Seeman, T. E., Huang, M.-H., Bretsky, P., Crimmins, E., Launer, L., & Guralnik, J. M. (2005). Education and APOE-e4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Journals of Gerontology. Series B; Psychological Sciences and Social Sciences*, **60**, 74–83.

Shimokata, H., Ando, F., & Niino, N. (2000). A new comprehensive study on aging: The National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA). *Journal of Epidemiology/Japan Epidemiological Association*, **10**, S1–S9.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, **8**, 448–460.

Tucker-Drob, E. M., Johnson, K. E., & Jones, R. N. (2009). The cognitive reserve hypothesis: A longitudinal examination of age-associated declines in reasoning and processing speed. *Developmental Psychology*, **45**, 431–446.

Van Dijk, K. R. A., Van Gerven, P. W. M., Van Boxtel, M. P. J., Van der Elst, W., & Jolles, J. (2008). No protective effects of education during normal cognitive aging: Results from the 6-year follow-up of the Maastricht Aging Study. *Psychology and Aging*, **23**, 119–130.

Verbeke, G., & Molenberghs, G. (1997). *Linear mixed models in practice: A SAS oriented approach*. New York: Springer-Verlag.

Wechsler, D. (1944). *The measurement of adult intelligence*. 3rd ed. Baltimore, OH: The Williams & Wilkins Company.

Wechsler, D. (1981). *Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R)*. San Antonio, TX: The Psychological Corporation.

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., & Bennett, D. A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychology and Aging*, **17**, 179–193.

Wilson, R. S. S., Hebert, L. E. E., Scherr, P. A., Barnes, L. L., Mendes de Leon, C. F., & Evans, D. A. (2009). Educational attainment and cognitive decline in old age. *Neurology*, **72**, 460–465.

Winkens, B., Schouten, H. J. A., Van Breukelen, G. J., & Berger, M. P. F. (2006). Optimal number of repeated measures and group sizes in clinical trials with linearly divergent treatment effects. *Contemporary Clinical Trials*, **27**, 57–69.

Zahodne, L. B., Glymour, M. M., Sparks, C., Bontempo, D., Dixon, R. A., Macdonald, S. W. S., & Manly, J. J. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the Victoria longitudinal study. *Journal of the International Neuropsychological Society*, **17**, 1039–1046.

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Original Study

Combined Prevalence of Frailty and Mild Cognitive Impairment in a Population of Elderly Japanese People

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A B S T R A C T

Objective: Preventive strategies for frailty and mild cognitive impairment (MCI) are important for avoiding future functional decline and dementia in older adults. The purpose of this study was to use a population-based survey to ascertain the single and combined prevalence of frailty and MCI and to identify the relationships between frailty and MCI in older Japanese adults.
Design: Cross-sectional study.
Setting: General community.
Participants: A total of 5104 older adults (aged 65 years or older, mean age 71 years) who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE).
Measurements: Each participant underwent detailed physical and cognitive testing to assess frailty and MCI. We considered the frailty phenotype to be characterized by limitations in 3 or more of the following 5 domains: mobility, strength, endurance, physical activity, and nutrition. Screening for MCI included a standardized personal interview, the Mini-Mental State Examination, and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT), which included 8 tasks used to assess logical memory (immediate and delayed recognition), word list memory (immediate and delayed recall), attention and executive function (tablet version of Trail Making Test-part A and B), processing speed (tablet version of digit symbol substitution test), and visuospatial skill (figure selection).
Results: The overall prevalence of frailty, MCI, and frailty and MCI combined was 11.3%, 18.8%, and 2.7%, respectively. We found significant relationships between frailty and MCI (the odds ratio adjusted for age, sex, and education was 2.0 (95% confidence interval 1.5–2.5).
Conclusions: Using the OSHPE criteria, we found more participants with MCI than with frailty. The prevalence of frailty and MCI combined was 2.7% in our population. Future investigation is necessary to determine whether this population is at increased risk for disability or mortality.

The rate of frailty and mild cognitive impairment (MCI), which increases with age, is a major risk factor for dependency, institutionalization, and mortality.[1,2,3,4] Individuals with disabilities have greater health care needs compared with those without.[5] The elderly population is highly heterogeneous, such that elderly people in the same age range may have a widely varied risk of disability. To prevent disability, population-based intervention programs should be targeted at those in the population with an increased risk of frailty and MCI.

Many studies have worked within research and clinical settings to identify target populations with frailty and MCI. For instance, the Interventions on Frailty Working Group assessed various methods for screening, recruiting, evaluating, and retaining frail elderly individuals in clinical trials.[6] They reported that most researchers focused on the following domains when identifying physical frailty: mobility,

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such as lower-extremity performance and gait abnormalities; muscle weakness; poor exercise tolerance; unstable balance; and factors related to body composition, such as weight loss, malnutrition, and muscle loss.[6] Participants with MCI in a community cohort were described by a group of investigators from the Mayo Clinic in 1999, who then produced a series of diagnostic criteria.[7] A conference of international MCI experts then revised these criteria,[8] and the National Institute on Aging joined the Alzheimer's Association to revise the diagnostic criteria for the symptomatic predementia phase of Alzheimer disease (AD). They outlined the following factors for the identification of MCI: concern regarding a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, and absence of dementia.[9]

Using the frailty criteria developed by the Cardiovascular Health Study (CHS), the overall prevalence of frailty in community-dwelling adults aged 65 or older in the United States has been found to range from 7% to 12%. In the CHS, the prevalence of frailty increased with age from 3.9% in the 65 to 74 age group to 25.0% in the 85+ age group, and was greater in women than in men (8% vs 5%).[10] Using the MCI criteria in the CHS cognition study, the overall prevalence of MCI was found to be 18.8%, and the prevalence increased with age from 18.8% in participants younger than 75 years to 28.9% in those older than 85 years.[11]

Several cross-sectional studies have reported an association between physical frailty and cognitive function.[6,10,12,13] In addition, longitudinal studies have revealed that a higher level of physical frailty is associated with an increased risk of incident AD[14] and MCI.[15] These studies suggest that in some older adults, physical frailty is associated with the development of MCI. Older adults who show signs of both physical frailty and MCI may be more likely to exhibit functional decline than those with either frailty or MCI. However, the combined prevalence of frailty and MCI and the relationships between frailty and MCI in the Japanese population has not been clearly established. Thus, the purpose of this study was to ascertain the combined prevalence of frailty and MCI and to identify the relationships among frailty, MCI, and demographics including age, sex, and education in the Japanese population, using a community-based survey.

Methods

Participants

Our national study assessed 5104 individuals 65 years and older (mean age 71 years) who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). Each individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. Inclusion criteria required each participant to be 65 years or older at the time of examination (2011 or 2012), and to reside in Obu city. Based on previous reports, we excluded participants with a history of Parkinson disease, stroke, or Mini-Mental State scores less than 18, as these conditions could produce characteristics of frailty.[3,10,16] We also excluded participants who had participated in similar studies, those with severe disabilities, and those with missing data values regarding determinants for frailty and MCI. In the present study, we examined the prevalence of frailty in 4745 participants, MCI in 5025 participants, and the combined prevalence of frailty and MCI in 4681 participants. Informed consent was obtained from all participants before their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

Measurements

The assessments were conducted by well-trained staff who had nursing, allied health, or similar qualifications. Before commencement of the study, all staff received training from the authors in the correct protocols for administering the assessment measures.

Operationalization of the Frailty Phenotype in OSHPE

We considered the frailty phenotype to be characterized by limitations in 3 or more of the following 5 domains: mobility, strength, endurance, physical activity, and nutrition. Mobility was measured in seconds using a stopwatch. Participants were asked to walk on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-meter walk path, with a 2-meter section to be traversed before passing the start marker so that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 meters past the end of the path to ensure a consistent walking pace while on the timed path. A low level of mobility was established according to a cutoff (<1.0 m/s). Grip strength was measured in kilograms using a Smedley-type handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). Low grip strength was established according to a sex-specific cutoff (male: <26 kg, female: <17 kg). Endurance was assessed via a self-report of exhaustion, which included questions from the Geriatric Depression Scale,[17] such as: "Do you feel full of energy?" If participants answered "no" to this question, we classified them as low endurance. We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" If participants answered "no" to both of these questions, we considered them to be physically inactive. Nutritional status was established according to self-reports of weight loss in response to the following question: "In the past 2 years, have you lost more than 5% of your body weight irrespective of intent to lose weight?" Patients with impairments in at least 3 of the 5 domains were considered to be frail.

Operationalization of the MCI in OSHPE

We defined MCI based on previous studies,[18,19,20] using the following criteria: subjective memory complaints, cognitive impairment (indicated by an age-adjusted score at least 1.5 SDs below the reference threshold of any of the tests, all of which are commonly used for detailed neuropsychological assessments); no evidence of functional dependency (no need for supervision or external help in performing activities in daily life); and exclusion from the clinical criteria for dementia. Screening for MCI included a standardized personal interview for collection of sociodemographic, lifestyle, medical history, and functional status (activities of daily living) data, along with cognitive screening that was conducted using the Mini-Mental State Examination (MMSE)[21] and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT).[22] Individuals with 23 or fewer points on the MMSE were considered to have a general cognitive impairment.[23] The NCGG-FAT consists of 8 tasks used to assess logical memory (immediate and delayed recognition), word list memory (immediate and delayed recall), attention and executive function (tablet version of Trail Making Test-part A and B), processing speed (tablet version of Digit Symbol Substitution Test), and visuospatial skill (figure selection). The participants were given 20 to 30 minutes to complete the battery, which consisted of the previously mentioned 8 tasks. High test-retest reliability and moderate to high validity were confirmed in community-dwelling older adults for all task components of the NCGG-FAT.[22] All tests used in this study had previously established standardized thresholds for the definition of impairment in the corresponding domain (score <1.5 SDs below the age-specific mean) for population-based OSHPE cohort consisting of older adults.

