utilizing self-reported questionnaires. Recent studies have used accelerometers in an attempt to assess the pattern of physical activity more accurately [6-8], and these studies have shown

a positive relationship between habitual physical activity and cognitive functioning in healthy older adults [7]. In addition, to promote and maintain good health in older adults, moderate-intensity physical activity for a minimum of 30 min on 5 days each week is recommended [9]. A better understanding of the influences of moderate-intensity physical activity and the *APOE* genotype on cognitive function may help promote lifestyle changes to decrease the risk of conversion of MCI to AD.

Thus, the aim of this cross-sectional study was to investigate the association between moderate levels of physical activity and cognitive function among older subjects having MCI who were *APOE* ε4 carriers or non-carriers.

MATERIALS AND METHODS

In total, 317 participants with MCI who were aged 65 and more (mean age 71.3 years, 54.6% women) were examined. All participants met the following criteria for MCI [10,11]: having subjective memory complaints, exhibiting intact general cognitive functioning [scoring ≥ 24/30 on the Mini-Mental State Examination [12]], exhibiting age-adjusted objective cognitive impairment, not using Japanese long-term care insurance or not showing evidence of functional dependency (no need for supervision or external help to perform activities of daily living), and not fulfilling the clinical criteria for dementia. We assessed for age-adjusted objective cognitive impairment (age-adjusted score of ≤1.5 SDs below average) using the National Center for Geriatrics and Gerontology-Functional Assessment Tool [13,14]. We excluded participants who were diagnosed with dementia, had a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, or clinical depression, in this study. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

All participants completed neurocognitive assessments and measurements of physical activity. The participants performed the neurocognitive assessments including tests of visual and verbal memory, working memory, language, attention/executive function, and processing speed domains under the supervision of licensed and well-trained clinical speech therapists. The Wechsler Memory Scale-Revised (*WMS-R) Visual* Reproduction subtest [15] was used to assess participants' visual memory. This test measures immediate (Visual Reproduction-I) and delayed retention (Visual Reproduction-II) of geometric figures. The Rey Auditory Verbal Learning Test (RAVLT) [16] performance was used to assess participants' verbal memory. We analyzed subjects' performance immediate (fifth trial score of five times free recall) and 30-min delayed recall from the RAVLT. We used the verbal forward and backward digit tests to assess working memory [17]. The difference between the digits forward test score and the digits backward test score was used as an index of working memory. To test language functions, we used the Verbal Fluency Test (VFT) [18]. In the VFT, participants were asked to name as many animals as possible in 1 minute. Attention and executive function were assessed using the tablet version of the trail making test [13]. This test consists of two parts (A and B) and we recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s. A shorter time to complete the tasks represents better performance. We used the tablet version of the symbol digit substitution test to assess processing speed [13]. In this task, 9 pairs of numbers and symbols were presented at the top of the display. A target symbol was presented at the center of the display. Subjects then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s.

Physical activity levels were monitored using portable triaxial accelerometers (modified HJA-350IT, Active style Pro, Omron Healthcare Co., Ltd.) [19]. Participants were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. The output was expressed in metabolic equivalents (METs, multiples of resting metabolic rate) [19,20]. Participants who did not record 75% or more of each daytime activity, daytime being from 6 A.M. to 6 P.M., for 7 days during the 2-week period were excluded from the study. During the 2-week period, the displays of accelerometers were disabled to prevent the participants from checking their counts and values, in order to ensure that they were pursuing their normal daily activity. The activity group included participants who satisfied the criterion of weekly physical activity for ≥150 minutes at an intensity of ≥3 METs (moderate-intensity physical activity) based on the recommendation of the American College of Sports Medicine and the American Heart Association [9].

All the data entry and analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS Inc. Chicago, IL, USA). The significance threshold was 0.05. Means, standard deviations, and proportions were calculated. Student's *t*-tests and chi-square tests were used to compare characteristics between the active (weekly moderate-intensity physical activity for ≥150 min) and inactive (weekly moderate-intensity physical activity for <150 min) groups among both *APOE* ε4 carrier and non-carrier participants. We used analysis of covariance (ANCOVA) adjusted for age to compare group differences in performance of neurocognitive tests among the participants carrying and not carrying *APOE* ε4.

