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References

1. Barnes DE, Yaffe K: **The projected effect of risk factor reduction on Alzheimer's disease prevalence.** *Lancet Neurol* 2011, **10**:819–828.
2. Petersen RC: **Mild cognitive impairment as a diagnostic entity.** *J Intern Med* 2004, **256**:183–194.
3. Reitz C, Brayne C, Mayeux R: **Epidemiology of Alzheimer disease.** *Nat Rev Neurol* 2011, **7**:137–152.
4. Allan LM, Ballard CG, Burn DJ, Kenny RA: **Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias.** *J Am Geriatr Soc* 2005, **53**:1681–1687.
5. Gillain S, Warzee E, Lekeu F, Wojtasik V, Maquet D, Croisier JL, Salmon E, Petermans J: **The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions.** *Ann Phys Rehabil Med* 2009, **52**:453–474.
6. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue XN, Lipton RB: **Gait dysfunction in mild cognitive impairment syndromes.** *J Am Geriatr Soc* 2008, **56**:1244–1251.
7. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J: **The trajectory of gait speed preceding mild cognitive impairment.** *Arch Neurol* 2010, **67**:980–986.
8. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X: **Quantitative gait dysfunction and risk of cognitive decline and dementia.** *J Neurol Neurosurg Psychiatry* 2007, **78**:929–935.
9. Holtzer R, Wang C, Lipton R, Verghese J: **The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve.** *J Am Geriatr Soc* 2012, **60**:2093–2098.
10. Martin KL, Blizzard L, Wood AG, Srikanth V, Thomson R, Sanders LM, Callisaya ML: **Cognitive function, gait, and gait variability in older people: a population-based study.** *J Gerontol A Biol Sci Med Sci* 2013, **68**(6):726–732.
11. Watson NL, Rosano C, Boudreau RM, Simonsick EM, Ferrucci L, Sutton-Tyrrell K, Hardy SE, Atkinson HH, Yaffe K, Satterfield S, Harris TB, Newman AB: **Executive function, memory, and gait speed decline in well-functioning older adults.** *J Gerontol A Biol Sci Med Sci* 2010, **65**:1093–1100.
12. Inzitari M, Newman AB, Yaffe K, Boudreau R, de Rekeneire N, Shorr R, Harris TB, Rosano C: **Gait speed predicts decline in attention and psychomotor speed in older adults: the health aging and body composition study.** *Neuroepidemiology* 2007, **29**:156–162.
13. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, Rapp SR, Cesari M, Newman AB, Harris TB, Rubin SM, Yaffe K, Satterfield S, Kritchevsky SB: **Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study.** *J Gerontol A Biol Sci Med Sci* 2007, **62**:844–850.
14. Mielke MM, Roberts RO, Savica R, Cha R, Drubach DI, Christianson T, Pankratz VS, Geda YE, Machulda MM, Ivnik RJ, Knopman DS, Boeve BF, Rocca WA, Petersen RC: **Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the mayo clinic study of aging.** *J Gerontol A Biol Sci Med Sci* 2013, **68**(8):929–937.
15. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM: **Gait and cognition: a complementary approach to understanding brain function and the risk of falling.** *J Am Geriatr Soc* 2012, **60**:2127–2136.
16. Fischer P, Jungwirth S, Zehetmayer S, Weissgram S, Hoenigschnabl S, Gelpi E, Krampla W, Tragl KH: **Conversion from subtypes of mild cognitive impairment to Alzheimer dementia.** *Neurology* 2007, **68**:288–291.
17. Marra C, Ferraccioli M, Vita MG, Quaranta D, Gainotti G: **Patterns of cognitive decline and rates of conversion to dementia in patients with degenerative and vascular forms of MCI.** *Curr Alzheimer Res* 2011, **8**:24–31.
18. Jungwirth S, Zehetmayer S, Hinterberger M, Tragl KH, Fischer P: **The validity of amnestic MCI and non-amnestic MCI at age 75 in the prediction of Alzheimer's dementia and vascular dementia.** *Int Psychogeriatr* 2012, **24**:959–966.
19. Rasquin SM, Lodder J, Visser PJ, Lousberg R, Verhey FR: **Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study.** *Dement Geriatr Cogn Disord* 2005, **19**:113–119.
20. Zanetti M, Ballabio C, Abbate C, Cutaia C, Vergani C, Bergamaschini L: **Mild cognitive impairment subtypes and vascular dementia in community-dwelling elderly people: a 3-year follow-up study.** *J Am Geriatr Soc* 2006, **54**:580–586.
21. Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N: **Dual-task decrements in gait: contributing factors among healthy older adults.** *J Gerontol A Biol Sci Med Sci* 2008, **63**:1335–1343.
22. van Iersel MB, Kessels RP, Bloem BR, Verbeek AL, Olde Rikkert MG: **Executive functions are associated with gait and balance in community-living elderly people.** *J Gerontol A Biol Sci Med Sci* 2008, **63**:1344–1349.
23. Coppin AK, Shumway-Cook A, Saczynski JS, Patel KV, Ble A, Ferrucci L, Guralnik JM: **Association of executive function and performance of dual-task physical tests among older adults: analyses from the InChianti study.** *Age Ageing* 2006, **35**:619–624.
24. Al-Yahya E, Dawes H, Smith L, Dennis A, Howells K, Cockburn J: **Cognitive motor interference while walking: A systematic review and meta-analysis.** *Neurosci Biobehav Rev* 2011, **35**:715–728.
25. Shumway-Cook AWM: *Motor Control: Translating Research into Clinical Practice.* 3rd edition. Baltimore: Lippincott Williams & Wilkins; 2006.
26. Montero-Odasso M, Bergman H, Phillips NA, Wong CH, Sourial N, Chertkow H: **Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory.** *BMC Geriatr* 2009, **9**:41.
27. Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Ito T, Lee S, Park H, Suzuki T: **Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people.** *J Am Med Dir Assoc* 2013, **14**:518–524.
28. Yesavage JA: **Geriatric Depression Scale.** *Psychopharmacol Bull* 1988, **24**:709–711.
29. 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.
30. Makizako H, Shimada H, Park H, Doi T, Yoshida D, Uemura K, Tsutsumimoto K, Suzuki T: **Evaluation of multidimensional neurocognitive function using a tablet personal computer: Test-retest reliability and validity in community-dwelling older adults.** *Geriatr Gerontol Int* 2013, **13**(4):860–866.
31. Shum DHK, McFarland KA, Bain JD: **Construct validity of eight tests of attention: Comparison of normal and closed head injured samples.** *Clin Neuropsychol* 1990, **4**:151–162.
32. Wechsler D: *Wechsler Adult Intelligence Scale—III.* San Antonio: The Psychological Corporation; 1997.
33. Rey A: *Léxamen clinique en psychologie.* Paris: Presses Universitaires de France; 1964.
34. Wechsler D: *Wechsler Memory Scale-Revised Manual.* San Antonio, Texas: The Psychological Corporation; 1987.
35. Whitehair DC, Sherzai A, Emond J, Raman R, Aisen PS, Petersen RC, Fleisher AS: **Influence of apolipoprotein E varepsilon4 on rates of cognitive and functional decline in mild cognitive impairment.** *Alzheimers Dement* 2010, **6**:412–419.
36. Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y: **Measurement of competence: reliability and validity of the TMIG Index of Competence.** *Arch Gerontol Geriatr* 1991, **13**:103–116.
37. Baker PS, Bodner EV, Allman RM: **Measuring life-space mobility in community-dwelling older adults.** *J Am Geriatr Soc* 2003, **51**:1610–1614.

38. McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, Teri L: **Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test.** *Phys Ther* 2011, **91**:1198–1207.
39. 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**:58–64.
40. Wood JN, Grafman J: **Human prefrontal cortex: processing and representational perspectives.** *Nat Rev Neurosci* 2003, **4**:139–147.
41. 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**:1380–1388.
42. Zimmerman ME, Lipton RB, Pan JW, Hetherington HP, Verghese J: **MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults.** *Brain Res* 2009, **1291**:73–81.
43. de Laat KF, Reid AT, Grim DC, Evans AC, Kotter R, van Norden AG, de Leeuw FE: **Cortical thickness is associated with gait disturbances in cerebral small vessel disease.** *Neuroimage* 2012, **59**:1478–1484.
44. Bu G: **Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy.** *Nat Rev Neurosci* 2009, **10**:333–344.

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Effects of mild and global cognitive impairment on the prevalence of fear of falling in community-dwelling older adults

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ABSTRACT

Objectives: Few studies have reported the relationship between fear of falling (FoF) and mild and global cognitive impairment in community-dwelling older adults. We aimed to determine whether the status of cognitive impairment affects the prevalence of FoF in community-dwelling older adults.
Study design: Cross-sectional study among 4474 community-dwelling older adults who participated in the Obu Study of Health Promotion for the Elderly.
Main outcome measures: Participants underwent cognitive tests and were divided into three groups: cognitive healthy, mild cognitive impairment (MCI), and global cognitive impairment (GCI). FoF and related variables, such as fall history, physical function, and depression, were also investigated.
Results: The prevalence of FoF was significantly different by group ($p < 0.001$; healthy: 43.6%, MCI: 50.6%, GCI: 40.6%). Logistic regression analysis showed that GCI (odds ratio = 0.63; 95% confidence interval = 0.526–0.76) was independently associated with FoF, after controlling for confounding factors. Older adults with GCI showed the lowest prevalence of FoF, although they had the lowest physical function comparing with the other groups ($p < 0.001$).
Conclusion: MCI and GCI in community-dwelling older adults affect the prevalence of FoF in a completely different manner. Further study is required to determine whether insensitivity to FoF with GCI increases the risk of falling in older adults.

1. Introduction

Fear of falling (FoF) is defined as "a lasting concern about falling that leads to an individual avoiding activities that he/she remains capable of performing" [1]. The main consequences of FoF are an increased risk for falling, restriction and avoidance of activities, and ultimately, deteriorated physical and mental performance, as well as decreased quality of life [2]. The prevalence of FoF ranges from 33% to 85%, being higher in women than in men, and increases with age [3,4]. FoF is associated with a history of falls, gait speed, use of walking aids, polypharmacy, and depression [5,6]. In spite of a number of reports regarding various factors associated with FoF, few studies have examined the relationship between FoF and cognitive decline, although it is almost universal in the general elderly population and increases with age [7].

Cognitive impairment, such as impairment of global cognition and executive function, contributes to the deterioration in the ability to carry out tasks in activities of daily living (ADL) [8,9]. Additionally, these cognitive impairments have been identified as a fall risk factor in clinical practice guidelines [10]. FoF also has been recognized as an important psychological factor associated with accidental falls and restricting everyday functioning [11]. However, whether the prevalence of FoF is affected according to the severity

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of cognitive impairment is still unclear. In addition to studying the risk of falling, investigation of FoF may be important in medical management of older adults with cognitive impairment.

Although many studies have reported that global cognitive impairment (GCI) confers a moderate to high risk of serious fall-related injury [10], recent evidence indicates that even mild cognitive impairment (MCI) is a risk factor for falls [12]. MCI is conceptualized to be the earliest feature of cognitive disorders and a prodromal condition between normal and dementia [13]. We have previously reported that memory decline is associated with a lower prevalence of FoF among older adults [14]. However, the sample size of our previous study was relatively small ($n = 101$) and the variety of cognitive impairments (i.e. MCI and GCI) was not considered in that study.

Therefore, the purpose of this study was to examine the effects of severity of cognitive impairment on the prevalence of FoF in a larger cohort of community-dwelling older adults. We hypothesized that mild and global cognitive impairment influence the prevalence of FoF in a different manner because of a difference in the nature of cognitive deficits.

