Cigarette Smoking and Cognitive Health in Elderly Japanese

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***Objective*: To examine the relationships between smoking status and various domains of cognitive function in community-dwelling elderly subjects. *Methods*: Participants (N = 4348) were asked about smoking status, demographic variables, and lifestyle factors, and underwent multidimensional neurocognitive tests. *Results*: All analyses were conducted separately by sex. Women never smokers exhibited significantly better scores than past and/or current smokers in some neurocognitive tests. Among men, never smokers had significantly higher scores, such as in the Symbol Digit Substitution Test. Multiple linear regression analysis showed that pack-years (history of smoking) were significantly associated with the Symbol Digit Substitution Test in men. *Conclusions*: Smoking status may be associated with a decline in processing speed, and this decline varies by sex.**

***Key words*: smoking; pack-years; cognitive function; elderly**

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There are approximately one billion smokers worldwide.[1] Cigarette smoking is associated with various diseases such as ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer;[2-7] approximately 6 million people die annually of diseases related to cigarette smoking.[1] Moreover, cigarette smoking also appears to be related to neurocognition[8] and constitutes a serious health problem for the elderly.

Smoking increases the risk of Alzheimer's disease.[9] Previous studies suggest that compared to never smokers, smokers in the middle-aged and aged population have poorer cognitive functions such as working memory, attention, executive function, and information-processing speed.[10-14] One study classified smokers into 4 types: *current smokers*, *ever smokers who smoked at least 100 cigarettes in their life*, *former smokers*, and *never smokers*, and reviewed previous studies examining the relationship between dementia and cognitive decline.[15] Current smokers in this study had a higher risk of incident Alzheimer's disease and cognitive decline in comparison with former and never smokers. Additionally, former smokers had a higher rate of cognitive decline than never smokers. These findings indicate that current cigarette smoking behavior, as well as a history of smoking (eg, how long and/or much cigarette smoking), may have an impact on cognitive health.

To examine the effects of smoking in terms of how long and/or how much, many previous studies have measured smoking status using "pack-years" (eg, Glass et al[16]), calculated by multiplying average daily use in packs by the number of years of smoking. Numerous studies used this parameter to investigate the association between smoking and cancer, especially lung cancer; pack-years were found to be related directly to an increased risk for lung cancer.[17] Meanwhile, several studies examined the link between pack-years and cognitive function, and showed that more pack-years correlated with a significantly higher rate of cognitive decline.[16,18] Another study examined the effect of pack-years on changes in global cognitive function in nondemented elderly persons.[19] The investigators found that more cigarette pack-years correlated with a significantly greater cognitive de-

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Table 1
Relationships among Demographics, Disease, and Lifestyle by Smoking Status among Men and Women in Japan

	Women				Men			
Measure	Never smokers	Past smokers	Current smokers	p value	Never smokers	Past smokers	Current smokers	p value
Demographics								
Number (%)	2100 (94.0)	71(3.2)	62 (2.8)	< .001	489 (23.1)	1255 (59.3)	371 (17.5)	< .001
Age (years) (SD)	71.68 (5.37)	71.56 (4.83)	69.85 (4.82)	.029	72.06 (5.14)	72.18 (5.43)	70.13 (4.60)	<.001
Education level (years) (SD)	10.95 (2.15)	10.62 (2.42)	11.08 (2.03)	.400	11.92 (2.78)	11.91 (2.72)	12.09 (2.70)	.541
Disease								
Hypertension (%)	905 (43.1)	35 (49.3)	26 (41.9)	.571	216 (44.2)	629 (50.1)	145 (39.1)	< .001
Cardiovascular disease (%)	285 (13.6)	10 (14.1)	9 (14.5)	.971	91 (18.6)	263 (21.0)	41 (11.1)	< .001
Diabetes (%)	217 (10.3)	7 (9.9)	6 (9.7)	.978	68 (13.9)	220 (17.5)	53 (14.3)	.103
Hyperlipidemia (%)	1021 (48.6)	32 (45.1)	24 (38.7)	.264	157 (32.1)	448 (35.7)	98 (26.4)	< .01
Osteoporosis (%)	411 (19.6)	9 (12.7)	6 (9.7)	.055	8 (1.6)	19 (1.5)	1 (0.3)	.145
Fracture (since over 60 years) (%)	306 (14.6)	9 (12.7)	4 (6.5)	.183	35 (7.2)	72 (5.7)	23 (6.2)	.540
Lifestyle								
Current alcohol drinking (%)	552 (26.3)	28 (39.4)	26 (41.9)	< .001	293 (59.9)	872 (69.5)	247 (66.6)	< .001
Regular exercise (> 4 days per week) (%)	94 (4.5)	6 (8.4)	3 (4.8)	.100	38 (7.8)	86 (6.9)	23 (6.2)	.860

