early stages of AD, but not in the late stages.[18,20] If this is true, WML might have greater influence on cognitive profiles in amnestic mild cognitive impairment (aMCI) patients than AD patients, because aMCI has been considered a preclinical and prodromal stage of AD. In some studies of MCI patients, WML were associated with cognitive decline,[21] and predicted a higher rate of conversion to dementia.[22,23] Studies investigating the influence of WML on cognitive function both in AD and aMCI patients have been sparse to date.

In view of investigating the influence of small WML on cognitive profiles of AD pathology, one has to preclude with caution a possible contamination of mixed pathology, such as vascular dementia or vascular mild cognitive impairment, from analysis. Therefore, in the present study, we focused on investigating neuropsychological traits in patients with AD or aMCI, and examined their associations with the degree of small WML, assessed by a semi-quantitative method based on MRI findings after carefully excluding patients with diffuse or extensive WML. If any difference was observed between the groups, the finding might suggest temporal profiles regarding the influence of small WML on cognitive performances during the progression of this neurocognitive disorder.

Methods

Participants

The present study was carried out among outpatients attending the Nagoya University Hospital department of geriatrics in Nagoya, Japan, between January 2010 and March 2012. Among 641 consecutive patients aged 60 years or older, 268 patients who were diagnosed with neither AD nor aMCI, and 109 patients who could not complete the relevant cognitive tasks were excluded. Regarding methods for objectively assessing the degree of WML, the Fazekas rating scale[24] was used in the present study. It is a visual semi-quantitative rating scale of WML volume, and this scale is one of the most widely-used and well-validated. This scoring system is a four-point scale, rated on a 0- to 3-point scale of increasing severity. As explained in the Introduction, in order to eliminate a possible contamination of mixed pathology, those who were graded more than 2 on the Fazekas rating scale (64 patients) were not included in the study, and only those who were graded either 0 or 1 on the scale were included, eventually leaving 200 patients subjected for analyses.

Of the participants, 160 patients were diagnosed as probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[25] and 40 cases were diagnosed as aMCI according to the Mayo Clinic Criteria.[26] The patients with aMCI all met the criteria for single-domain amnestic MCI or multiple-domain amnestic MCI proposed by Petersen.[27] All of them had the complaint of memory impairment. Patients with single-domain amnestic MCI had impaired performance (more than 1.5 SD below controls) on one or more of the memory tests used in the neuropsychological battery, but not on the other tests. Patients with multiple-domain amnestic MCI had impaired performance on one or more of the memory tests, and impaired performance on one or more of the other tests. None of them had dementia according to the clinical assessment. Hereafter, aMCI includes both the single- and multiple-domain subtypes.

The evaluation procedure consisted of a detailed medical history, cognitive assessment, laboratory tests and cerebral MRI. The patients also underwent a clinical examination to exclude other etiologies. Patients who had a history of cerebrovascular disorders or the presence of significant vascular risk factors were excluded, as well as patients who had previously received an actual diagnosis of major depression.[28] Japanese was the primary language for all participants.

Cognitive assessment

All participants underwent a battery of neuropsychological tests. The battery of neuropsychological tests included the following tests: the Mini-Mental State Examination (MMSE)[29] for general cognitive function; the Logical Memory I and II subtests of the Wechsler Memory Scale-revised (WMS-R)[30] for memory; the category fluency test (participants were required to generate as many animal names as possible within 1 min) and the letter fluency test (participants were required to generate as many words beginning with the syllable "ka" (the Japanese version of the phonemic fluency task) as possible within 1 min for verbal fluency; the Digit Span Forward and Backward subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R)[31] for working memory; the Digit Symbol subtests of WAIS-R[31] for processing speed; and the Stroop colored word test for executive functions (controlled inhibition). All patients were also assessed for depressive mood using the Geriatric Depression Scale-15 (GDS-15).[32]

Testing and scoring of the neuropsychological tests were carried out by a trained clinical psychologist with a Master's degree in clinical psychology. Participants were tested individually in a single session. Written informed consent was obtained at the start of the evaluation from all participants or their closest relative.