2. Methods

2.1. Participants

We performed a cohort study "Obu Study of Health Promotion for the Elderly" (OSHPE) from August in 2011 to February in 2012. Enrollment in the OSHPE was available to 15,974 older people living in Obu, Japan. Inclusion criteria required that participants lived in Obu and were aged 65 years or older at examination in 2011 or 2012. Before recruitment, 1661 people were excluded because they had participated in another study, required hospitalization or residential care, or were certified as requiring more than level 3 care, requiring support or care by the Japanese public long-term care insurance (LTCI) system. Recruitment was conducted by mail sent to 14,313 people and 5104 people underwent a health check. A total of 4474 subjects satisfied the inclusion criteria and conducted all assessments. The inclusion criterion in this study was persons not certified as any grade requiring support or care by the Japanese public LTCI system. The participants were classified into three groups: cognitive healthy ($n = 2735$; mean age ± standard deviation [SD], 71.3 ± 5.1 years), MCI ($n = 938$; age ± SD = 71.9 ± 5.5 years) and GCI ($n = 801$; age, $M = 74.4 \pm 6.2$ years). GCI was defined as a deficit in general cognitive function; the Mini-Mental State Examination (MMSE) score was 23 or lower [15]. The criteria of MCI were those described by Petersen [13]. These criteria involved the following: (1) having subjective memory complaint, (2) having objective cognitive decline, (3) intact general cognitive function; MMSE score >23 [15], (4) absent from of clinical criteria for dementia, and (5) independent in ADL. Objective cognitive decline was defined as a lower cognitive function in multiple domains more than 1.5 SD from the healthy database. Cognitive functions in multiple domains were assessed using the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT). NCGG-FAT contains cognitive battery tests and the contents of measurement were described in detail in a previous study [16]. The battery consists of eight tasks to assess memory, attention and execution, processing speed, and visuospatial skill. The term "cognitive healthy" in this study was defined as having intact cognitive ability, and not having objective cognitive impairment. 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.

2.2. FoF/fall history

FoF and fall history was assessed by face-to-face interview with participants. FoF was assessed by a fourth-ordered choice, closed-ended question about participants' general FoF. The question was phrased as follows: "Are you afraid of falling?" Participants who responded "very much" or "somewhat" were assigned to the fear group. Participants who responded "a little" or "not at all" were assigned to the no-fear group [14,17], which has a high test–retest reliability [18]. The question "Do you have any history of a fall within the past year?" was used for detecting fall. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [19]. Falls resulting from extraordinary environmental factors (e.g. traffic accidents or falls while riding a bicycle) were excluded. On the basis of their fall history, participants were classified as fallers if they fell twice or more times within the past year [20].

2.3. Potential correlates with FoF

Demographic data were recorded, including age, gender, and educational history. Participants completed a questionnaire on medical condition, including current medications and lifestyle. The medical questionnaire found a variety of diseases (hypertension, heart disease, stroke, and diabetes mellitus) and total medication used administered by a nurse. Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS) [21].

The timed up & go test (TUG) was used to assess physical performance [22]. The TUG involves rising from a chair, walking 3 meters, turning around, walking back to the chair, and sitting down. Participants were instructed to complete the task at their usual walking pace. The score for this test represents the time (in seconds) that the participant needed to complete the assessment. Lower times indicate better physical performance. Participants were also asked about their use of walking aids in daily life.

2.4. Statistical analysis

One-way analysis of variance (ANOVA) was used to test differences between groups. When a significant main effect was found from these analyses, the Bonferroni post hoc test was employed was performed to determine differences between pairs of means. The Chi-square test was used to test differences in proportions between groups.

When there is a large number of cell sizes for some of the cross-tabulations, it can be difficult to determine which groups have significant differences within the analyses. Therefore, standardized adjusted residuals were calculated for each of the cells to determine which cell differences contributed to the Chi-square test results. Cells with significant standardized adjusted residuals (>±1.96) are indicated by underlining their percentages in the tables [23,24].

Logistic regression analysis, performed as a stepwise analysis, was carried out to examine whether the classification schema based on cognitive function was independently associated with FoF. In this analysis, the presence or absence of FoF was used as the dependent variable (no-fear = 0, fear = 1). Individual group classification was entered as dichotomous categorical variables (fitting into that group = 1; others = 0). Other independent variables also included possible confounders were age, gender, educational history, TUG, use of walking aids, GDS, and medications. Gender, fall history, and use of walking aids were created as categorical variables (male = 0, female = 1; non-faller = 0, faller = 1; non-user = 0, user = 1). All analyses were performed using commercially available software, IBM SPSS statistics software (Version 20; IBM Corp., Chicago). Statistical significance was set at $p < 0.05$ a priori.

Table 1
Demographic characteristics, and health outcomes of the groups.

	Cognitive healthy (n = 2735)	MCI (n = 938)	GCI (n = 801)	p-Value
Age (years)	71.3 ± 5.1	71.9 ± 5.5††	74.4 ± 6.2$^{\$\$,**}$	<0.001
Gender (males)	1298 (47.5)	451 (48.1)	325 (60.3)	<0.001[a]
Educational history (years)	11.9 ± 2.5	10.9 ± 2.4††	10.3 ± 2.5	<0.001
MMSE (points)	27.4 ± 1.8	26.6 ± 1.8††	21.6 ± 1.8$^{\$\$,**}$	<0.001
Fear of falling	1193 (43.6)	475 (50.6)	325 (40.6)	<0.001[a]
Fall history (fallers)	110 (4.0)	67 (7.1)	48 (6.0)	<0.001[a]
Medical illness (%)				
Hypertension	1237 (45.2)	464 (49.5)	395 (49.3)	<0.001[a]
Heart disease	443 (16.2)	193 (20.6)	128 (15.9)	0.006[a]
Stroke	98 (3.6)	61 (6.5)	64 (7.9)	<0.001[a]
Diabetes mellitus	362 (13.2)	138 (14.7)	102 (12.7)	0.41[a]
TUG (s)	8.1 ± 1.5	8.6 ± 2.3††	9.2 ± 3.2$^{\$\$,**}$	<0.001
Walking aids use	60 (2.2)	37 (4.0)	67 (8.4)	<0.001[a]
GDS (points)	2.6 ± 2.5	3.4 ± 2.7††	3.4 ± 2.8$^{\$\$,**}$	<0.001
Total number of medication doses	1.9 ± 2.1	2.3 ± 2.2††	2.2 ± 2.2**	<0.001

Underlined % = cells with significant adjusted standardized residuals; MMSE: Mini-Mental State Examination; TUG: timed up & go test; GDS: Geriatric Depression Scale.
[a] Values are means ± SD or n (%). All p-values were generated from one-way ANOVA or Chi-square.
†† Significant difference between cognitive healthy and MCI (Bonferroni test, $p < 0.01$).
** Significant difference between cognitive healthy and GCI (Bonferroni test, $p < 0.01$).
$\$\$$ Significant difference between MCI and GCI (Bonferroni test, $p < 0.01$).