Note.
Values are means (SD) or N (%). Statistical significance was set at p < .05

cline, and a cutoff point of 10 pack-years or more correlated with a decline in the Mini-Mental State Examination (MMSE) by 0.013 points per year. Data reported by Mons et al[20] revealed that current smokers with 21–40 pack-years had lower scores in cognitive tests that measured memory when compared with never smokers. However, these studies did not examine the relationships between cigarette smoking using pack-years and multidimensional cognitive function other than global cognition. Measurement of multiple domains in cognitive function is important to assess cognition for the early detection of mild cognitive impairment or Alzheimer's disease.[21] Additionally, decline in cognitive function among elderly people is related to such factors as age, education level, physical activity, and alcohol consumption; consequently, these variables should be considered as covariates when investigating the association between pack-years and multiple domains in cognitive function. The number of female smokers has increased gradually, although there are still more male than female smokers. The rate of smoking in adults worldwide was approximately 39.4% among men and 16.0% among women according to the 2002 WHO survey.[22] Hence, owing to the disparity between male and female smoking rates, one must consider the influence of sex when conducting studies on smoking. The aim of this study was to examine the relationships between smoking status and various domains of cognitive function in a community-dwelling elderly population, controlling for potential confounding factors.

METHODS

Participants

Participants were selected from 5104 community-dwelling elderly persons who took part in the Obu Study of Health Promotion for the Elderly (OSHPE). Persons who participated in OSHPE were selected from 15,974 people over 65 years living in Obu, a residential suburb of Nagoya, Japan. An invitation letter was sent to them to enroll in the OSHPE; the inclusion criteria consisted of being over 65 years of age, living in Obu, and not participating in other studies. Other details have been reported in a previous paper.[23] Exclusion criteria in this study were: a history of stroke (N = 283), Alzheimer's disease (N = 8), Parkinson's disease (N = 23), and/or depression (N = 131); being certified to require long-term care insurance in Japan (N = 127); having a disability (not independent of activities of daily living) (N = 13); and having severe cognitive decline (MMSE ≤20)[24] (N = 109). Exclusive of those who had a missing value (N = 59) and refused to participate (N = 3), the final number of participants was 4348 (2233 women and 2115 men).

Measures

Smoking status. Participants were asked about

Table 2
Relationship between Smoking Status and Cognitive Function in Elderly Men and Women in Japan