RESULTS AND DISCUSSION

Of the 317 participants, 67 (21.1%) were determined to be *APOE* ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4 genotypes). In both *APOE* ε4 carriers and non-carriers, the active and inactive groups showed no statistically significant differences in characteristics such as age, sex, education, body mass index, diagnosis, functional capacity, and blood markers (Table 1). Age-adjusted ANCOVA showed a significantly higher WMS-R-Visual recall II score (age-adjusted $P = .039$), RAVLT-immediate score (age-adjusted $P = .024$), and VFT performance (age-adjusted $P = .022$) in the active group than in the inactive group among *APOE* ε4 carriers with MCI. In contrast, among *APOE* ε4 non-carriers with MCI, the active and inactive groups showed no statistical differences in performance on neurocognitive tests (Table 2).

This study indicated that recommended moderate-intensity physical activity (≥150 minutes of weekly physical activity at an intensity ≥3 METs) affects cognitive function in older adults with MCI who were *APOE* ε4 carriers, but not in those who were *APOE* ε4 non-carriers.

Table 1: Participant characteristics.

	APOE ε4 carriers (n = 67)			*APOE* ε4 non-carriers (n = 250)		
	Active (n = 27)	Inactive (n = 40)	*P* value	Active (n = 109)	Inactive (n = 141)	*P* value
Age, years	70.4±3.1	72.4±5.4	0.08	70.7±4.5	71.6±4.3	0.084
Women, No. (%)	15 (55.6)	27 (67.5)	0.321[a]	58 (53.2)	73 (51.8)	0.821[a]
Education, years	11.5±2.6	11.4±3.0	0.937	10.8±2.1	10.8±2.1	0.842
Body mass index, kg/m^2	22.8±2.6	22.7±2.4	0.861	23.4±2.5	23.8±3.2	0.258
Diagnosis, No. (%)						
Hypertension	14 (51.9)	15 (37.5)	0.245[a]	39 (35.8)	55 (39.8)	0.571[a]
Diabetes mellitus	4 (14.8)	5 (12.5)	0.785[a]	11 (10.1)	17 (12.1)	0.611[a]
Heart disease	3 (11.1)	5 (12.5)	0.863[a]	9 (8.3)	21 (14.9)	0.109[a]
Osteoporosis	4 (14.8)	6 (15.0)	0.983[a]	8 (7.3)	15 (10.6)	0.371[a]
Functional capacity[†], score	12.5±0.9	12.5±0.8	0.933	12.4±1.1	12.4±1.1	0.838
Blood markers						
Albumin, g/ml	4.4±0.3	4.4±0.3	0.854	4.4±0.3	4.3±0.3	0.142
Total cholesterol, mg/dl	217.3±44.4	209.3±37.9	0.434	208.1±30.7	202.1±31.5	0.135
HbA1c, %	5.4±0.6	5.6±0.8	0.253	5.6±0.6	5.6±0.8	0.861

Note: Values are mean ± SD and numbers (proportion) for sex, APOE ε4, and diagnosis. *P*-value are based on t-test or chi-square ([a]). [†]The Tokyo Metropolitan Institute of Gerontology Index.

Table 2: Comparison of cognitive tests between active and inactive groups of *APOE* ε4 carriers and non-carriers.

	APOE ε4 carriers (n = 67)			*APOE* ε4 non-carriers (n = 250)		
	Active (n = 27)	Inactive (n = 40)	Age-adjusted *P* value	Active (n = 109)	Inactive (n = 141)	Age-adjusted P value
Visual memory						
WMS-R-Visual recall I, score	31.8 ± 6.8	27.7 ± 7.0	0.077	30.9 ± 5.7	30.8 ± 5.7	0.716
WMS-R-Visual recall II, score	25.0 ± 7.8	19.2 ± 9.0	0.039	22.5 ± 8.5	23.2 ± 8.7	0.248
Verbal memory						
RAVLT-immediate, score	10.9 ± 2.2	9.1 ± 2.6	0.024	9.7 ± 2.6	9.8 ± 2.5	0.556
RAVLT-delay, score	8.2 ± 2.7	6.5 ± 3.4	0.135	7.5 ± 3.3	7.6 ± 3.4	0.746
Working memory						
Digit Span: Forward–Backward, score	2.6 ± 1.6	3.1 ± 1.8	0.270	2.3 ± 1.9	2.6 ± 1.9	0.358
Language						
Verbal fluency test, score	17.6 ± 3.4	14.8 ± 4.7	0.022	15.7 ± 3.9	15.7 ± 4.0	0.715
Attention/Executive function						
Tablet TMT-A, sec	19.9 ± 4.9	21.5 ± 6.0	0.640	21.6 ± 7.6	21.8 ± 5.9	0.881
Tablet TMT-B, sec	36.7±12.1	44.2±18.1	0.288	41.3±15.9	44.1±15.8	0.446
Processing speed						
Tablet SDST, score	42.3 ± 6.9	38.1 ± 7.0	0.081	40.7 ± 6.9	38.5 ± 7.1	0.065