3. Results

The characteristics in participants and comparison between groups are summarized in Table 1. Cognitive healthy participants were significantly younger, had a higher educational history, higher MMSE, faster TUG, lower rate of walking aids use, GDS, and number of medications than those with MCI and GCI ($p < 0.001$). Participants with GCI were significantly older, had a lower educational history, lower MMSE, slower TUG, and a higher rate of walking aid use than the other groups ($p < 0.001$). The rate of males was significantly different by group ($p < 0.001$; healthy: 47.5%, MCI: 48.1%, GCI: 60.3%). The prevalence of FoF was significantly different by group ($p < 0.001$; healthy: 43.6%, MCI: 50.6%, GCI: 40.6%). Participants with MCI showed the highest prevalence of FoF (standardized adjusted residuals = 4.2), while those with GCI showed the lowest prevalence of FoF (standardized adjusted residuals = −2.5). The prevalence of fallers was significantly different by group ($p < 0.001$; healthy: 4.0%, MCI: 7.1%, GCI: 6.0%). Participants with MCI showed the highest prevalence of fallers (standardized adjusted residuals = 3.3), while cognitive healthy participants showed the lowest prevalence of fallers (standardized adjusted residuals = −3.9).

Logistic regression analysis showed that classification to GCI (odds ratio [OR] = 0.63; 95% confidence interval [CI] = 0.53–0.76; $p < 0.001$) was independently associated with FoF accounting for the following confounding factors: age (OR = 1.03; 95% CI = 1.02–1.05; $p < 0.001$), gender (OR = 0.28; 95% CI = 0.25–0.32; $p < 0.001$), educational history (OR = 0.96; 95% CI = 0.93–0.99; $p = 0.003$), TUG (OR = 1.1; 95% CI = 1.06–1.16; $p < 0.001$), use of walking aids (OR = 2.07; 95% CI = 1.33–3.23; $p < 0.001$), GDS (OR = 1.16; 95% CI = 1.13–1.19; $p < 0.001$), and number of medications (OR = 1.08; 95% CI = 1.04–1.12; $p < 0.001$). Fall history, and classification to cognitive healthy and MCI did not show a significant relationship. The model was well calibrated between declines of observed and expected risk (Hosmer–Lemeshow $\chi^2 = 8.0$, $p = 0.44$) (Table 2).

4. Discussion

This is the first study to clarify the effect of cognitive impairment, by dividing participants into several groups based on cognitive performance, on the prevalence of FoF in community-dwelling older adults. The present study found that MCI and GCI in community-dwelling older adults affect the prevalence of FoF in a completely different manner; the prevalence of FoF was highest with MCI and lowest with GCI. Furthermore, GCI was independently associated with a lower prevalence of FoF, even after accounting for confounding factors, such as demographic, physical, and mental factors.

Subjects with GCI might have underestimated their functional deficits and disregarded their risk of falling because they had the lowest prevalence of FoF, despite having the lowest physical function (i.e. slowest TUG and highest rate of users with walking aids). Older adults with dementia are often unable to appreciate or recognize their own deficiencies in motor, behavioral or cognitive functioning, which are evident to clinicians and caregivers [25]. This condition is regarded as "anosognosia" and is described as lack of awareness of impairments in ADL or of neuropsychological deficits [26], particularly in patients with Alzheimer's disease [27]. This impaired awareness is significantly correlated with the severity of global cognitive impairment, as assessed by the MMSE [28]. Therefore, GCI may contribute to insensitivity to FoF and be more likely to lead to adopting dangerous behaviors, and is likely to be observed in Alzheimer's disease [27].

Subjects with MCI had a higher prevalence of FoF and fallers than the cognitive healthy subjects and lower physical function than them. This is in line with a previous study, which found that MCI increases the risk of falling in older adults [12]. Anosognosia (i.e. lack of awareness) is frequent in patients with Alzheimer's

Table 2
Factors associated with FoF in stepwise logistic regression.

Factor	OR	95% CI	p-Value
Age	1.03	1.02–1.05	<0.001
Gender	0.28	0.25–0.32	<0.001
Educational history	0.96	0.93–0.99	0.003
TUG	1.1	1.06–1.16	<0.001
Walking aids usage	2.07	1.33–3.23	0.001
GDS	1.16	1.13–1.19	<0.001
No. of medication	1.08	1.04–1.12	<0.001
GCI	0.63	0.53–0.76	<0.001
Cognitive healthy	–	–	0.26
MCI	–	–	0.26
MMSE	–	–	0.99
Fall history	–	–	0.06

FoF, fear of falling; TUG, timed up & go test; GDS, Geriatric Depression Scale; GCI, global cognitive impairment; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

disease but not in those with MCI [25,29]. However, having anxiety is the most frequent behavioral symptom in MCI subjects [30]. Fall experience, decreased physical function, and feeling anxiety may contribute to the increased prevalence of FoF in MCI subjects. Therefore, the feeling of FoF may depend on the severity of cognitive impairment, and there may have been prevalent differences between the MCI and GCI groups in the present study.