		Never smokers (N = 2100)		Past smokers (N = 71)		Current smokers (N = 62)			
	Cognitive Test	Mean	SD	Mean	SD	Mean	SD	F	Adjusted p value*
Women	Immediate word test	7.52 (7.53)	1.26	7.37 (7.39)	1.42	7.13 (7.02)	1.35	5.648	< .01
	TMT-A	1.38 (1.38)	0.44	1.46 (1.46)	0.39	1.43 (1.49)	0.44	3.184	.042
	TMT-B	3.03 (3.03)	2.47	4.51 (4.49)	10.56	3.21 (3.47)	2.31	9.074	< .001
	SDST	38.28 (38.33)	8.37	36.08 (36.15)	7.17	37.85 (36.38)	8.50	5.874	< .01
	Delayed word test	4.09 (4.09)	1.92	3.80 (3.82)	1.97	3.98 (3.76)	1.90	1.824	.162
	MMSE	26.82 (26.83)	2.33	26.69 (26.74)	2.24	25.85 (25.68)	2.48	8.020	< .001
		Never Smokers (N = 489)		Past Smokers (N = 1255)		Current Smokers (N = 371)			
	Cognitive Test	Mean	SD	Mean	SD	Mean	SD	F	Adjusted p value*
Men	Immediate word test	7.17 (7.19)	1.34	7.22 (7.24)	1.31	7.34 (7.25)	1.25	0.243	.784
	TMT-A	1.39 (1.38)	0.35	1.40 (1.39)	0.38	1.36 (1.40)	0.38	0.493	.611
	TMT-B	3.20 (3.17)	4.39	3.05 (3.00)	3.13	2.90 (3.12)	1.37	0.595	.552
	SDST	39.16 (39.36)	8.28	39.00 (39.24)	7.73	39.25 (38.15)	7.08	4.478	.011
	Delayed word test	3.46 (3.51)	1.94	3.53 (3.57)	1.89	3.78 (3.60)	1.84	0.315	.730
	MMSE	26.08 (26.09)	2.49	26.19 (26.22)	2.34	26.18 (26.06)	2.43	0.983	.374

Note.
TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; SDST, Symbol Digit Substitution Test; MMSE, Mini Mental Examination Test. Statistical significance was set at $p < .05$
*: Adjusted for age, education level, alcohol drinking status, and regular exercise
( ): estimate value

smoking status (never smokers, past smokers, or current smokers). Past smokers also were asked the following questions: (1) "How many cigarettes did you smoke in a day?" (2) "How old were you when you started to smoke?" and (3) "How old were you when you stopped smoking?" Current smokers were asked: (1) "How many cigarettes do you smoke in a day?" and (2) "How old were you when you started to smoke?" Participants were classified into *never smokers*, *past smokers*, and *current smokers*. For the purposes of this study, "smoking" refers to cigarette smoking. Pack-years were calculated by multiplying average daily use in packs by the number of years of smoking, thereby enabling compilation of one's lifetime history of smoking.

Cognitive function. We measured cognitive function using the MMSE and the National Center for Geriatrics and Gerontology Functional Assessment Tool (NCGG-FAT). The MMSE is used worldwide to measure global cognitive function.[25] Scores on the MMSE range from 0 to 30. However, the NCGG-FAT consists of 8 tasks that are used to evaluate memory (word list memory), attention (tablet version of Trail-Making Test part A: TMT-A), executive function (tablet version of Trail-Making Test part B: TMT-B), and processing speed (tablet version of Symbol Digit Substitution Test: SDST). For word memory, participants were required to memorize 10 words presented in series and recall as many as possible: recall of more words signifies a better memory. In TMT-A, participants were asked to navigate successive numbers and connect them in order as fast as possible. The time taken to complete the task was recorded, with a shorter time indicating better performance. In TMT-B, participants were required to navigate a series of alternating numbers and letters, and connect them in alternating sequential order as quickly as possible, with a shorter time representing better performance. For SDST, participants were shown sets of digits and symbols in pairs, and asked to choose digits matching symbols as quickly as possible over 90 seconds. More matches completed indicate a better performance. A well-trained operator supported each participant to set up the tablet PC, help in understanding the task protocols, and record the data. The tests of NCGG-FAT have high test-retest reliability and moderate to high validity.[26]

Other variables. Other variables with a potential influence on cognitive function included age, sex, education level, diseases, exercise, and alcohol consumption.[11,27,28] We inquired about the frequency of regular exercise per week (every day,