Statistical Analysis

We compared age-, sex-, and education-specific prevalence, as well as the combined prevalence rates of frailty and MCI using χ^2 tests. The prevalence of frailty and MCI were explored in 4745 and 5025 participants, respectively. In calculating the combined prevalence, we found that 4681 participants did not meet the exclusion criteria for frailty or MCI. A multivariate logistic regression model was used to determine the odds ratios of MCI or frailty with respect to age category, sex, and education level. Participants with low general cognitive function were excluded from the multivariate analysis. As a result, the multivariate analysis included data from 3497 participants. All data management and statistical computations were performed using the IBM SPSS Statistics 19.0 software package (SPSS Inc., Chicago, IL).

Results

The OSHPE identified 538 (11.3%) elderly participants who had symptoms of frailty and 945 (18.8%) who had MCI (Table 1). Figures 1 and 2 show our findings regarding the prevalence of frailty and MCI, respectively. We found that the prevalence of frailty increased with advancing age. Of the 538 participants who were classified as frail, 192 (34.9%) were 80 years and older. The prevalence of frailty was higher in women than in men ($P < .05$), and a lower level of education was significantly associated with prevalence of frailty ($P < .01$). Participants who reported 9 or fewer years of education had a 16.4% rate of frailty, whereas in those who reported at least 13 years of education, this rate was 7.7% (Table 1 and Figure 1).

The OSHPE found young-old, 65 to 74 years, participants to have a higher rate of MCI than old-old, 75 years and older, participants. Educational level was significantly associated with MCI ($P < .01$). Participants who reported 9 or fewer years of education had a 23.4% rate of MCI, whereas this rate was reduced to 14.1% in participants who reported at least 13 years of education (Table 1 and Figure 2). The OSHPE found no significant sex-specific differences in the prevalence of MCI.

Table 1 shows the distribution of the combined prevalence of frailty and MCI by age, sex, and educational level. The OSHIPE revealed 126 (2.7%) participants with a combined incidence of frailty and MCI. Combined prevalence increased with age, with the highest rate found in the age group containing participants who were 80 years and older (6.9%). Participants with a low educational level had a higher rate of MCI combined with frailty (4.4% for 9 or fewer years) than those with higher education (1.3% for 13 years and more). No clear pattern emerged for any sex-specific differences in the prevalence of combined frailty and MCI (Table 1).

Our multivariate analysis found 3497 participants from the OSHPE cohort who did not meet the exclusion criteria for frailty and MCI and who maintained objective cognitive function. We found several significant relationships between frailty and MCI (odds ratio [OR] = 2.0, 95% confidence interval [95% CI] 1.5–2.5). In terms of the relationship between frailty and sociodemographics, participants aged 65 to 69 years were less likely to be frail than older participants (OR = 2.7, 95% CI 1.9–3.8, for the group 75 to 79 years of age, and OR = 6.9, 95% CI 4.9–9.7, for the group 80 years and older). There were no significant associations observed between frailty and sex. Participants with 9 or fewer years of education had a higher OR (1.4) than participants with at least 13 years of education (Table 2).

In terms of the relationship between MCI and sociodemographics, female participants had a significantly lower OR (0.8, 95% CI 0.7–1.0) than male participants. There was an evident relationship between MCI and educational level. In comparison with participants with at least 13 years of education, participants with a lower level of education were more likely to have MCI (OR = 1.5, 95% CI 1.2–1.8, for those with 10–12 years of education, and OR = 3.2, 95% CI 2.5–4.0, for those with 9 or fewer years of education) (Table 2).

Discussion

This study presents original data regarding vulnerability for physical and cognitive decline in a sample of 5104 elderly community dwellers in Japan. To our knowledge, this is the first study about frailty and MCI in this region of the world. Japan has a rapidly aging population in comparison with North, Central, and South America, as well as Europe. An examination of the differences in levels of frailty and MCI between countries may be useful in developing health care policies, especially in countries where the population is expected to rapidly age in the near future.

Growing evidence has indicated that there is a connection between frailty and cognitive impairment. Several studies have reported a longitudinal association between frailty and rate of MCI in elderly community-dwelling individuals. Boyle et al[15] reported, in an assessment that used 12 years of annual follow-up data, that physical frailty was associated with a high risk of MCI, such that each 1-unit (grip strength, timed walk, body composition, and fatigue) increase in physical frailty was associated with a 63% increase in the risk of MCI. Auyeung et al[24] identified that physical frailty, as indicated by

Table 1
Number of Participants and Prevalence of Frailty and Mild Cognitive Impairment (MCI)

	Frailty (n = 4745)			MCI (n = 5025)			Combined (n = 4681)
	Without Frailty	With Frailty	Prevalence	Without MCI	With MCI	Prevalence	Prevalence
All participants	4207	538	11.3%	4080	945	18.8%	2.7%
Age, y			$P < .01$			$P < .02$	
65–69	1794	106	5.6%	1583	390	19.80%	1.6%
70–74	1344	105	7.2%	1221	307	20.10%	2.2%
75–79	711	135	16.0%	771	145	15.80%	3.4%
≥80	358	192	34.9%	505	103	16.90%	6.9%
Sex			$P < .05$			$P < .05$	
Females	2157	302	12.3%	2073	489	19.10%	3.0%
Males	2050	236	10.3%	2007	456	18.50%	2.4%
Educational level, y			$P < .01$			$P < .01$	
≤9	1420	279	16.4%	1414	431	23.40%	4.4%
10–12	1812	179	9.0%	1712	357	17.30%	2.0%
≥13	963	80	7.7%	943	155	14.10%	1.3%

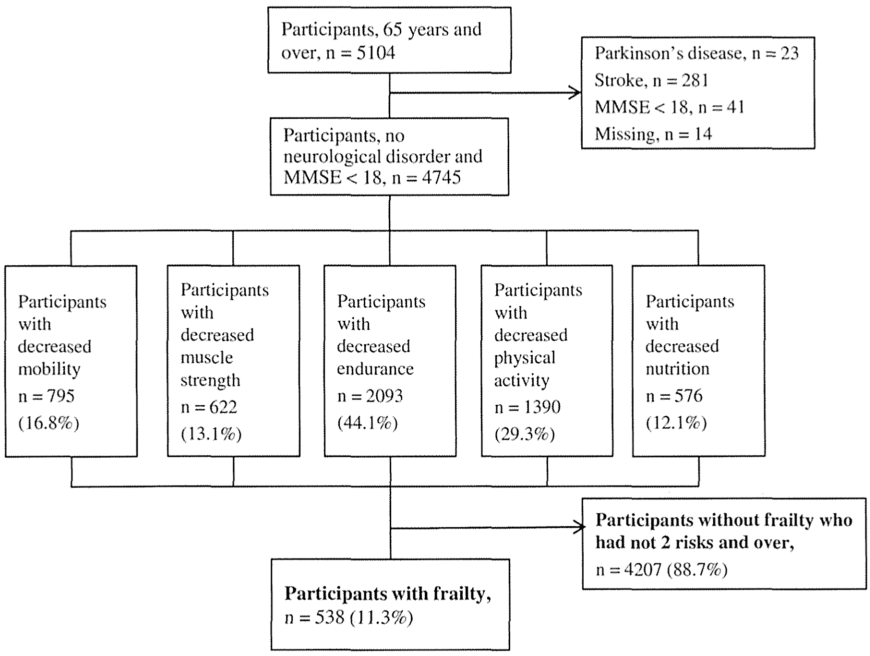

Fig. 1. Participants' flow to find frail older adults.

low body weight, weaker grip strength, slower performance in the chair-stand test, and shorter step-length in men and weaker grip strength in women, was associated with a decline in MMSE score over a 4-year period. Similarly, low cognitive function was independently associated with an increased risk of frailty in older adults. Raji et al. reported that nonfrail participants with a poor MMSE score (<21) at baseline had a 9% probability per year of becoming frail over a 10-year period, compared to individuals with normal cognition (MMSE