GCI has been reported as a major risk factor of fall and serious fall-related injury [10]. GCI subjects might be unable to recognize their risks of falling and select a safety strategy during ambulation and transfer, despite having decreased physical function. This insensitivity to FoF may be one of the characteristics of psychological changes in older adults with GCI and account for an increased risk of falling derived from GCI. However, the design of the current study, as with other cross sectional studies, limits the interpretation of the results with regard to causality between FoF and associated factors. A longitudinal study is necessary to examine whether the insensitivity to FoF in GCI subjects who have decreased physical function leads to an increased incidence of accidental falls. If this hypothesis is verified, education and an exercise program specifically designed to address the cognitive needs and insensitivity to FoF among participants with GCI may be beneficial for preventing falls.

Another limitation of this study is the sub-optimal use of the single-item FoF measure. Further study is needed to examine the relationship between cognitive impairment and fear of falling during various activities of daily living using measures of falls efficacy which has been validated in older people with cognitive impairment [31,32]. However, as it is reported that single item FoF measurement shows good correlation with the Fall Efficacy Scale-International [33], a single question regarding FoF has been found to have high validity with continuous measures of FoF [34]. Thus, we consider that the relevance of our research is not lost by the way of FoF measurement. Finally, the incidence of falling in our subjects was relatively low compared with that in other studies [35], while a recent systematic review estimated that the incidence of falls among older people ranged from 14.7% to 34% [36]. Additionally, Milat and colleague [37] reported that older adults who fell more than twice were only 9.9% of all participants. These differences may be due to differences between races and/or physical function status of the participants. The findings of the present study differ from available comparable studies in which fall history was associated with FoF [5,6]. However, Austin and colleague [3] also reported that fall history was not found to predict FoF. Like this previous study, low rate of fall incidence might have weakened any relationship between falls and FoF. The strengths of the present study include its much larger sample size and that it is the first study to clarify the significant difference in prevalence of FoF between cognitive statuses which were classified strictly based on objective assessment measures.

5. Conclusion

Older adults with GCI have lower prevalence of FoF despite having lower physical function. GCI is independently associated with a lower prevalence of FoF while accounting for confounding factors, such as demographic, physical, and mental factors. However, MCI subjects have a higher prevalence of FoF and fallers than those with GCI and cognitive healthy subjects. GCI may induce disparity between awareness and function, which leads to insensitivity to FoF. Further study is required to determine whether insensitivity to FoF with GCI induces the risk of falling in older adults.

Contributors

Kazuki Uemura, Hiroyuki Shimada, Hyuma Makizako and Takehiko Doi were responsible for study concept and design; Takao Suzuki and Hyuntae Park contributed to study supervision and funding; Kota Tsutsumimoto, Daisuke Yoshida, Yuya Anan, Tadashi Ito and Sangyoon Lee contributed to data analysis, interpretation and draft of the manuscript; all the authors did critical revisions of the manuscript and approved the final manuscript.

Competing interest

The authors declare no conflict of interest.

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Ethical approval

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.

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References

[1] Tinetti ME, Powell L. Fear of falling and low self-efficacy: a case of dependence in elderly persons. J Gerontol 1993;48. Spec No: 35-8.
[2] Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing 2008;37:19–24.
[3] Austin N, Devine A, Dick I, Prince R, Bruce D. Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors. J Am Geriatr Soc 2007;55:1598–603.
[4] Zijlstra GA, van Haastregt JC, van Eijk JT, van Rossum E, Stalenhoef PA, Kempen GI. Prevalence and correlates of fear of falling, and associated avoidance of activity in the general population of community-living older people. Age Ageing 2007;36:304–9.
[5] Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. J Am Geriatr Soc 2002;50:1329–35.
[6] Perez-Jara J, Olmos P, Abad MA, Heslop P, Walker D, Reyes-Ortiz CA. Differences in fear of falling in the elderly with or without dizziness. Maturitas 2012;73:261–4.
[7] Park HL, O'Connell JE, Thomson RG. A systematic review of cognitive decline in the general elderly population. Int J Geriatr Psychiatry 2003;18:1121–34.
[8] Ishizaki T, Yoshida H, Suzuki T, Watanabe S, Niino N, Ihara K, et al. Effects of cognitive function on functional decline among community-dwelling non-disabled older Japanese. Arch Gerontol Geriatr 2006;42:47–58.
[9] Johnson JK, Lui LY, Yaffe K. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. J Gerontol A Biol Sci Med Sci 2007;62:1134–41.
[10] 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;41:299–308.
[11] Deshpande N, Metter EJ, Bandinelli S, Lauretani F, Windham BG, Ferrucci L. Psychological, physical, and sensory correlates of fear of falling and consequent activity restriction in the elderly: the Inchianti study. Am J Phys Med Rehabil 2008;87:354–62.
[12] Delbaere K, Kochan NA, Close JC, Menant JC, Sturnieks DL, Brodaty H, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. Am J Geriatr Psychiatry 2012;20:845–53.
[13] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.