Table 3
Hierarchical Multiple Linear Regression Analysis among Pack-years and Cognitive Function in Elderly Men in Japan

	Immediate word		TMT-A		TMT-B	
	β	t	β	t	β	t
Age	-.218	-8.970**	.320	13.709**	.233	9.609**
Education level	.117	4.822**	-.151	-6.507**	-.138	-5.723**
Alcohol status	.049	2.056*	-.010	-.420	.014	.597
Exercise	-.040	-1.655	.066	2.895**	.028	1.189
Pack-years	.010	.419	.031	1.350	-.004	-.150
R^2	.081		.154		.087	
	SDST		Delayed word		MMSE	
	β	t	β	t	β	t
Age	-.421	-19.623**	-.290	-12.385**	-.144	-5.913**
Education level	.227	10.629**	.183	7.856**	.204	8.396**
Alcohol status	.016	.746	.035	1.512	.002	.070
Exercise	-.079	-3.742**	-.048	-2.105*	-.052	-2.176*
Pack-years	-.063	-3.019**	-.040	-1.771	-.011	-.448
R^2	.284		.149		.079	

Note.
TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B;
SDST, Symbol Digit Substitution Test; MMSE, Mini Mental Examination Test. * p < .05, ** p < .01

5–6 days, 2–4 days, <1 day, not at all), and about alcohol status by asking about past and current alcohol-drinking status, categorizing it similarly to smoking status (never drinking, past drinking, or current drinking).

Statistical Analyses

We conducted one-way analysis of variance (ANOVA) and chi-square tests to examine the differences in age, education level, exercise, and alcohol consumption in regard of smoking status. We then performed analyses of covariance (ANCOVA) to determine whether smoking status is associated with cognitive function after adjusting for age, education level, alcohol-consumption status, and regular exercise. Lastly, we confirmed the relationship between a history of smoking and cognitive function using hierarchical multiple linear regression analysis adjusted for age, education level, exercise, and alcohol consumption. Missing data were excluded from analyses and all analyses were performed using the IBM SPSS Statistical Statistics 19.0 software package (SPSS Inc., Tokyo, Japan). Statistical significance was set at $p < .05$.

RESULTS

Among study participants, the mean age was 71.71 years; there were 2115 men (48.6%) and 2233 women (51.4%). We conducted one-way ANOVA and chi-square tests separately by sex to examine the difference between measured variables according to smoking status, because the proportion of never smokers, past smokers, and current smokers varied greatly between men and women (Table 1). In the case of women, never smokers were significantly older than current smokers ($p = .029$). The chi-square test also showed that never smokers had significantly less current alcohol drinking than past smokers and current smokers ($p < .001$). Among men, past smokers had a higher incidence of diseases such as hypertension ($p < .001$), cardiovascular disease ($p < .001$), and hyperlipidemia ($p < .01$) than never smokers and/or current smokers, although the results of age and alcohol status were similar to those for women.

Next, we looked for a difference in cognitive function according to smoking status to determine the influence of smoking on cognitive function in the elderly. We conducted ANCOVA separately by sex, adjusting for age, education level, alcohol-drinking status, and regular exercise (Table 2). The results showed that female never smokers had higher scores than current smokers in the immediate word test ($F_{2, 2230} = 5.648$, $p < .01$). Also among women, never smokers had better TMT-A ($F_{2, 2230} = 3.184$, $p = .042$), TMT-B ($F_{2, 2230} = 9.074$, $p < .001$), SDST ($F_{2, 2230} = 5.874$, $p < .01$), and MMSE ($F_{2, 2230} = 8.020$, $p < .001$) scores than past or current smokers. In the case of men, never smokers had better SDST scores ($F_{2, 2212} = 4.478$, $p = .011$) than current

and/or past smokers.