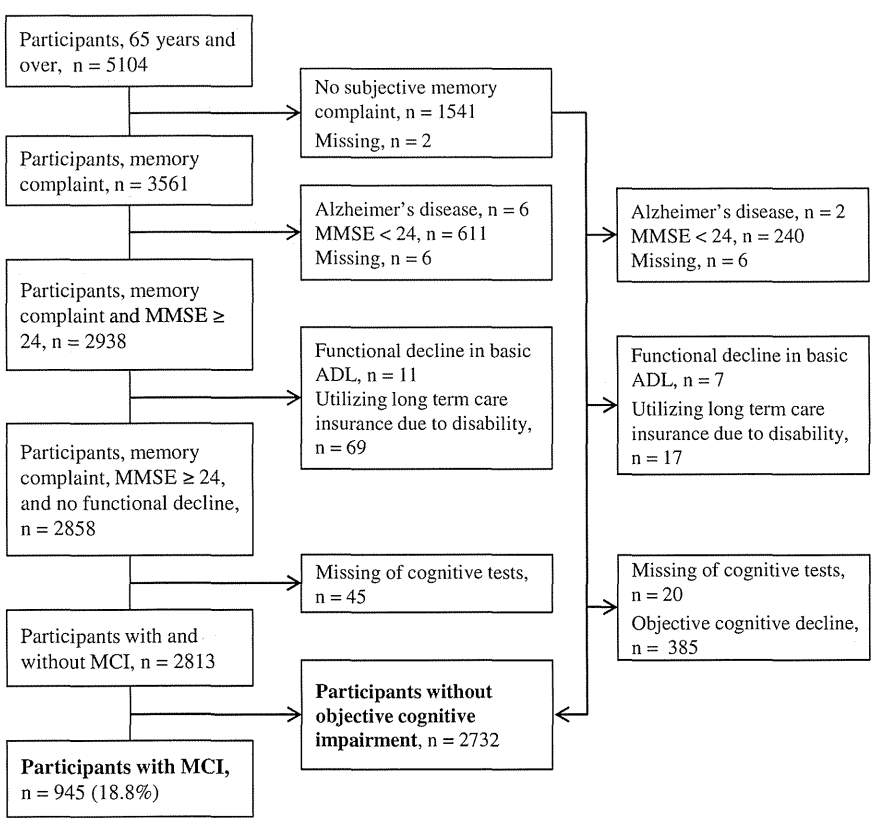

Fig. 2. Participants' flow to find MCI older adults.

Table 2
Relationships Between Frailty, Mild Cognitive Impairment (MCI), and Sociodemographics

	Frailty		MCI	
	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
MCI	2.0 (1.5–2.5)	<.01		
Frailty			2.0 (1.5–2.5)	<.01
Age, y	*P* for trend	<.01	*P* for trend	>.05
65–69	1		1	
70–74	1.2 (0.9–1.7)	.30	1.0 (0.8–1.2)	.95
75–79	2.7 (1.9–3.8)	<.01	0.7 (0.6–0.9)	.01
≥80	6.9 (4.9–9.7)	<.01	0.9 (0.7–1.2)	.54
Sex				
Males	1		1	
Females	1.1 (0.9–1.4)	.45	0.8 (0.7–1.0)	.04
Educational level, y	*P* for trend	.02	*P* for trend	<.01
≥13	1		1	
10–12	1.0 (0.7–1.4)	.85	1.5 (1.2–1.8)	<.01
≤9	1.4 (1.0–2.0)	<.05	3.2 (2.5–4.0)	<.01

21+).[25] Although the criteria for determining frailty and MCI vary slightly between studies, our results were in accordance with previous findings, and thus add support to the association between frailty and MCI.

The prevalence of frailty was 11.3% in our participant group, a rate slightly higher than that of previous studies that also used the CHS frailty criteria. In the American Cardiovascular Health Study, the prevalence of frailty among 5317 community-dwelling men and women aged 65 years and older was 6.9%, and frailty was associated with older age, male gender, being African American, having lower education and income, poorer health, and higher rates of comorbid chronic disease and disability.[10] The French Three-City Study demonstrated a frailty prevalence of 7% among 6078 community-dwelling men and women aged 65 years and older, and frailty was associated with older age, female gender, lower education, lower income, a poorer self-reported health status, and more chronic disease in addition to incident disability.[26] The Hertfordshire Cohort Study (HCS), UK, reported that the prevalence of frailty, as defined by CHS frailty criteria, among 638 community-dwelling participants aged 64 to 74 years was 8.5% for women and 4.1% for men.[27] The principal difference in the frailty criteria used by the CHS and OSHPE is the cutoff point for walking speed: in the CHS it is set at 0.65 m/s (height ≤173 cm) and in the OSHPE it is 1.0 m/s. This difference may be one explanation for the higher prevalence observed in studies using the OSHPE. The Survey of Health, Aging, and Retirement in Europe (SHARE) studied 16,584 men and women aged 50 years and older, and found that the prevalence of frailty in the nondisabled population aged 65 years and over ranged from 3.9% to 21.0%. The SHARE study demonstrated a higher prevalence of frailty in southern (9.3% to 21.0%) compared with northern Europe (<9.0%).[28] The SHARE study defined slowness using the following 2 questions regarding mobility: "Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 meters" and "... climbing 1 flight of stairs without resting." Gait velocity has consistently been reported to differentiate between participants with and without functional decline, as frail elderly individuals walk significantly slower than their nonfrail peers.[29,30] Thus, gait velocity has been found to be a strong predictor of adverse events, such as disability,[31-37] mortality,[32,33,38,39] hospitalization,[32,33,35,40] and falls.[40,41] The cutoff point for walking speed in the present study was 1.0 m/s, which appears to be a critical point for predicting future functional decline in community-dwelling elderly individuals.[32,33,35,36,37] These results suggest that walking speed may be the most useful measurement for determining frailty and predicting future functional decline in older adults.[42,43]

It is likely that the reported prevalence of MCI varies between studies as a result of different diagnostic criteria, as well as different sampling and assessment procedures. Despite some methodological differences, most previous studies report prevalence figures for MCI or for cognitive impairment without dementia ranging from 11% to 23%. The Women's Cognitive Impairment Study used global and domain-specific cognitive measures and found the prevalence of MCI or cognitive impairment without dementia to be 23.2% in a sample of 1299 participants aged 85 years and older.[19] The Mayo Clinic Study of Aging diagnosed 329 of 1969 study participants (16.7%) with MCI or cognitive impairment without dementia using the Clinical Dementia Rating Scale, a neurologic evaluation, and neuropsychological testing to assess 4 cognitive domains: memory, executive function, language, and visuospatial skills.[44] A study from Leipzig, Germany, that used a 55-point composite instrument found the overall prevalence of MCI or cognitive impairment without dementia to be 19.3% in participants aged 75 years and older.[45] The Cardiovascular Health Study found the overall rate of MCI or cognitive impairment without dementia to be 19% in participants aged 75 years and older.[11] In the Aging, Demographics, and Memory Study, an estimated 5.4 million people (22.2% of the total population of the country) in the United States aged 71 years or older were found to have cognitive impairment without dementia.[46] In a Japanese study, MCI was diagnosed in 271 of 1433 study participants (18.9%).[47] In the above-mentioned study, a diagnosis of MCI was contingent on cognitive performance 1.0[44,45,47] or 1.5 SDs[11,19,46] below at least one test measure. In the present study, we found the prevalence of MCI to be 18.8%, which is similar to previous studies that used multiple cognitive tests to detect MCI.

In the present study, we found the combined prevalence of frailty and MCI to be 2.7% among 4681 community-dwelling elderly participants. Our analyses of the relationships among frailty, MCI, and sociodemographics revealed a significant relationship between frailty and MCI (OR 2.0). These results suggest that frailty may coincide with MCI in older adults who exhibit vulnerability factors for both conditions. Many researchers believe that the definition of frailty should include mental health as well as physical functioning. The Frailty Operative Definition-Consensus Conference Project reported that experts agreed on the importance of a more comprehensive definition of frailty that should include assessment of physical performance, including gait speed and mobility, nutritional status, mental health, and cognition.[48] The results of the present study were in line with the new concept of frailty, which included cognition. Individuals with a co-occurrence of frailty and MCI may face a higher risk of incidence disability than healthy older adults or older adults with either frailty or MCI. The French Three-City Study established that frail persons with a cognitive impairment are significantly more likely to develop disabilities in activities of daily living (ADL) and instrumental ADL disabilities.[49] Moreover, the Hispanic Established Populations for the Epidemiologic Study of the Elderly demonstrated that frailty and cognitive impairment affect mortality differently when they occur independently compared with when they are present together. For instance, individuals with cognitive impairment and frailty had higher mortality compared with individuals with either frailty or cognitive decline.[50] Further longitudinal study is needed to clarify the ways in which frailty and MCI might affect vulnerability among older adults.

Our multivariate analysis indicated that the participants with the highest risk of developing frailty were 80 years and older or had received fewer than 9 years of education. Many studies have reported relationships among frailty, age, and education. For instance, the Women's Health Initiative Observational Study found that age is significantly correlated with incident frailty. In contrast, the previously mentioned study found no clear relationship between MCI and age. The MCI criteria in the OSHPE is based on cognitive score (ie, <1.5 SDs below the age-specific mean of healthy peers). Our inability to find a relationship between MCI and age may have been because of our use of age-specific criteria.

Our logistic model revealed that participants with the highest risk of MCI were predominantly male and had received 9 or fewer years of education. The Mayo Clinic Study of Aging reported that the prevalence OR for MCI in men was 1.54 (95% CI 1.21–1.96; adjusted for age, and education). Several other studies have reported a higher rate of MCI in older adults who received fewer years of education.[19,20,44,51] In one study, this result remained essentially unchanged after adjusting for several demographic and clinical variables, as well as the Apolipoprotein E genotype, suggesting that this association is not due to comorbid conditions or to a differential rate of MCI in men compared with women.[44] Our results support these previous discoveries while adding the finding that ethnic differences do not explain the higher prevalence of MCI in men than in women. There is a clear relationship between educational level and prevalence of MCI. Indeed, our results suggest that educational level is more closely associated with MCI risk than age in the OSHPE criteria.