[14] Uemura K, Shimada H, Makizako H, Yoshida D, Doi T, Tsutsumimoto K, et al. A lower prevalence of self-reported fear of falling is associated with memory decline among older adults. Gerontology 2012;58:413–8.
[15] 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;12:189–98.
[16] Makizako H, Shimada H, Park H, Doi T, Yoshida D, Uemura K, et al. Evaluation of multidimensional neurocognitive function using a tablet personal computer: test–retest reliability and validity in community-dwelling older adults. Geriatr Gerontol Int 2012;13:860–6.
[17] Maki BE, Holliday PJ, Topper AK. Fear of falling and postural performance in the elderly. J Gerontol 1991;46:M123–31.
[18] Yamada M, Tanaka B, Nagai K, Aoyama T, Ichihashi N. Rhythmic stepping exercise under cognitive conditions improves fall risk factors in community-dwelling older adults: preliminary results of a cluster-randomized controlled trial. Aging Ment Health 2011;15:647–53.
[19] 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;53:1618–22.
[20] Melzer I, Kurz I, Shahar D, Levi M, Oddsson L. Application of the voluntary step execution test to identify elderly fallers. Age Ageing 2007;36:532–7.
[21] Yesavage JA. Geriatric depression scale. Psychopharmacol Bull 1988;24:709–11.
[22] Podsiadlo D, Richardson S. The timed up & go: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–8.
[23] Saewyc EM, Brown D, Plane M, Mundt MP, Zakletskaia L, Wiegel J, et al. Gender differences in violence exposure among university students attending campus health clinics in the United States and Canada. J Adolesc Health 2009;45:587–94.
[24] Agresti A. Categorical data analysis. 2nd ed. New York: Wiley; 2002.
[25] Orfei MD, Varsi AE, Blundo C, Celia E, Casini AR, Caltagirone C, et al. Anosognosia in mild cognitive impairment and mild Alzheimer's disease: frequency and neuropsychological correlates. Am J Geriatr Psychiatry 2010;18:1133–40.
[26] Lin F, Wharton W, Dowling NM, Ries ML, Johnson SC, Carlsson CM, et al. Awareness of memory abilities in community-dwelling older adults with suspected dementia and mild cognitive impairment. Dement Geriatr Cogn Disord 2010;30:83–92.
[27] Starkstein SE, Jorge R, Mizrahi R, Adrian J, Robinson RG. Insight and danger in Alzheimer's disease. Eur J Neurol 2007;14:455–60.
[28] Vogel A, Hasselbalch SG, Gade A, Ziebell M, Waldemar G. Cognitive and functional neuroimaging correlate for anosognosia in mild cognitive impairment and Alzheimer's disease. Int J Geriatr Psychiatry 2005;20:238–46.
[29] Kalbe E, Salmon E, Perani D, Holthoff V, Sorbi S, Elsner A, et al. Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. Dement Geriatr Cogn Disord 2005;19:349–56.
[30] Van der Mussele S, Le Bastard N, Vermeiren Y, Saerens J, Somers N, Mariën P, et al. Behavioral symptoms in mild cognitive impairment as compared with Alzheimer's disease and healthy older adults. Int J Geriatr Psychiatry 2013;28:265–75.
[31] Hauer KA, Kempen GI, Schwenk M, Yardley L, Beyer N, Todd C, et al. Validity and sensitivity to change of the falls efficacy scales international to assess fear of falling in older adults with and without cognitive impairment. Gerontology 2011;57:462–72.
[32] Hauer K, Yardley L, Beyer N, Kempen G, Dias N, Campbell M, et al. Validation of the falls efficacy scale and falls efficacy scale international in geriatric patients with and without cognitive impairment: results of self-report and interview-based questionnaires. Gerontology 2010;56:190–9.
[33] Visschedijk J, van Balen R, Hertogh C, Achterberg W. Fear of falling in patients with hip fractures: prevalence and related psychological factors. J Am Med Dir Assoc 2013;14:218–20.
[34] Lachman ME, Howland J, Tennstedt S, Jette A, Assmann S, Peterson EW. Fear of falling and activity restriction: the survey of activities and fear of falling in the elderly (safe). J Gerontol B Psychol Sci Soc Sci 1998;53:43–50.
[35] Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med 2003;348:42–9.
[36] Kwan MM, Close JC, Wong AK, Lord SR. Falls incidence, risk factors, and consequences in Chinese older people: a systematic review. J Am Geriatr Soc 2011;59:536–43.
[37] Milat AJ, Watson WL, Monger C, Barr M, Giffin M, Reid M. Prevalence, circumstances and consequences of falls among community-dwelling older people: Results of the 2009 NSW falls prevention baseline survey. N S W Public Health Bull 2011;22:43–8.

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Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment

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ABSTRACT

Physical activity may help to prevent or delay brain atrophy. Numerous studies have shown associations between physical activity and age-related changes in the brain. However, most of these studies involved self-reported physical activity, not objectively measured physical activity. Therefore, the aim of this study was to examine the association between objectively measured physical activity, as determined using accelerometers, and brain magnetic resonance imaging (MRI) measures in older adults with mild cognitive impairment (MCI). We analyzed 323 older subjects with MCI (mean age 71.4 years) who were recruited from the participants of the Obu Study of Health Promotion for the Elderly. We recorded demographic data and measured physical activity using a tri-axial accelerometer. Physical activity was classified as light-intensity physical activity (LPA) or moderate-to-vigorous physical activity (MVPA). Brain atrophy and the severity of white matter lesions (WML) were determined by MRI. Low levels of LPA and MVPA were associated with severe WML. Subjects with severe WML were older, had lower mobility, and had greater brain atrophy than subjects with mild WML (all $P < 0.05$). Multivariate analysis revealed that more MVPA was associated with less brain atrophy, even after adjustment for WML ($\beta = -0.126$, $P = 0.015$), but LPA was not ($\beta = -0.102$, $P = 0.136$). Our study revealed that objectively measured physical activity, especially MVPA, was associated with brain atrophy in MCI subjects, even after adjusting for WML. These findings support the hypothesis that physical activity plays a crucial role in maintaining brain health.

1. Introduction

Alzheimer disease (AD) is a serious health problem, and its prevalence is dramatically increasing worldwide. Because of the absence of disease-modifying treatments, numerous studies have sought to identify potentially modifiable risk factors for AD (Barnes and Yaffe, 2011). In particular, physical inactivity has been recognized as a significant risk factor for cognitive decline (Sofi et al., 2011) and cognitive impairments, including AD and mild cognitive impairment (MCI) (Barnes and Yaffe, 2011; Lautenschlager et al., 2010),

MCI is considered to be a clinical feature that typifies the prodromal phase of AD and most types of dementia (Petersen, 2004). MCI is associated with a relatively high rate of conversion to dementia, but may also revert to a healthy cognitive state (Brodaty et al., 2013). Physical activity (PA)-based interventions were tested to improve cognitive function in people with MCI, and studies have suggested associations between PA and preservation of cognitive function. However, a meta-analysis revealed some inconsistencies in the effects of PA (Gates et al., 2013). Thus, better understanding of the association between PA and cognition should allow us to refine PA interventions.