Finally, to investigate whether there was a relationship between a history of smoking (pack-years) and cognitive function in smokers, we conducted hierarchical multiple linear regression analysis separately by sex, adjusting for age, education level, alcohol-drinking status, and exercise. The results indicated that pack-years were significantly associated with SDST scores in men (Table 3). Table 3 shows that the correlation (R^2) change was significant after entering smoking status ($F_{5, 1639} = 130.119$, $p < .01$). Pack-years had a significant relationship with scores in SDST ($\beta = -0.063$, $p < .01$). Conversely, there was no significant relationship between smoking status and scores in the immediate word test ($\beta = 0.010$, $p = .675$), delayed word test ($\beta = -0.040$, $p = .077$), TMT-A ($\beta = 0.031$, $p = .177$), TMT-B ($\beta = -0.004$, $p = .881$), and MMSE ($\beta = -0.011$, $p = .654$) among men (Table 3). For women, however, a history of smoking was not related to any measures of cognitive function.

DISCUSSION

In this study, never smokers had a lower rate of some diseases in both men and women, although the types of disease varied according to sex. For both men and women, never smokers had a lower rate of current alcohol consumption than past and current smokers. Female never smokers had better memory, attention, executive function, processing speed, and global cognitive function than past and/or current smokers. Pack-years were not related to cognitive function in women, whereas more pack-years were associated with slower processing speed in elderly men.

Our findings indicated sex differences regarding the association between smoking status and cognitive function. The proportion of smokers in the elderly Japanese population shows obvious differences between the sexes.[29] Some studies have examined sex difference regarding the influence of smoking on disease, and have shown that women may be more sensitive than men to some of the negative effects of smoking.[30] That is, compared with men, women may be more susceptible to some diseases as a result of smoking, especially in the vascular system (eg, cardiovascular disease). In addition, some diseases associated with smoking, such as cardiovascular disease, respiratory disease, and malignant neoplasm are directly linked to cognitive decline.[31–33] In this study, never smokers had better cognitive function if they were female, a result consistent with ones reported in previous studies.

Of particular note, when we used pack-years as a measure of smoking status, pack-years were related to processing speed even after adjustment for age, education level, alcohol-drinking status, and exercise habit in men, but not in women. Gallinat et al[34] showed that smokers had significantly smaller gray-matter volume and lower gray-matter density in the frontal regions than never smokers. Additionally, they indicated that a history of smoking (pack-years) was inversely correlated with volume of the frontal lobe, which is activated during tasks measuring cognitive processing speed.[35,36] Our results concurred with these data, although the effects of smoking on cognitive function differed between the sexes. As another potential factor that might affect the association between pack-years and processing speed, previous studies pointed out the possibility of the effects of nicotine on the brain. Nicotine is a psychoactive substance that acts directly on the brain region activated during cognitive processing.[37] Some studies examined the association between nicotine exposure and brain function, and revealed that nicotine results in neuritic damage.[38,39] Moreover, Goriounova and Mansvelder[37] examined the relation between nicotine exposure during adolescence and cognitive deficits in later life, and concluded that nicotine modulates information processing by activating and desensitizing nicotine receptors in the prefrontal network. Although it may be less certain as to whether there is a sex difference regarding the relationship between smoking and cognitive function, one previous study[40] indicated the possibility of sex-related confounding factors such as nicotine independence; future study is required to verify such an influence.

There are some limitations to this study. First, the design was cross-sectional, and the time-oriented effect of smoking on cognitive function remained unclear. A longitudinal study will be required to reveal the temporal impact of smoking on cognitive function in the elderly. Second, a self-reported history of smoking involves recall bias[41] although we tried to minimize the impact of this by taking histories accurately and carefully. However, information regarding secondhand smoke, which lately has come under scrutiny as a serious problem, was lacking, thereby representing a potential limitation.

In conclusion, our study revealed that among the elderly, female never smokers had better performance in some domains of cognitive function, especially memory, attention, executive function, processing speed, and global cognitive function; among men, a history of smoking assessed using pack-years was associated with processing speed.