One strength of the present study is the size of the cohort assessed in a specific community. Our findings are backed by comprehensive geriatric assessments intended to identify frailty and cognitive impairments. To our knowledge, this is the first study to demonstrate the combined prevalence of frailty and MCI in a large sample of older adults. We identified MCI using the NCGG-FAT, which is useful for multidimensional cognitive screening in population-based samples to assess the risk of cognitive decline. In a hospital setting, psychologists, neurologists, and other specialists are available to perform psychological tests. It can be difficult to assemble specialists in Japan for assessments in a community setting. The NCGG-FAT is easily administered using a tablet PC with the instructions shown on the display. Therefore, it is not necessary for those collecting the data to have a thorough knowledge of neurocognitive measures, and the identity of the person administering the questionnaire will not strongly affect the results.

An important limitation of our study is that participants were not recruited randomly to complete the OSHPE. This may lead to an underestimation of the prevalence of frailty and MCI, as the participants were relatively healthy elderly persons who were able to access the health checkup from their homes. Second, for some participants, we were not able to contact an informant, such as family member, to verify medical records, lifestyle information, and asymptomatic aberrant behavior.

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References

1. Fried LP, Ettinger WH, Lind B, et al. Physical disability in older adults: A physiological approach. Cardiovascular Health Study Research Group. J Clin Epidemiol 1994;47:747–760.
2. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2007;62:744–751.
3. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc 2005;53:1321–1330.
4. Gnjidic D, Stanaway FF, Cumming R, et al. Mild cognitive impairment predicts institutionalization among older men: A population-based cohort study. PLoS One 2012;7:e46061.
5. Guralnik JM, Fried LP, Simonsick EM, et al. The Women's Health and Aging Study: Health and Social Characteristics of Older Women With Disability. Bethesda, MD: National Institute of Aging; 1995. NIH Pub. No: 95–4009.
6. Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. J Am Geriatr Soc 2004; 52:625–634.
7. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 1999;56:303–308.
8. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–246.
9. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.
10. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
11. Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 1. Arch Neurol 2003;60:1385–1389.
12. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–263.
13. Mitnitski AB, Song X, Rockwood K. The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. J Gerontol A Biol Sci Med Sci 2004;59:M627–M632.
14. Buchman AS, Boyle PA, Wilson RS, et al. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007; 69:483–489.
15. Boyle PA, Buchman AS, Wilson RS, et al. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc 2010;58:248–255.
16. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009;64:675–681.
17. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982;17: 37–49.
18. Jungwirth S, Weissgram S, Zehetmayer S, et al. VITA: Subtypes of mild cognitive impairment in a community-based cohort at the age of 75 years. Int J Geriatr Psychiatry 2005;20:452–458.
19. Yaffe K, Middleton LE, Lui LY, et al. Mild cognitive impairment, dementia, and their subtypes in oldest old women. Arch Neurol 2011;68:631–636.
20. Hanninen T, Hallikainen M, Tuomainen S, et al. Prevalence of mild cognitive impairment: A population-based study in elderly subjects. Acta Neurol Scand 2002;106:148–154.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198.
22. Makizako H, Shimada H, Park H, et al. Evaluation of multidimensional neurocognitive function using a tablet personal computer: Test-retest reliability and validity in community-dwelling older adults [published online ahead of print December 12, 2012]. Geriatr Gerontol Int doi:10.1111/ggi.12014.
23. Anthony JC, LeResche L, Niaz U, et al. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. Psychol Med 1982;12:397–408.
24. Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. J Nutr Health Aging 2011;15:690–694.
25. Raji MA, Al Snih S, Ostir GV, et al. Cognitive status and future risk of frailty in older Mexican Americans. J Gerontol A Biol Sci Med Sci 2010;65: 1228–1234.
26. Avila-Funes JA, Helmer C, Amieva H, et al. Frailty among community-dwelling elderly people in France: The three-city study. J Gerontol A Biol Sci Med Sci 2008;63:1089–1096.
27. Syddall H, Roberts HC, Evandrou M, et al. Prevalence and correlates of frailty among community-dwelling older men and women: Findings from the Hertfordshire Cohort Study. Age Ageing 2010;39:197–203.
28. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009;64:675–681.
29. Shimada H, Suzukawa M, Tiedemann A, et al. Which neuromuscular or cognitive test is the optimal screening tool to predict falls in frail community-dwelling older people? Gerontology 2009;55:532–538.
30. Tiedemann A, Shimada H, Sherrington C, et al. The comparative ability of eight functional mobility tests for predicting falls in community-dwelling older people. Age Ageing 2008;37:430–435.
31. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55:M221–M231.

32. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people—results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675–1680.
33. Cesari M, Kritchevsky SB, Newman AB, et al. Added value of physical performance measures in predicting adverse health-related events: Results from the Health, Aging And Body Composition Study. J Am Geriatr Soc 2009;57: 251–259.
34. Onder G, Penninx BW, Ferrucci L, et al. Measures of physical performance and risk for progressive and catastrophic disability: Results from the Women's Health and Aging Study. J Gerontol A Biol Sci Med Sci 2005;60: 74–79.
35. Studenski S, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003;51:314–322.
36. Simonsick EM, Newman AB, Visser M, et al. Mobility limitation in self-described well-functioning older adults: Importance of endurance walk testing. J Gerontol A Biol Sci Med Sci 2008;63:841–847.
37. Shinkai S, Watanabe S, Kumagai S, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing 2000;29:441–446.
38. Markides KS, Black SA, Ostir GV, et al. Lower body function and mortality in Mexican American elderly people. J Gerontol A Biol Sci Med Sci 2001;56: M243–M247.
39. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58.
40. Montero-Odasso M, Schapira M, Soriano ER, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci 2005;60:1304–1309.
41. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: The EPIDOS prospective study. Lancet 1996;348: 145–149.
42. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 2009;13:881–889.
43. Vermeulen J, Neyens JC, van Rossum E, et al. Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: A systematic review. BMC Geriatr 2011;11:33.
44. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010; 75:889–897.
45. Busse A, Hensel A, Guhne U, et al. Mild cognitive impairment: Long-term course of four clinical subtypes. Neurology 2006;67:2176–2185.
46. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med 2008;148:427–434.
47. Sasaki M, Kodama C, Hidaka S, et al. Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community. Int J Geriatr Psychiatry 2009;24:1119–1126.
48. Rodriguez-Manas L, Feart C, Mann G, et al. Searching for an operational definition of frailty: A Delphi method based consensus statement: The frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 2013;68:62–67.
49. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The three-city study. J Am Geriatr Soc 2009;57:453–461.
50. Cano C, Samper-Ternent R, Al Snih S, et al. Frailty and cognitive impairment as predictors of mortality in older Mexican Americans. J Nutr Health Aging 2012; 16:142–147.
51. Nie H, Xu Y, Liu B, et al. The prevalence of mild cognitive impairment about elderly population in China: A meta-analysis. Int J Geriatr Psychiatry 2011;26: 558–563.

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RESEARCH ARTICLE Open Access

Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment

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Abstract

Background: The risk of falling is associated with cognitive dysfunction. Older adults with mild cognitive impairment (MCI) exhibit an accelerated reduction of brain volume, and face an increased risk of falling. The current study examined the relationship between baseline physical performance, baseline gray matter volume and falls during a 12-month follow-up period among community-dwelling older adults with MCI.

Methods: Forty-two older adults with MCI (75.6 years, 43% women) underwent structural magnetic resonance imaging and baseline physical performance assessment, including knee-extension strength, one-legged standing time, and walking speed with normal pace. 'Fallers' were defined as people who had one or more falls during the 12-month follow-up period.

Results: Of the 42 participants, 26.2% (n = 11) experienced at least one fall during the 12-month follow-up period. Fallers exhibited slower walking speed and shorter one-legged standing time compared with non-fallers (both $p < .01$). One-legged standing time (sec) (standardized odds ratio [95% confidence interval]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. Voxel-based morphometry was used to examine differences in baseline gray matter volume between fallers and non-fallers, revealing that fallers exhibited a significantly greater reduction in the bilateral middle frontal gyrus and superior frontal gyrus.

Conclusions: Poor balance predicts falls over 12 months, and baseline lower gray matter densities in the middle frontal gyrus and superior frontal gyrus were associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.

Background

Falls and fall-related injuries are a common healthcare problem, and represent important causes of morbidity and mortality in older populations. One-third of all community-dwelling adults age 65 years and older experience at least one fall annually [1]. Many distinct causes for falls in older people have been reported by a large number of studies [1-4]. Impaired physical function, particularly muscle weakness and problems with gait and balance, are the most important contributors to the risk of falling [5]. The ageing of the worldwide population in recent decades has resulted in an increasing number of older adults with cognitive decline [6], and cognitive impairment has also been found to increase the risk of falling [7-10]. As such, correctly identifying the risk factors for falling among older adults with cognitive impairment is an important research question. In addition, people with cognitive impairment recover less well after a fall than those without cognitive impairment [11]. Therefore, the falling may have negative impact on health in older people with cognitive

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impairment compare with those without cognitive impairment. In older individuals with mild cognitive impairment (MCI) in particular, consideration of a broad range of causes of falls could play a role in reducing the fall risk and providing strategies to prevent falls among the high-risk population.