Emerging evidence also suggests that PA could protect against age-related changes in the brain, including structural changes observed on magnetic resonance imaging (MRI). Several studies have shown that greater PA is associated with larger brain volume or less atrophy (Benedict et al., 2013; Erickson et al., 2010; Flöel et al., 2010; Gow et al., 2012). Brain atrophy is strongly associated with the presence of white matter lesions (WML), but the association between WML and PA is still debated (Burzynska et al., 2014; Kooistra et al., 2014; Podewils et al., 2007; Wirth et al., 2014). The coexistence of WML and brain atrophy was thought to depend on underlying vascular risk factors

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; WML, white matter lesions; LPA, light-intensity physical activity; METs, multiples of the resting metabolic rate; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity; TE, echo time; TI, inversion time; TR, repetition time; TUG, timed up and go test

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or on a contribution of altered white matter integrity to the pathogenesis of brain atrophy, although the mechanisms were unclear (Appelman et al., 2009). The severity of WML was also associated with brain atrophy in older adults, including those with cognitive impairment (Appelman et al., 2009). However, it is still unclear whether the association between PA and brain atrophy is independent of the severity of WML. It is also notable that, in these earlier studies, PA was assessed using self-reported questionnaires. An earlier study reported that objectively measured PA was associated with cognitive function, but self-reported PA was not (Buchman et al., 2008). Even young adults had difficulty in evaluating PA because of recall bias with subjective assessments, and over- or under-estimated PA (Hagstromer et al., 2010).

Thus, we examined whether objectively measured PA is associated with brain atrophy, independent of WML, in older adults with MCI. Studies using objectively measured PA have revealed that the intensity of PA, rather than the amount of PA, is associated with cognitive performance in older people (Brown et al., 2012; Kerr et al., 2013). Therefore, we also examined whether the intensity of PA has an impact on the association between PA and brain atrophy. In this study, we objectively measured PA using tri-axial accelerometers and calculated the mean daily duration of PA for several intensity levels.

2. Materials and methods

2.1. Subjects

Overall, 649 subjects participating in the Obu Study of Health Promotion for the Elderly (Shimada et al., 2013) were considered for this study, and met the following criteria: age > 65 years; diagnosis of MCI; no specific medical history of cerebrovascular disease, Parkinson disease, connective tissue disease, or depression; no severe visual or auditory impairment; no current symptoms of depression defined as Geriatric Depression Scale ≥ 6 (Yesavage, 1988); not participating in other research projects; and not receiving support from the Japanese public long-term-care insurance system, which certifies a person as "Support Level 1 or 2" if they need support for daily activities or "Care Level 1, 2, 3, 4, or 5" if they need continuous care (Tsutsui and Muramatsu, 2007). MCI was defined based on the criteria established and revised by Petersen (2004) as follows: 1) subjective memory complaints; 2) objective cognitive impairment; 3) no dementia; and 4) independent function in daily life activities. The subjects with MCI included in our study were not diagnosed with dementia and their general cognitive function was considered intact with a Mini-Mental State Examination score of >23 (Folstein et al., 1975). Objective cognitive impairment was defined as a cognitive function score at least 1.5 standard deviations below the normal score (Shimada et al., 2013). Cognitive function was assessed in multiple domains (attention, executive function, processing speed, visuospatial skill, and memory) using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). Subjects with cognitive impairment in the memory domain were classified as having amnestic MCI; the remaining subjects were classified as having non-amnestic MCI. Overall, 409 people responded to the invitation to participate, 400 participated after providing informed consent in accordance with the ethical policy, and 336 completed all examinations and the MRI analysis. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. MRI

MRI was performed on a 3T system (TIM Trio; Siemens, Berlin, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation with rapid-acquisition (inversion time [TI], 800 ms; echo time [TE], 1.98 ms; repetition time [TR], 1800 ms; slice thickness, 1.1 mm). Then, axial T2-weighted, spin-echo images (TR, 4200 ms; TE, 89.0 ms; slice thickness, 5 mm) and axial fluid-attenuated inversion recovery images (TI, 2500 ms; TR, 9000 ms; TE, 100 ms; slice thickness, 5 mm) were obtained for diagnosis. WML were assessed based on periventricular hyperintensity and deep and subcortical white matter hyperintensity. Subjects were classified as having severe WML if periventricular hyperintensity or white matter hyperintensity was classified as grade III (Fazekas et al., 1993).

Brain atrophy was evaluated using the voxel-based, specific regional analysis system for Alzheimer's disease advance, which has been validated and described in more detail elsewhere (Hirata et al., 2005; Matsuda et al., 2012). Normalized MRI images were segmented into gray matter, white matter, cerebrospinal fluid, and other components. The segmented gray matter images were then subjected to affine and non-linear anatomical standardization using a gray matter template established a priori. Then, gray matter images were smoothed with an isotropic Gaussian kernel with a full-width-at-half-maximum of 12 mm. We compared the gray matter images of each subject with the mean and standard deviation of gray matter images obtained from healthy older adults using voxel-by-voxel Z-score analysis (Hirata et al., 2005; Matsuda et al., 2012). Regions of brain atrophy were defined as voxels with a Z-score >2. A brain atrophy index was defined as the proportion of atrophic voxels relative to the total number of voxels for the entire brain.

2.3. Physical activity

To objectively measure PA, we used a small tri-axial accelerometer (74 × 46 × 34 mm; modified HJA-350IT, Active style Pro; Omron Healthcare Co., Ltd., Kyoto, Japan) (Kim et al., 2013; Oshima et al., 2010) according to a previously described protocol (Makizako et al., 2014). The number of steps and the intensity of PA were measured every 4 s throughout each day. The intensity of PA was calculated in multiples of the resting metabolic rate (METs). Subjects were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. To assess normal daily activity, the displays of the accelerometers were masked to the subjects. We excluded the data for 13 subjects lacking activity data for ≥75% of the daytime period (6 am to 6 pm) on 7 days or more in the 2-week period. Accelerometer data were classified as light-intensity physical activity (LPA; 1.5–2.9 METs) or moderate-to-vigorous physical activity (MVPA; more than 3.0 METs), which were calculated from the mean duration of each intensity of PA in min/day.