Conflict of Interest Statement

Authors declare no conflict of interest.

Human Subjects Approval

We obtained informed consent from all participants before their participation in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol, approval number 490.

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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.

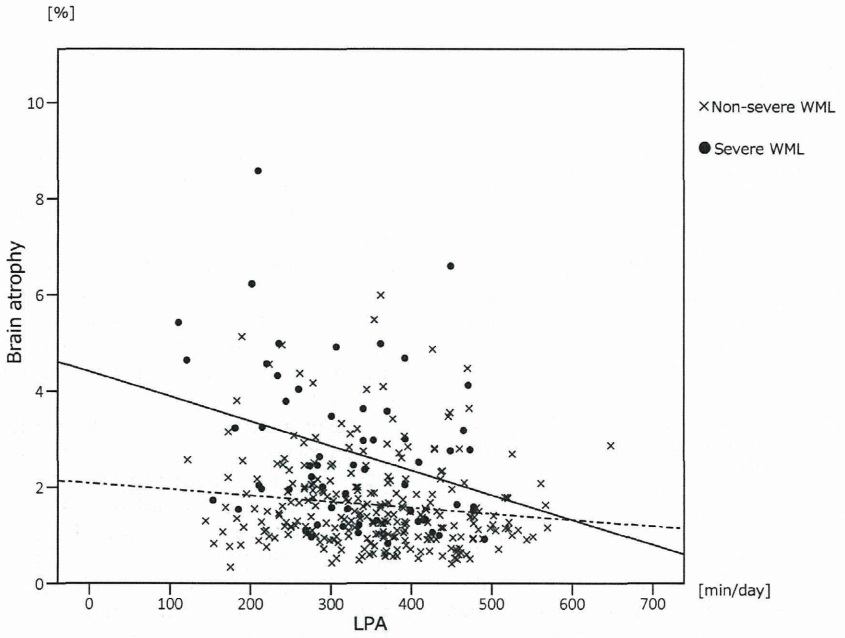

Fig. 1. Scatterplot showing the relationship between LPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).

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

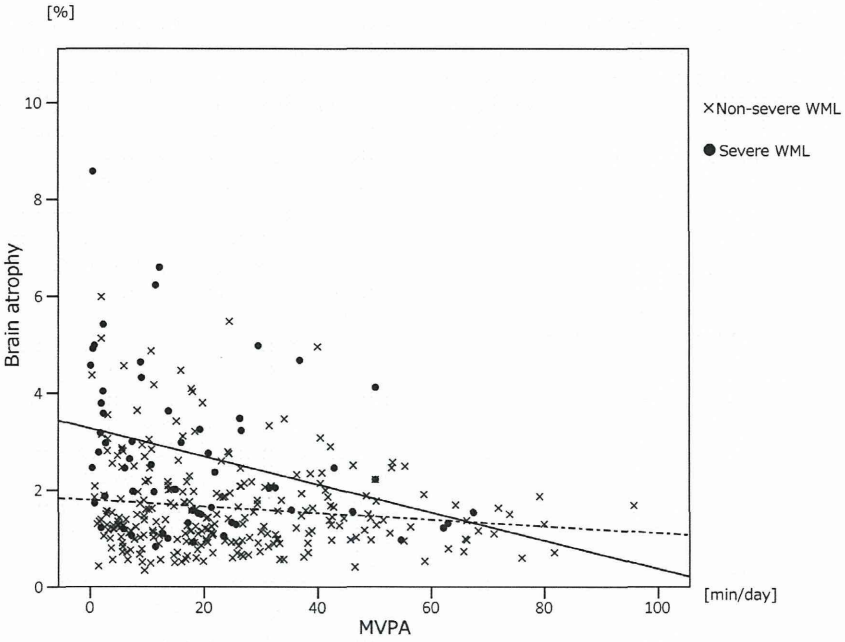

Fig. 2. Scatterplot showing the relationship between MVPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).