Several studies have examined falling in older adults with dementia, such as Alzheimer's disease [11,12]. However, little research has focused on falling among people with MCI, even though mild declines in cognitive function have been reported to be an important factor associated with falling [13]. Liu-Ambrose et al. demonstrated that older community-dwelling people with MCI but not dementia were at greater risk of falling than those without MCI [14]. Brain structural changes represent one of the key clinical features associated with MCI, including gray matter volume loss [15] and white matter hyperintensities (WMH) [16]. A recent prospective study indicated that greater WMH burden predicts falls over 12 months in non-demented community-dwelling older adults [17].

Although prospective evidence suggests that WMH are an important risk factor for falls in community-based older populations [17,18], it remains unclear whether gray matter volume predicts falls and which regions are related to a greater risk of falls in older adults with MCI. Structural changes in the brain have been linked to motor performance deficits [19]. WMH was reported to exhibit a negative correlation with postural stability involved balance, stepping and gait [20], while reduced gray matter density is associated with impaired gait performance [21-23] and postural instability [24]. Kido et al. [24] suggested that postural instability is associated with gray matter volume loss, and is related to pathological cognitive decline, such as MCI and AD. Lower gray matter volume has been found to be related not only to cognitive decline, but also to decreased physical function. Thus, gray matter volume loss may increase the risk of falls in older adults with MCI. In particular, a smaller volume of the prefrontal area might be associated with poor physical performance [22,23], such as slower gait and poor balance, but no evidence has been reported that smaller brain volume of specific regions is related to the occurrence of subsequent falls in older adults with MCI. In the current study, we sought to examine whether physical performance and gray matter volume were related to falls during a 12-month follow-up period among community-dwelling older adults with MCI.

Methods

Participants

The sample for this longitudinal study consisted of 42 community-dwelling older adults with MCI who completed a randomized controlled trial (RCT) (trial registration: UMIN-CTR UMIN000003662) evaluating the effects of multicomponent exercise on cognitive function. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The study design and the primary results of the RCT have been described previously [25]. All participants gave written informed consent prior to taking part in the study. Briefly, participants enrolled in the RCT were: aged 65 years and over, community dwelling, and did not suffer from dementia. All participants met the Petersen criteria for MCI [26]. Participants who had a Clinical Dementia Rating (CDR) = 0, or a CDR of 1–3, a history of neurological, psychiatric, or cardiac disorders or other severe health issues, use of donepezil, impairment in basic activities of daily living (ADL), and participation in other research projects were excluded from the RCT study. A total of 100 participants took part in the RCT and completed neuropsychological assessments including language, memory, attention, and executive function tests. All subjects in this study had objective impairments at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. The participants were classified to an amnestic MCI (aMCI) group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were then randomly assigned to either a multicomponent exercise group or an education control group using a ratio of 1:1. The sample for this longitudinal study involved participants in a control group. Of the 50 participants in the control group, 42 completed fall follow-up assessments during the 12-month follow-up period.

Physical performance measures

At baseline, all participants underwent an extensive assessment of measures by licensed and well-trained physical therapists.

Knee-extension strength

Isometric knee extension strength was tested twice using a dynamometer (Model MDKKS, Molten Co Ltd, Hiroshima, Japan) from the dominant leg (self-reported side they would use to kick a ball as far as possible). Knee extension was measured while the participant was sitting on a chair with a backrest and the knee flexed to 90°. A testing pad was attached to the front lower leg of the participant and strapped to the leg of the chair. The participant was instructed to push the pad with maximal strength. Licensed and well-trained physical therapists confirmed compensatory movement and assessed muscle strength. Participants practiced several times before data collection. Two trials were conducted, and the maximal isometric strength was determined as the peak torque (Nm) in the data analysis.

One-legged standing (OLS) test

The OLS test is a commonly used balance assessment of postural stability. For the OLS test, we asked participants to look straight ahead at a dot 50 cm in front of them, then to stand on their preferred leg with their eyes open and hands down alongside the trunk. OLS balance was measured as the length of time (0–60 s) participants were able to stand on one leg. The better of the two trials was used for statistical analysis.

Walking speed

WS was measured using a 5-m walking test. The participants' usual WS was measured over an 11-m straight and level path. The time taken (in seconds) to pass the 5-m mark on the path was used as the participant's score. A 3-m approach was allowed before the starting marker, and an additional 3 m of space was provided after the end marker of the 5-m path to ensure a usual walking pace throughout the task. Participants were instructed to walk the 11-m path at their usual walking pace. The time to complete the 5-m walking test was measured once and was used to calculate walking speed (m/min).

Falls follow-up

Fall frequency during the 12-month follow-up period was measured with two face-to-face interviews at 6 months and 12 months after baseline measurements. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [27]. In this study, 'fallers' were defined as people who had at least one fall during the 12-month follow-up period [28].

Magnetic resonance imaging (MRI) procedure

Magnetic resonance imaging (MRI) was performed using a 1.5-T system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1,700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 × 256, 1.3-mm slice thickness). Tissue segmentation, regulation, registration, and normalization were conducted in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) [29] was conducted for the image analysis. The normalized images were transformed into Montreal Neurological Institute space. The gray matter images were then smoothened using a Gaussian kernel of 12-mm full-width at half-maximum.

Statistical analysis

For baseline comparisons, basic characteristics and physical performance tests including knee-extension strength, OLS, and WS were compared between fallers and non-fallers using *t*-tests. Chi-square tests for differences in proportions were used to compare differences in sex and history of falling in the past year at baseline between the faller and non-faller groups. To describe variations in different physical performance factors related to falls, multivariate logistic regression analyses were performed to reveal the physical performance factors independently related to falls during the 12-month follow-up after adjusting for age, sex, body mass index (kg/m^2), and history of falling in the past year at baseline. We calculated the odds ratios (OR) with 95% confidence intervals (CI). These statistical analyses were calculated using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL).

In the voxel-based morphometry (VBM) analysis, data preprocessing and analysis was performed with the VBM8 toolbox, which is incorporated in the SPM8 software. VBM [30] was used to examine differences in baseline gray matter volume between fallers and non-fallers. We used unpaired t-tests in SPM8 to identify the locations of smaller gray matter volume in fallers compared to non-fallers during the 12-month follow-up period using MRI data at baseline. Age and sex were included as covariates. The statistical threshold selected for these analyses was $P < .001$ (uncorrected), with an extent threshold of 100 voxels.

Results

The characteristics and physical performance tests at baseline are presented in Table 1. Over the 12-month follow-up period, 11 of the 42 participants (26.2%) experienced at least one fall. Fallers exhibited poorer one-legged standing time ($p < .01$) and slower walking speed ($p < .01$) compared with non-fallers. In addition, the faller group had a significantly higher rate of fall history at baseline compared with the non-faller group ($p < .01$). In the multivariate logistic regression, OLS time (sec) (OR [95% CI]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. There was no statistical evidence of associations between falls and knee-extension strength (Nm) (1.02 [0.96, 1.08], $p = .59$) and walking speed (m/min) (0.91 [0.81, 1.03], $p = .13$) (Table 2).

Table 1 Comparison of characteristics and physical performance tests between non-fallers and fallers at baseline

	Total (n = 42)	Non-fallers (n = 31)	Fallers (n = 11)	P-value
Age, years	75.6 ± 6.3	75.2 ± 6.5	76.8 ± 5.9	0.462
Female, n (%)	18 (42.9)	12 (38.7)	6 (54.4)	0.362
History of falling in the past year, n (%)	13 (31.0)	6 (19.4)	7 (63.6)	0.006
Knee-extension strength, Nm	60.5 ± 26.8	63.4 ± 23.3	52.3 ± 34.7	0.242
One-legged standing time, sec	32.3 ± 24.2	38.9 ± 22.3	13.8 ± 19.7	0.002
Walking speed, m/m	66.7 ± 12.6	70.0 ± 11.8	57.5 ± 10.4	0.004
Mini-mental state examination, score	26.3 ± 2.7	26.6 ± 2.0	25.5 ± 3.9	0.112

The gray matter density profiles used for examining differences between fallers and non-fallers at baseline are shown in Figure 1. VBM analysis revealed that fallers exhibited lower gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus (Table 3). These regions correspond to the premotor cortex and supplementary motor area.

Discussion

The present study examined whether baseline physical performance and gray matter volume are related to falls during a 12-month follow-up period in community-dwelling older adults with MCI. Our results indicated that older adults with MCI exhibiting poor balance had a greater risk of falls during the 12-month follow-up period, while adjusting for age, sex, body mass index, and history of falling at baseline. In addition, baseline lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with the occurrence of subsequent falls. To our knowledge, this is the first study to examine the association between lower gray matter density and risk of falls in older adults with MCI.