White matter assessment

The MRI scans were carried out on a 1.5T machine. Ratings of WML on MRI images were carried out on a

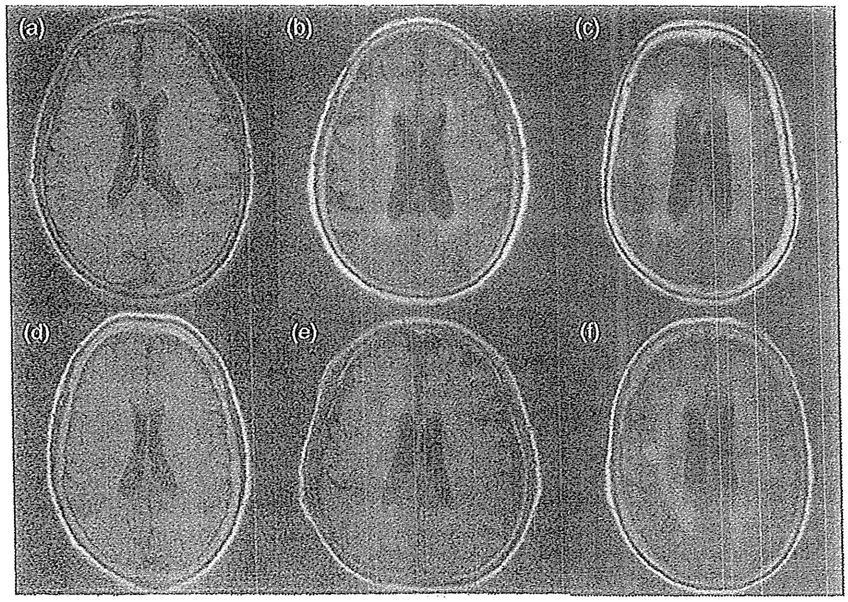

Figure 1 Examples of Fazekas scale ratings. (a) Periventricular hyperintensities (PVH) score = 1. (b) PVH score = 2. (c) PVH score = 3. (d) Deep white matter hyperintensities (DWMH) score = 1. (e) DWMH score = 2. (f) DWMH score = 3.

Table 1 Numbers of patients for Fazekas scale ratings

		AD (n = 160) DWMH Grade 0	Grade 1			aMCI (n = 40) DWMH Grade 0	Grade 1
PVH	Grade 0	30	14	PVH	Grade 0	5	4
	Grade 1	21	95		Grade 1	7	24

Definitions of rating scores of periventricular white matter hyperintensity (PVH): grade 0, absence; grade 1, caps or pencil-thin lining. Definitions of rating scores of deep subcortical white matter hyperintensity (DWMH): grade 0, absence; grade 1, punctate.
AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment.

computer screen with axial fluid-attenuated inversion recovery (FLAIR) images. The visual semi-quantitative rating scale of WML volume described by Fazekas *et al.*[24] was used. This scoring system is a four-point scale for separately assessing the increasing severity of periventricular white matter hyperintensity (PVH) and deep subcortical white matter hyperintensity (DWMH). PVH severity was scored according to the following categories: absence (grade 0); caps or pencil-thin lining (grade 1); smooth halo (grade 2) and irregular PVH extending into the deep white matter (grade 3). DWMH severity was scored according to the following categories: absence (grade 0); punctate (grade 1); beginning confluence (grade 2) and large confluence (grade 3). Examples of PVH and DWMH severities are shown in Figure 1. Participants who were graded more than grade 2 of PVH or DWMH were excluded from the present study. Table 1 shows the numbers of patients for the Fazekas rating scale included in this study. All ratings were carried out by two raters (the second and third authors). Each rater rated each case individually and then consulted with each other to reach a consensus.

Statistical analysis

The statistical analyses were carried out using IBM SPSS Statistics version 19 for Windows (SPSS Japan, Tokyo, Japan). A value of $P < 0.05$ was used in all analyses to show statistical significance.

First, we carried out descriptive analyses of sociodemographic and clinical characteristics. Table 2 shows the mean and standard deviations, and the frequency and percentage. We used the χ^2-test for the comparison of categorical data, and we applied Student's t-test for continuous data.

Analysis of covariance (ANCOVA) was used to determine the correlation of WML and cognitive data between AD and aMCI. It is well known that age and

Table 2 Clinical characteristics and cognitive performance of Alzheimer's disease and amnestic mild cognitive impairment patients