Abbreviations: *WMS-R:* Wechsler Memory Scale-Revised; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test; SDST: Symbol Digit Substitution Test

A previous longitudinal study indicated an association between physical inactivity in middle age and the risk of AD, especially among *APOE* ε4 carriers. Thus, *APOE* ε4 carriers might be more vulnerable to environmental factors, such as physical inactivity, dietary fat intake, consumption of alcohol, and smoking [21]. In contrast, in a previous prospective cohort study of community-dwelling older adults, an inverse association between physical activity and dementia risk was found for *APOE* ε4 non-carriers but not for *APOE* ε4 carriers [22]. Although both the presence of the *APOE* ε4 allele and low levels of physical

activity are important risk factors for dementia, it is unclear how the interactions between these two factors affect the development of cognitive impairment.

Previous cohort studies examining the effects of *APOE* genotype and physical activity on the risk of dementia and AD assessed physical activity levels using self-reported questionnaires [21,22]. In the current study, we monitored physical activity levels using portable triaxial accelerometers and provided objective data of physical activity levels, including whether the activity reached the recommended levels (≥150 minutes at ≥3.0 METs per week). Our findings suggested that the associations between moderate-intensity physical activity behavior and cognitive function might be more remarkable in MCI subjects carrying *APOE* ε4. Habitual moderate-intensity physical activity at the recommended levels (≥150 minutes per a week) seems to be not only beneficial for physical health but also provides cognitive protection in older people [23]. Furthermore, our data indicated that this level of moderate-intensity physical activity might help maintain cognitive functions even in older adults with increased risks for dementia, such as those with MCI or those carrying the *APOE* ε4 allele.

However, our data was collected by a cross-sectional design. Therefore, longitudinal studies and clinical trials are needed to understand the temporal direction of associations among moderate-intensity physical activity, cognition, and *APOE* genotype in older adults with MCI. In addition, investigations on healthy individuals and subjects with AD are needed to clarify the effects of the *APOE* ε4 allele and objectively determined physical activity levels on AD-related pathology.

CONCLUSION

In summary, this study found that low levels of moderate-intensity physical activity are associated with poor cognitive functions, especially memory and language functions, in subjects with MCI who are *APOE* ε4 carriers. Our findings imply that a habitual physical activity for ≥150 minutes per week at an intensity of ≥3 METs may have a greater impact on cognitive functioning among subjects with MCI who are *APOE* ε4 carriers compared to those who are non-carriers.

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RESEARCH ARTICLE Open Access

Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment

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Abstract

Background: Gait ability and cognitive function are interrelated during both normal walking (NW) and dual-task walking (DTW), and gait ability is thus adversely affected by cognitive impairment in both situations. However, this association is insufficiently understood in people with mild cognitive impairment (MCI). Here, we conducted a study with MCI participants, to examine whether the association depends on walking conditions and MCI subtypes.

Methods: We classified 389 elderly adults into amnestic MCI (n = 191) and non-amnestic MCI (n = 198), assessed their cognitive functions, and administered gait experiments under NW and DTW conditions. Gait ability was defined as gait speed. Five aspects of cognitive function were assessed: processing speed, executive function, working memory, verbal memory, and visual memory.

Results: Regression analysis adjusted for covariates showed a significant association between cognitive functions and gait speed. Processing speed and executive function correlated with gait speed during both NW and DTW ($p < .05$). Gait speed during DTW was also significantly associated with working memory ($p < .001$). Visual memory was associated during NW and DTW, particularly for amnestic MCI participants ($p < .05$).

Conclusions: Our findings support the idea that the association between gait speed and cognitive function depends on walking condition and MCI subtypes. Additional studies are necessary to determine the neural basis for the disruption in gait control in older adults with MCI.

Background

Dementia is a notable health issue because of its extensive impact on the activities and quality of life of older adults. Given the current absence of disease-modifying treatments, as well as increasing awareness that symptoms develop over many years or even decades, there has been growing interest in early detection and effective strategies for prevention [1]. Mild cognitive impairment (MCI) is considered a clinical characteristic that typifies the prodromal phase of Alzheimer's disease (AD), the most common type of dementia [2]. Numerous studies have identified a wide range of potentially modifiable risk factors for AD and dementia, including cardiovascular risk factors, psychosocial factors, and health behaviors [1,3]. Gait impairment is a common characteristic in participants with cognitive impairments [4-6] and is a risk factor for developmental MCI and dementia [7,8]. Cognition and gait are thought to be strongly linked, a contention supported by findings from experimental studies using a dual-task paradigm to epidemiology.