Problems with gait and balance have been reported to have the strongest association with falling [2,31]. Slower walking speed has been found to be an independent predictor of falling [32,33]. Poor balance represented by increased postural sway and gait asymmetry has been reported to approximately triple the risk of falling [2]. A previous systematic review and meta-analysis provided a summary estimate for falls due to balance impairment at a relative risk of 1.42 [34]. Therefore, an assessment of balance and gait for older adults, particularly those without a history of falling, has been recommended [35]. Moreover, cognitive impairment has been associated with the risk of falls as well as deficits of physical function [2]. A recent systematic review and meta-analysis confirmed that cognitive deficits detected in clinical assessment are associated with an increased fall risk in community and institution-dwelling older adults [36]. A number of studies have examined the risk of falls in older adults with dementia [37]. However, little research has focused on individuals with MCI. MCI is increasingly recognized as a substantial clinical problem in older populations [38], so it is important to determine risk factors for falling among older individuals with MCI, and to develop effective fall-prevention strategies. A previous study showed that older women with MCI demonstrated a greater number of risk factors for falling compared with older women without MCI [14]. The results of the present study indicate that poor balance assessed by one-legged standing time predicts falls in people with MCI prospectively over 12 months. Although fallers exhibited slower walking speed compared with non-fallers, walking speed was not associated with the occurrence of subsequent falls after adjusting for age, sex, body mass index, and history of falling at baseline. There was no difference in the extension strength between fallers and non-fallers. The results of this study indicate that poor balance is the important factor related to an increased risk of falling among people with MCI. Muscle weakness and problems with mobility had been considered to be the important contributors to the risk of falling in older people [5], and there are presumably some relationships. In study cohorts including older people with MCI and similar lower muscle strength, like the present study, poor balance may have a greater impact on increased risk of falling

Table 2 Multivariate logistic regression summary for physical performance on falls (n = 42)

Variables	Odds ratio	95% confidence intervals	*p* Value
Knee-extension strength, Nm	1.017	0.957-1.080	0.588
One-legged standing time, sec	0.891	0.809-0.981	0.019
Walking speed, m/m	0.911	0.806-1.029	0.133

Notes: Age, sex, body mass index (kg/m^2) and history of falling in the past year at baseline were included as covariates.

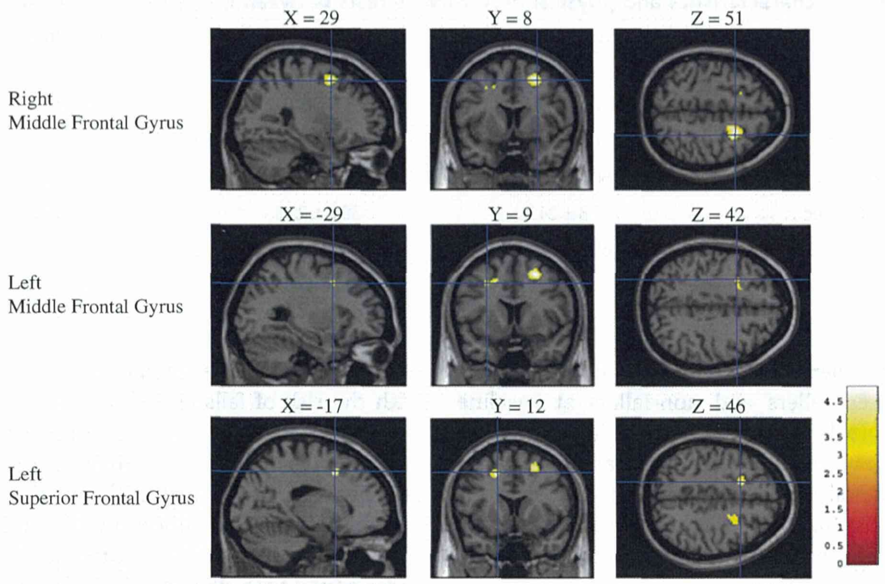

Figure 1 Gray matter density in fallers versus non-fallers. Regions of gray matter reduction in fallers compared to non-fallers ($p < 0.001$, uncorrected). Fallers exhibited a greater reduction of gray matter loss in the bilateral middle frontal gyrus and superior frontal gyrus.

than walking performance. Certainly, poor balance could be one of the predictors of walking decline among older people [39]. Balance ability may be an important dimension of physical functioning to predict the occurrence of subsequent falls among older people with MCI, as well as those with intact cognition. The present study has advantages including the examination of occurrence of subsequent falls during a 12-month follow-up period and neuroimaging assessments in older adults with MCI. However, our sample was not large, and selection bias may affect the results of the relationships between physical performance and occurrence of subsequent falls. Therefore, future studies with larger numbers of MCI subjects and a longitudinal design are needed to add evidence to the present results.

Unlike previous investigations, the current study included MRI scanning and a follow-up assessment of falls in community-dwelling older adults with MCI. The results provide the first evidence that lower gray matter volume in the middle and superior frontal gyrus is related to the occurrence of subsequent falls among older adults with MCI. Age-related changes in the brain may contribute to the subtle onset of motor disturbances in older people. Previous brain-imaging studies of older adults have reported that age-related changes in the brain, such as lower global brain volume, WMH, and microbleeds, are associated with clinical measures of poor balance and slow gait [40-43]. The association between MRI-detected lower brain volume and falls in older adults with MCI has not been examined longitudinally. In the present study, fallers exhibited decreased gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus corresponding to premotor cortex and supplementary motor area. These particular regions are likely to play an important role in predicting fall-risk because the middle frontal gyrus is involved in controlling behavior with spatial and sensory guidance.

Growing evidence suggests that brain function is associated with physical function, as confirmed by neuroimaging techniques. Structural changes of the brain in older people are reported to be related to physical performance, such as gait dysfunction [44,45], postural instability [24], and lack of cardiorespiratory fitness [46].

Table 3 VBM results including age and sex as covariates

					MNI coordinates		
Location	Cluster size (K)	Peak T	Z score	P (uncorrected)	X	Y	Z
Right middle frontal gyrus	594	4.87	4.27	< 0.001	29	8	51
Left middle frontal gyrus	165	4.35	3.90	< 0.001	−29	9	42
Left superior frontal gyrus		4.78	4.20	< 0.001	−17	12	46

Note: *VBM* voxel-based morphometry.

Activation in the frontal cortex, including the premotor cortex and the supplementary motor areas, have been reported to increase during human gait by studies using near-infrared spectroscopic imaging [47-50]. Previous studies have reported that lower brain volume in the prefrontal areas is associated with slower gait in high-functioning or cognitively normal older adults [23,40,51]. Other neuroimaging studies have indicated that gait requires complex visuo-sensorimotor coordination, and is associated with activation of the medial frontoparietal region, e.g. the primary sensory and motor areas, supplementary motor area, lateral premotor cortex, cingulate cortex, superior parietal lobule, precuneus, and the infratentorial region including the dorsal region [52-54]. The middle frontal gyrus is involved in motor output and the direct control of behavior, as well as planning, spatial guidance, and sensory guidance of movement [55]. Lower gray matter volume in the premotor cortex and supplementary motor area may be risk factors for falls in older adults. Falls often occur when older individuals attempt to avoid an obstacle in their path, requiring the control of behavior and the planning of movement under sensory guidance. The premotor cortex and supplementary motor area may play an important role in preventing falls when spatial and sensory guidance are required for movement.

Several limitations of the current study should be noted. First, fall experience during the 12-month follow-up period were confirmed with two face-to-face interviews at 6-months and 12-months after baseline, while previous studies have reported that monthly fall diaries and follow-up telephone calls provide more accurate measures of fall frequency [56,57]. Second, participants who had at least one fall during the 12-month follow-up period were categorized as fallers in this study. A previous study reported that single fallers are more similar to nonfallers than to recurrent fallers on a range of medical, physical, and psychological risk factors [58]. Other studies defined fallers as people who had at least one injurious or two non-injurious falls [17,59]. In addition, our MRI scans were performed using a 1.5-T system with relatively low resolution. We performed the VBM analysis to identify the locations of group differences in gray matter volume. Therefore, we consider that our results cannot provide evidence for whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk. Although it is unclear whether lower gray matter volume is related to poor balance in older adults with MCI, the current study revealed that poor balance and lower gray matter volume in the middle frontal gyrus and superior frontal gyrus were associated with falls. To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed.

Conclusions

The current findings indicate that poor balance predicts falls over a 12-month period, and that lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HM has made substantial contributions to conception and design, subject recruitment, analysis and interpretation of data, and writing the manuscript. HS has made substantial contributions to conception and design, subject recruitment, interpretation of data, and writing the manuscript. TD has made substantial contributions to subject recruitment, acquisition of data, interpretation of data, and manuscript preparation. HP has made substantial contributions to conception and design, interpretation of data, and writing the manuscript. DY contributed subject recruitment and manuscript preparation. KU and KT contributed subject recruitment and acquisition of data. TLA has been involved in drafting the manuscript or revising it critically for important intellectual content. TS has made substantial contributions to conception and design and writing the manuscript. All authors read and approved the final manuscript.

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References

1. Masud T, Morris RO: **Epidemiology of falls.** *Age Ageing* 2001, 30(Suppl 4):3–7.
2. American Geriatrics Society, British Geriatrics Society, American Academy of Orthopaedic Surgeons Panel on Falls Prevention: **Guideline for the prevention of falls in older persons.** *J Am Geriatr Soc* 2001, 49(5):664–672.
3. Robbins AS, Rubenstein LZ, Josephson KR, Schulman BL, Osterweil D, Fine G: **Predictors of falls among elderly people. Results of two population-based studies.** *Arch Intern Med* 1989, 149(7):1628–1633.