	AD (n = 160)				aMCI (n = 40)				
Sex (male/female)	66/94				15/25				
Diabetes mellitus (%)	29 (18.13%)				7 (17.50%)				
Hypertension (%)	70 (43.75%)				20 (50.00%)				
Hyperlipidemia (%)	70 (43.75%)				20 (50.00%)				
aMCI subtype (single domain/multiple domain)					19/21				
	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	P-value
Age (years)	77.01	6.87	61	92	76.08	6.56	60	90	0.440
Education (years)	11.40	2.78	6	20	12.26	2.95	8	18	0.084
GDS15	4.33	3.37	0	14	3.83	2.94	0	13	0.390
MMSE	21.94	3.69	11	29	27.13	1.49	24	30	<0.001
WMS-R Logical Memory I	6.26	4.30	0	22	10.05	4.65	1	22	<0.001
WMS-R Logical Memory I	1.16	2.40	0	12	3.20	2.83	0	9	<0.001
Category Fluency Test	11.67	3.72	2	23	14.90	4.02	6	24	<0.001
Letter Fluency Test	7.76	3.15	2	20	9.18	3.40	0	15	0.013
WAIS-R Digit-Span Forward	5.63	1.89	2	10	6.20	1.68	3	9	0.084
WAIS-R Digit-Span Backward	4.34	1.45	1	8	5.05	1.38	2	8	0.006
WAIS-R Digit-Symbol	33.22	11.73	3	77	38.38	12.01	9	68	0.014
Stroop Test Color	21.86	10.03	9.56	78.09	17.67	3.94	8.85	30.79	<0.001
Stroop Test Colored Word	46.75	20.04	15.40	134.19	40.08	18.03	20.32	113.21	0.056

P-values were calculated by Student's t-tests. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; Education, total number of years of schooling; GDS15, 15-item version of the Geriatric Depression Scale; MAX, maximum score; MIN, minimum score; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

education level influence cognitive function, so these two variables were considered to be covariables in the analysis carried out later. As a post-hoc analysis, pairwise multiple comparisons of the cognitive data were tested with Bonferroni test after ANCOVA.

Results

Table 2 presents the sociodemographic and clinical characteristics of the participants, and the raw neuropsychological test results for both AD and aMCI. The means and standard deviations, and maximal and minimal values are shown.

The groups with different diagnoses were not statistically different in terms of the following variables: distribution of sex, clinical comorbidity (diabetes mellitus, hypertension, hyperlipidemia), age, years of education and depressive mood (GDS-15). Likewise, the MCI subtypes were similar in their distributions of the variables. Regarding the comparison of cognitive performances between the two groups, AD group performed significantly worse than did the aMCI group in tests as follows: MMSE (t [158.87] = 13.84, $P < 0.001$), logical memory I (t [198] = 4.91, $P < 0.001$), logical memory II (t [198] = 4.63, $P < 0.001$), category fluency (t [198] = 4.83, $P < 0.001$), letter fluency (t [198] = 2.51, $P < 0.05$), digit span backward (t [198] = 2.80, $P < 0.01$), digit symbol (t [198] = 2.47, $P < 0.05$) and Stroop color test (t [162.81] = 2.59, $P < 0.001$).

Table 3 shows the influence diagnosis and PVH had on participants' performances in the neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE (F [1,194] = 49.43, $P < 0.001$), logical memory I (F [1,194] = 16.81, $P < 0.001$), logical memory II (F [1,194] = 14.68, $P < 0.001$), category fluency (F [1,194] = 29.43, $P < 0.001$), letter fluency (F [1,194] = 8.02, $P < 0.01$), digit symbol (F [1,194] = 4.86, $P < 0.05$) and Stroop colored word test (F [1,194] = 4.06, $P < 0.05$). PVH had a significant influence on the results of the tests that assess the following variables: category fluency (F [1,194] = 8.11, $P < 0.01$) and letter fluency (F [1,194] = 5.47, $P < 0.05$). Individuals having small PVH, independent of their diagnosis, performed worse than those having no PVH in terms of verbal fluency. We found significant effects of interaction on the results of the category fluency test (F [1,194] = 7.01, $P < 0.01$). The

Table 3 Cognitive performance according to periventricular hyperintensities

	AD				aMCI						
	PVH grade0 (n = 44)		PVH grade1 (n = 116)		PVH grade0 (n = 9)		PVH grade1 (n = 31)		P Diagnosis	P PVH	P Diagnosis × PVH
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
MMSE	22.82	3.04	21.60	3.86	27.67	1.22	26.97	1.54	<0.001	0.294	0.678
WMS-R Logical Memory-I	6.77	4.19	6.06	4.35	11.22	5.45	9.71	4.43	<0.001	0.500	0.651
WMS-R Logical Memory-II	1.09	2.61	1.19	2.32	3.44	3.32	3.13	2.73	<0.001	0.819	0.676
Category Fluency Test	12.25	3.11	11.45	3.92	18.44	3.68	13.87	3.55	<0.001	0.005	0.009
Letter Fluency Test	8.34	2.96	7.53	3.20	11.44	1.33	8.52	3.54	0.005	0.020	0.094
WAIS-R Digit-Span Forward	6.11	1.98	5.45	1.83	6.22	1.79	6.19	1.68	0.473	0.723	0.402
WAIS-R Digit-Span Backward	4.86	1.29	4.14	1.47	5.33	1.80	4.97	1.25	0.074	0.165	0.503
WAIS-R Digit-Symbol	36.11	12.24	32.12	11.40	44.78	11.97	36.52	11.55	0.029	0.105	0.304
Stroop Test Color	20.54	8.28	22.36	10.61	16.46	3.13	18.01	4.13	0.051	0.701	0.991
Stroop Test Colored Word	44.37	16.03	47.66	21.36	30.75	7.09	42.78	19.38	0.045	0.163	0.259