Less is known about the relationships between specific cognitive functions and gait in people with MCI, though population studies have been conducted in older adults to examine this issue [9-14]. Prospective studies indicate that lower attention/executive function [9,13] or memory function [9,11] may lead to a decline in gait speed in older adults. Alternatively, a slow gait speed predicts deficits in the cognitive-processing speed [12] or in executive and memory functions [14]. Emerging evidence

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indicates that cognitive processes related to prefrontal lobe function such as attention and executive function are associated with slower gait and gait instability [15]. However, a consensus regarding the relationship between gait variables and memory deficits in particular has not yet been reached [9-11,14]. Mielke *et al.* has suggested that inconsistencies between studies may be partially due to variation in participant characteristics across studies, ranging from exclusively older adults with normal cognition to mixed participant pools that include those with MCI or AD [14]. In addition, the decline in cognitive function in people with MCI is not uniform, but rather depends on MCI subtype, i.e., amnestic (aMCI) or non-amnestic (naMCI) [2]. Furthermore, subtypes of MCI may potentially have different neuropathologies and courses of conversion, although the dependency of subtypes has not reached consensus [16-20]. Investigating cognitive function in MCI participants requires considering several cognitive function domains as well as these MCI subtypes.

The relationship between cognitive function and gait variables in conditions other than normal walking (NW) is insufficiently understood in people with MCI. Observing how people walk while they perform a secondary attention-demanding task, i.e., a dual-task paradigm, has been used to assess interactions between cognition and gait. Existing population studies have been conducted using both NW and dual-task paradigms with specific conditions [21-23], and gait coordination during dual-task walking (DTW) has been shown to be deteriorated [24,25] and to be associated with reduced executive function [21,22]. Although evidence is scarce, gait variables in older adults with MCI have been shown to be affected in both NW [6] and DTW [26]. Less focus has been given to the association between cognitive function and gait, and no strong conclusions can be drawn because of small MCI sample sizes, non-comprehensive cognitive measurements, or experiments that only examine NW. Thus, a large population study that combines comprehensive cognitive assessments with experiments that include DTW will contribute to a better understanding of the relationship between cognitive function and gait in people with MCI.

Untangling the relationship between early gait disturbances and early cognitive changes may be helpful in identifying older adults who are at risk of mobility decline, falls, and progression to dementia [15]. This study aimed to examine the association between cognitive function and gait speed in older people with MCI, and to examine whether these associations differed depending on walking condition (normal or dual-task) and subtypes of MCI. Gait ability was defined as gait speed following the standard method used in population studies of gait [14].

Methods

Participants

The study population and data were in a cohort study. Six hundred and forty-nine participants were selected as a potential study population from a cohort study (Obu Study of Health Promotion for the Elderly [27]) and met the following criteria: over 65 years old, diagnosed with MCI, no specific medical history of cerebrovascular disease, Parkinson's disease, connective tissue disease, or depression, no severe visual or auditory impairment, no current symptoms of depression (Geriatric Depression Scale ≥6 [28]), not part of other research projects, and not certified to receive support from the Japanese public long-term-care insurance system. As a result of recruitment, 409 responded and after giving their written informed consent 389 people completed the neuropsychological assessments and gait experiments. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

MCI criteria

MCI criteria followed those established and revised by Petersen [2], and in particular, participants satisfied the following conditions: 1) memory complaints; 2) objective cognitive decline; 3) intact general cognitive function; and 4) independent functioning in daily living activities. Intact general cognitive function was defined as a Mini-Mental State Examination score >23 [29]. Objective cognitive decline was defined as having cognitive function more than 1.5 standard deviations lower than normal. Normal scores were taken from the Obu Study of Health Promotion for the Elderly (OSHPE) database of healthy individuals [27]. Cognitive function was also assessed in multiple domains using the National Center for Geriatrics and Gerontology Functional Assessment Tool [30]. Participants who suffered from cognitive decline in the memory domain were classified as aMCI, while those who did not were classified as naMCI.

Gait measures

Participants wore the same type of appropriately sized shoes before each experiment. Participants were instructed to walk on a smooth 11-m horizontal walkway that had a 2-m buffer space at both ends for acceleration and deceleration. The time to walk 5 m to the mid-point of the walkway was measured, and gait speed was expressed in meters per second. Two gait experiments were performed sequentially: NW, in which participants walked at their preferred speed, was followed by DTW. Participants were instructed to walk while counting backward from 100 in DTW. This type of arithmetic task is commonly used in DTW investigations and its effects on gait have been confirmed in a meta-analysis [24].