4. Rubenstein LZ, Josephson KR: The epidemiology of falls and syncope. *Clin Geriatr Med* 2002, 18(2):141–158.
5. Rubenstein LZ: Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing* 2006, 35(Suppl 2):ii37–ii41.
6. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, *et al*: Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005, 366(9503):2112–2117.
7. Bueno-Cavanillas A, Padilla-Ruiz F, Jimenez-Moleon JJ, Peinado-Alonso CA, Galvez-Vargas R: Risk factors in falls among the elderly according to extrinsic and intrinsic precipitating causes. *Eur J Epidemiol* 2000, 16(9):849–859.
8. van Doorn C, Gruber-Baldini AL, Zimmerman S, Hebel JR, Port CL, Baumgarten M, Quinn CC, Taler G, May C, Magaziner J: Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc* 2003, 51(9):1213–1218.
9. Tinetti ME, Speechley M, Ginter SF: Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988, 319(26):1701–1707.
10. van Dijk PT, Meulenberg OG, van de Sande HJ, Habbema JD: Falls in dementia patients. *Gerontologist* 1993, 33(2):200–204.
11. Shaw FE: Falls in cognitive impairment and dementia. *Clin Geriatr Med* 2002, 18(2):159–173.
12. Buchner DM, Larson EB: Falls and fractures in patients with Alzheimer-type dementia. *JAMA* 1987, 257(11):1492–1495.
13. Anstey KJ, von Sanden C, Luszcz MA: An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. *J Am Geriatr Soc* 2006, 54(8):1169–1176.
14. Liu-Ambrose TY, Ashe MC, Graf P, Beattie BL, Khan KM: Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther* 2008, 88(12):1482–1491.
15. Whitwell JL, Petersen RC, Negash S, Weigand SD, Kantarci K, Ivnik RJ, Knopman DS, Boeve BF, Smith GE, Jack CR Jr: Patterns of atrophy differ among specific subtypes of mild cognitive impairment. *Arch Neurol* 2007, 64(8):1130–1138.
16. Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, Tanzi RE, Albert MS, Greenberg SM, Guttmann CR: Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol* 2008, 65(1):94–100.
17. Zheng JJ, Lord SR, Close JC, Sachdev PS, Wen W, Brodaty H, Delbaere K: Brain white matter hyperintensities, Executive dysfunction, instability, and falls in older people: a prospective cohort study. *J Gerontol A Biol Sci Med Sci* 2012, 67(10):1085–1091.
18. Srikanth V, Beare R, Blizzard L, Phan T, Stapleton J, Chen J, Callisaya M, Martin K, Reutens D: Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. *Stroke* 2009, 40(1):175–180.
19. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB: Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev* 2010, 34(5):721–733.
20. Zheng JJ, Delbaere K, Close JC, Sachdev PS, Lord SR: Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke* 2011, 42(7):2086–2090.
21. Rosano C, Aizenstein H, Brach J, Longenberger A, Studenski S, Newman AB: Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *J Gerontol A Biol Sci Med Sci* 2008, 63(12):1380–1388.
22. Rosano C, Aizenstein HJ, Studenski S, Newman AB: A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2007, 62(9):1048–1055.
23. Rosano C, Studenski SA, Aizenstein HJ, Boudreau RM, Longstreth WT Jr, Newman AB: Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing* 2012, 41(1):58–64.
24. Kido T, Tabara Y, Igase M, Ochi N, Uetani E, Nagai T, Yamamoto M, Taguchi K, Miki T, Kohara K: Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIPP study. *Dement Geriatr Cogn Disord* 2010, 29(5):379–387.
25. Suzuki T, Shimada H, Makizako H, Doi T, Yoshida D, Ito K, Shimokata H, Washimi Y, Endo H, Kato T: A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PloS one* 2013, 8(4):e61483.
26. Petersen RC: Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004, 256(3):183–194.
27. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C: Development of a common outcome data set for fall injury prevention trials: the prevention of falls network Europe consensus. *J Am Geriatr Soc* 2005, 53(9):1618–1622.
28. Bootsma-van der Wiel A, Gussekloo J, de Craen AJ, van Exel E, Bloem BR, Westendorp RG: Walking and talking as predictors of falls in the general population: the Leiden 85-plus study. *J Am Geriatr Soc* 2003, 51(10):1466–1471.
29. Ashburner J: A fast diffeomorphic image registration algorithm. *Neuroimage* 2007, 38(1):95–113.
30. Ashburner J, Friston KJ: Unified segmentation. *Neuroimage* 2005, 26(3):839–851.
31. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E: Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology* 2010, 21(5):658–668.
32. Woollacott MH: Age-related changes in posture and movement. *J Gerontol* 1993, 48(Spec No):56–60.
33. Shimada H, Suzukawa M, Tiedemann A, Kobayashi K, Yoshida H, Suzuki T: Which neuromuscular or cognitive test is the optimal screening tool to predict falls in frail community-dwelling older people? *Gerontology* 2009, 55(5):532–538.
34. Muir SW, Berg K, Chesworth B, Klar N, Speechley M: Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. *J Clin Epidemiol* 2010, 63(4):389–406.
35. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ: Will my patient fall? *JAMA* 2007, 297(1):77–86.
36. Muir SW, Gopaul K, Montero Odasso MM: The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing* 2012, 41(3):299–308.
37. Harlein J, Dassen T, Halfens RJ, Heinze C: Fall risk factors in older people with dementia or cognitive impairment: a systematic review. *J Adv Nurs* 2009, 65(5):922–933.
38. Feldman HH, Jacova C: Mild cognitive impairment. *Am J Geriatr Psychiatry* 2005, 13(8):645–655.
39. Rantanen T, Guralnik JM, Ferrucci L, Penninx BW, Leveille S, Sipila S, Fried LP: Coimpairments as predictors of severe walking disability in older women. *J Am Geriatr Soc* 2001, 49(1):21–27.
40. Rosano C, Brach J, Studenski S, Longstreth WT Jr, Newman AB: Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology* 2007, 29(3–4):193–200.
41. Choi P, Ren M, Phan TG, Callisaya M, Ly JV, Beare R, Chong W, Srikanth V: Silent infarcts and cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study. *Stroke* 2012, 43(6):1505–1510.
42. Carmelli D, DeCarli C, Swan GE, Kelly-Hayes M, Wolf PA, Reed T, Guralnik JM: The joint effect of apolipoprotein E epsilon4 and MRI findings on lower-extremity function and decline in cognitive function. *J Gerontol A Biol Sci Med Sci* 2000, 55(2):M103–M109.
43. Starr JM, Leaper SA, Murray AD, Lemmon HA, Staff RT, Deary IJ, Whalley LJ: Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatry* 2003, 74(1):94–98.
44. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Langhorne P, *et al*: Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology* 2008, 70(12):935–942.
45. Whitman GT, Tang Y, Lin A, Baloh RW: A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. *Neurology* 2001, 57(6):990–994.
46. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM, Swerdlow RH: Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology* 2008, 71(3):210–216.
47. Suzuki M, Miyai I, Ono T, Kubota K: Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *Neuroimage* 2008, 39(2):600–607.
48. Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K: Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* 2001, 14(5):1186–1192.
49. Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T, Kubota K: Prefrontal and premotor cortices are involved in adapting walking and running

speed on the treadmill: an optical imaging study. *Neuroimage* 2004, 23(3):1020–1026.
50. Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J: fNIRS study of walking and walking while talking in young and old individuals. *J Gerontol A Biol Sci Med Sci* 2011, 66(8):879–887.
51. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT Jr, Newman AB: Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc* 2005, 53(4):649–654.
52. Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J, Shibasaki H: Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett* 1997, 228(3):183–186.
53. Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H: Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain* 1999, 122(Pt 7):1271–1282.
54. la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M, Brandt T, Strupp M, Bartenstein P, Jahn K: Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. *Neuroimage* 2010, 50(4):1589–1598.
55. Graziano MS, Gross CG: Spatial maps for the control of movement. *Curr Opin Neurobiol* 1998, 8(2):195–201.
56. Ganz DA, Higashi T, Rubenstein LZ: Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *J Am Geriatr Soc* 2005, 53(12):2190–2194.
57. Hannan MT, Gagnon MM, Aneja J, Jones RN, Cupples LA, Lipsitz LA, Samelson EJ, Leveille SG, Kiel DP: Optimizing the tracking of falls in studies of older participants: comparison of quarterly telephone recall with monthly falls calendars in the MOBILIZE Boston Study. *Am J Epidemiol* 2010, 171(9):1031–1036.
58. Lord SR, Ward JA, Williams P, Anstey KJ: Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc* 1994, 42(10):1110–1117.
59. Delbaere K, Close JC, Heim J, Sachdev PS, Brodaty H, Slavin MJ, Kochan NA, Lord SR: A multifactorial approach to understanding fall risk in older people. *J Am Geriatr Soc* 2010, 58(9):1679–1685.