2.4. Other covariates

Age, sex, and body mass index (weight/height^2) were recorded as demographic characteristics. Comorbidities including hypertension, diabetes mellitus, lipidemia, and current medications were also recorded.

Table 1
Characteristics of subjects according to the severity of white matter lesions.

Variables	Non-severe WML ($n = 263$)	Severe WML ($n = 60$)	P
Age, years	70.7 ± 4.1	74.3 ± 5.2	<0.001
Sex (women), %	54.7	50.0	0.499
BMI, kg/m^2	23.3 ± 2.9	23.6 ± 2.5	0.509
Subjects with non-amnestic MCI, %	48.2	54.8	0.343
Hypertension, %	39.2	43.5	0.528
Diabetes mellitus, %	10.3	12.9	0.544
Lipidemia, %	28.6	24.2	0.487
Number of medications	2.0 ± 1.9	2.4 ± 1.8	0.143
TUG, s	8.4 ± 1.7	9.0 ± 1.7	0.013
LPA, min/day	353.6 ± 96.0	324.4 ± 96.7	0.035
MVPA, min/day	24.1 ± 18.7	18.6 ± 17.5	0.039
Brain atrophy, %	1.6 ± 1.0	2.7 ± 1.6	<0.001

Values are means ± standard deviation or % of subjects.
WML: white matter lesions; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; LPA: low-intensity physical activity. MVPA: moderate-to-vigorous intensity physical activity.

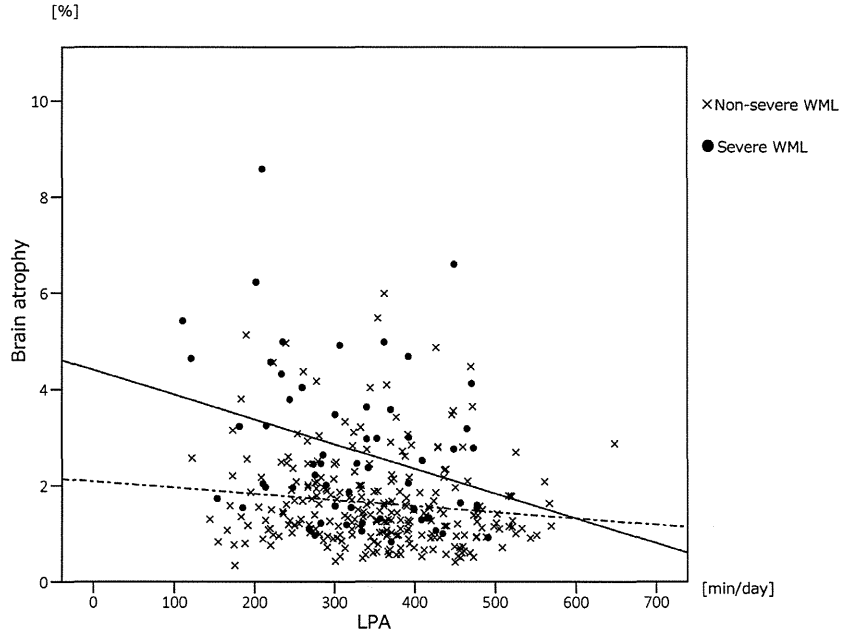

Fig. 1. Scatterplot showing the relationship between LPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).

Mobility was assessed using the Timed Up and Go test (TUG) (Podsiadlo and Richardson, 1991). The TUG is a mobility test in which subjects are asked to walk 3 m then turn around and walk back 3 m at their self-selected normal pace in a well-lit environment.

2.5. Statistical analysis

We compared subject characteristics, including brain atrophy and PA, between the WML groups using Student's *t* test for continuous variables or χ^2 tests for categorical variables. To examine the association between PA and brain atrophy, we first conducted a simple correlation analysis and a partial correlation analysis (controlling age, sex, and TUG). Next, multiple regression analysis was used to determine independent associations between PA and brain atrophy. Brain atrophy was used as the dependent variable. Explanatory variables included LPA or MVPA. To determine the effects of WML on the association between PA and brain atrophy, we established three models. Model 1 was limited to the PA measures. Model 2 included the variables in Model 1 plus demographic data and physical function as covariates. In Model 3, we also added WML to Model 2. The change in R^2 between

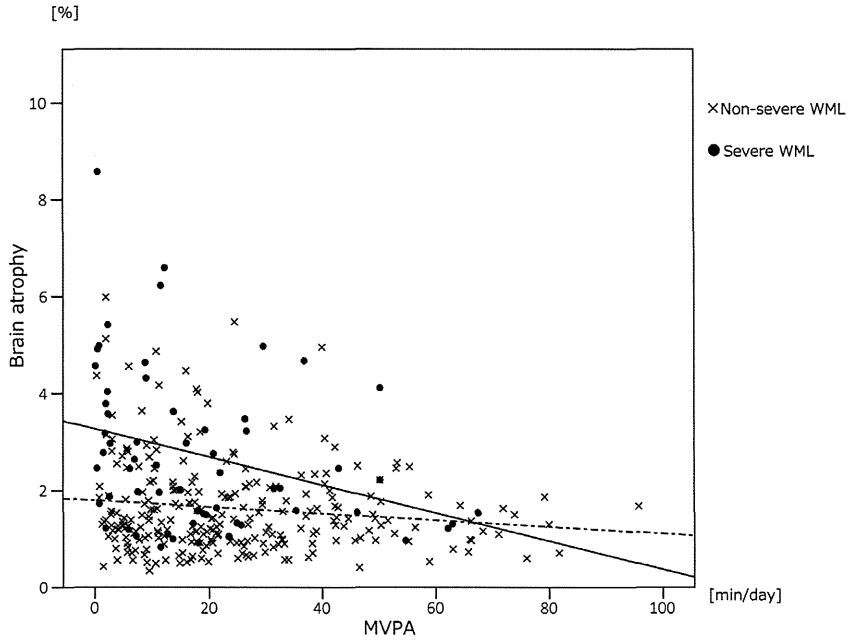

Fig. 2. Scatterplot showing the relationship between MVPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).