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Original Research Article

Six-Minute Walking Distance Correlated with Memory and Brain Volume in Older Adults with Mild Cognitive Impairment: A Voxel-Based Morphometry Study

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Key Words

Exercise capacity · Logical memory · Visual memory · Brain atrophy · Fitness · Walking · Cognitive impairment

Abstract

Background/Aims: High fitness levels play an important role in maintaining memory function and delaying the progression of structural brain changes in older people at risk of developing dementia. However, it is unclear which specific regions of the brain volume are associated with exercise capacity. We investigated whether exercise capacity, determined by a 6-min walking distance (6MWD), is associated with measures of logical and visual memory and where gray matter regions correlate with exercise capacity in older adults with mild cognitive impairment (MCI). ***Methods:*** Ninety-one community-dwelling older adults with MCI completed a 6-min walking test, structural magnetic resonance imaging scanning, and memory tests. The Wechsler Memory Scale-Revised Logical Memory and Rey-Osterrieth Complex Figure Tests were used to assess logical and visual memory, respectively. ***Results:*** The logical and visual memory tests were positively correlated with the 6MWD ($p < 0.01$). Poor performance in the 6MWD was correlated with a reduced cerebral gray matter volume in the left middle temporal gyrus, middle occipital gyrus, and hippocampus in older adults with MCI. ***Conclusions:*** These results suggest that a better 6MWD performance may be related to better memory function and the maintenance of gray matter volume in older adults with MCI.

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Introduction

Mild cognitive impairment (MCI) is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia [1]. Progression rates to dementia and Alzheimer's disease (AD) for individuals with MCI have been reported as being in the range of 6–25% per year [2]. MCI may be the optimum stage at which to intervene with preventive therapies.

Increased physical activity and higher aerobic fitness levels, defined as cardiorespiratory fitness, have been associated with the maintenance of cognitive function and a decreased risk for developing dementia [3, 4]. Recent randomized controlled trials (RCTs) of aerobic exercise for healthy older adults provided evidence that participation in exercise programs involving aerobic exercise leads to an improvement in cognitive function [5] and a greater brain volume in specific regions, e.g. in the prefrontal cortex [6] and hippocampus [7]. Previous cross-sectional studies have suggested that higher fitness levels associated with greater brain volumes in these regions were characteristic among healthy older adults [8, 9]. Some longitudinal studies have shown supportive results of the assumption that a greater physical activity predicts a stable cognitive function [10, 11] and gray matter volume [12].

Physical activity and exercise interventions can have a positive effect on cognitive function in older adults and even in those in the MCI stage [13, 14]. In addition, a recently proposed RCT will examine the effects of a moderate physical activity program on delaying the progression of structural brain changes in older adults with MCI [15]. These studies suggest that a higher exercise capacity plays an important role in maintaining cognitive function and delaying structural brain changes in MCI. However, it is unclear which specific brain regions are associated with exercise capacity performance in older adults with MCI.

We investigated whether a 6-min walking distance (6MWD), to be established as exercise capacity performance, is associated with measures of gray matter volume in older adults with MCI. The 6-min walking test (6MWT) is useful for predicting the maximal oxygen uptake related to cardiorespiratory fitness [16] and is easily administered in clinical settings [17]. The relationship between a 6MWD and memory performance was also examined in this study. A decline in memory performance represents a typical clinical sign of AD and can be observed 10 years prior to the expected symptom onset of AD [18]. In addition, poor memory performance and a lower gray matter volume in the medial temporal area, including the hippocampus, could predict progression to AD in older individuals with MCI [19, 20]. Maintaining exercise capacity may be related to a better memory performance and less brain atrophy in MCI subjects, and this positive relation may contribute to decreasing the risk of progression to AD. However, few studies have reported associations between fitness performance and memory performance in MCI subjects. We hypothesized that a better exercise capacity performance would correlate with a better memory performance and a greater brain volume among MCI subjects. A high exercise capacity may be sustained by a physically active lifestyle; this is potentially an important pathway for maintaining a healthy brain, both in terms of size and reduced damage.

Participants and Methods

Participants

Subjects in this study were recruited from our volunteer databases (n = 1,543), which included elderly individuals (≥65 years old). Participants had to be community-dwelling adults aged ≥65 years. Furthermore, all participants were required to meet the definition of MCI based on the Petersen criteria (not normal cognitive function for age, not demented, and

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Table 1. Demographic and health characteristics (n = 91)

Age, years	74.2±6.3
Female gender	47 (51.6)
BMI	23.2±3.2
Diagnosis	
Hypertension	40 (44.0)
Diabetes mellitus	8 (8.8)
Medication, ≥3	33 (36.3)
Mental status	
GDS, points	3.6±3.1
MMSE, points	27.0±1.9
Physical status	
Instrumental self-maintenance[a], points	4.9±0.3
Walking speed, m/s	1.1±0.3

Values are mean ± SD or number (percentage). GDS = Geriatric Depression Scale.

[a] The Tokyo Metropolitan Institute of Gerontology Index of Competence subscale (0–5).

essentially normal functional activities) [21]. A total of 528 potential participants exhibiting a Clinical Dementia Rating score of 0.5 or a subjective memory complaint were enrolled in the first eligibility assessment. Of these, 135 participants underwent the second eligibility assessment, including neuropsychological tests, physical performance tests, face-to-face interviews, and magnetic resonance imaging (MRI) scans. The inclusion criteria required that the participants were ≥65 years old, lived independently in the community (i.e., had no impairment of activities of daily living), were Japanese speaking with sufficient hearing and visual acuity to participate in the examinations, and had general cognitive function (Mini-Mental State Examination [22]) scores between 24 and 30. Exclusion criteria were a history of major psychiatric illness (e.g. schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, and clinical depression (Geriatric Depression Scale [23] score ≥10). In addition, we excluded 9 participants who could not perform the physical performance tests and did not meet satisfactory requirements for the MRI scan. Finally, 91 participants complied with the inclusion criteria, and their data were analyzed in the present study. This study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology, and all participants provided written informed consent. Table 1 summarizes the characteristics of the participants.

Logical and Visual Memory

Logical and visual memory performances were in a standardized format and were administered by licensed, well-trained clinical speech therapists.

The Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM) [24] was used to assess logical memory. The WMS-R LM subtest requires the examiner to read aloud two short stories to the participant, each with 25 content units. In this study, stories from the Japanese version of the WMS-R LM test were used. After each story, the participant was asked to repeat the story immediately as close to verbatim as possible (immediate recall, Logical Memory-I). The recall was recorded verbatim and scored later according to the manual guidelines. After a 30-min delay, the examiner asked the subject to repeat each of the two stories once again for the delayed recall measure (delayed recall, Logical Memory-II).

The Rey-Osterrieth Complex Figure Test (ROCFT) [25] was used to assess visual memory. The ROCFT is a widely used instrument for assessing visual memory. The participants were

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requested to copy the ROCFT figure and reproduce it immediately and again after a 30-min delay. They were not informed that they would be asked to recall the figure. The participants were allowed as much time as they needed for both copy and recall. During the retention interval, unrelated tests (e.g. Mini-Mental State Examination) were administered. The drawings were scored based on a 36-point scoring system.

Six-Minute Walking Test

We used the 6MWT to quantitatively measure participants' exercise capacity. The 6MWT measures the maximum distance that a person can walk in 6 min. The 6MWT is a modification of the 12-min walk/run test originally developed by Cooper [26] and is commonly used as an assessment of exercise capacity. The 6MWT is useful for predicting the maximal oxygen uptake related to cardiorespiratory fitness and is easily administered in clinical settings [17]. The 6MWT was assessed by licensed, well-trained physical therapists. The participants were instructed to walk from one end of a 10-meter course to the other and back again as many times as possible in 6 min, while under the supervision of a physical therapist. After each minute, participants were informed of the time elapsed and were given standardized encouragement. The distance (meters) walked in 6 min was recorded.

MRI Procedure

MRI was performed using a 1.5-tesla system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1,700 ms; echo time, 4.0 ms; flip angle, 15°; acquisition matrix, 256 × 256; slice thickness, 1.25 mm). Tissue segmentation, regulation, registration, and normalization were conducted in the voxel-based morphometry (VBM) 8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) [27] was conducted for the image analysis. The normalized images were transformed into the Montreal Neurological Institute (MNI) space. The gray matter images were then smoothened using a Gaussian kernel of 12 mm full width at half maximum.

Statistical and VBM Analyses

We calculated Pearson correlation coefficients, assessing simple relationships between memory tests and the 6MWD. We used linear regression analyses to assess independent relationships between the variables, while controlling for age and sex to minimize the confounding influence of age-related changes in exercise capacity and memory performance. Standardized beta values were calculated. These statistical analyses were performed using SPSS for Windows, version 19.0. Statistical significance was set at 0.05 for these analyses.

In the VBM analysis, data preprocessing and analysis was performed with the VBM8 toolbox, which is incorporated in the SPM8 software. VBM [28] was applied to determine regions where gray matter density showed a positive correlation with exercise capacity assessed by the 6MWT. We performed a multiple regression analysis on the smoothed gray matter images in SPM8. Age and sex were included in the model as covariates. The statistical threshold was set to $p < 0.05$, corrected for multiple comparisons across the reduced search volume using the family-wise error rate (FWE), with an extent threshold of 40 voxels. The detection of labeled regions from coordinates in the results was conducted using the SPM Anatomy Toolbox [29].