P-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; PVH, periventricular white matter hyperintensity; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

combination of aMCI and category fluency showed a significant negative influence (F [1,194] = 9.28, $P < 0.01$); whereas in the AD group, such an association was not observed.

Table 4 shows the influence that diagnosis and DWMH had on participants' performances on neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE (F [1,194] = 56.00, $P < 0.001$), logical memory I (F [1,194] = 22.54, $P < 0.001$), logical memory II (F [1,194] = 21.09, $P < 0.001$), category fluency (F [1,194] = 16.06, $P < 0.001$), letter fluency (F [1,194] = 4.34, $P < 0.05$), digit span backward (F [1,194] = 4.02, $P < 0.05$). DWMH did not significantly influence any other neuropsychological tests. We did not find any other significant effects of the interaction between diagnosis and DWMH.

Discussion

The primary objective of the present study was to examine the association between small WML and cognitive function in older patients with AD or aMCI. To this end, two subgroups of patients with AD or aMCI differed regarding the influence of small WML on cognitive function.

Among aMCI participants, those without PVH had higher scores than those with PVH on the category fluency test. In contrast, the existence of small PVH did not significantly affect the score on the same test in AD patients. These findings might support a notion suggesting that WML could influence cognitive performance in the early stage of cognitive impairment, but not in the later stage of degenerative dementia.[18,20] Changes of relative involvement of WML on cognition by disease progression could explain the results obtained. It is well known that as AD pathology advances, cortical atrophy extends. Therefore, one could speculate that the relative influence of cortical atrophy on cognition compared with that of WML becomes increased in the later stage of AD. Further investigations focusing on patients with earlier stages of AD whose extent of cortical atrophy are considered minimal could address this speculation.

We found significant effects of interaction between diagnosis and PVH on the results of the category fluency test, whereas on the results of the letter fluency such interaction was not found. The category fluency task is associated with the ability to access semantic knowledge, whereas letter fluency is considered an index of frontal control function.[33] In a meta-analysis of verbal fluency in AD, it was suggested that impairment in category fluency rather than letter fluency might be among the early changes associated with AD.[34] A previous study has shown that the aMCI groups have

Table 4 Cognitive performance according to deep subcortical white matter hyperintensity

	AD DWMH grade 0 (n = 51)		AD DWMH grade 1 (n = 109)		aMCI DWMH grade 0 (n = 12)		aMCI DWMH grade 1 (n = 28)		P Diagnosis	P DWMH	P Diagnosis × DWMH
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
MMSE	22.53	3.48	21.66	3.76	27.00	1.48	27.18	1.52	<0.001	0.756	0.444
WMS-R Logical Memory-I	6.45	3.98	6.17	4.46	11.75	4.58	9.32	4.56	<0.001	0.213	0.161
WMS-R Logical Memory-II	1.16	2.41	1.17	2.40	4.17	2.98	2.79	2.71	<0.001	0.254	0.126
Category Fluency Test	11.96	3.65	11.53	3.76	14.67	4.96	15.00	3.65	<0.001	0.590	0.670
Letter Fluency Test	8.24	3.62	7.53	2.89	9.75	3.14	8.93	3.53	0.038	0.394	0.856
WAIS-R Digit-Span Forward	5.94	2.01	5.49	1.82	6.75	1.42	5.96	1.75	0.147	0.170	0.569
WAIS-R Digit-Span Backward	4.39	1.36	4.31	1.50	5.08	1.51	5.04	1.35	0.032	0.874	0.975
WAIS-R Digit-Symbol	36.96	12.60	31.47	10.93	40.33	12.22	37.54	12.04	0.112	0.221	0.621
Stroop Test Color	20.13	6.60	22.67	11.22	17.43	3.74	17.77	4.09	0.056	0.656	0.574
Stroop Test Colored Word	46.58	16.92	46.84	21.42	40.89	26.01	39.73	13.92	0.158	0.606	0.913

P-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; DWMH, deep subcortical white matter hyperintensity; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

greater impairment in category fluency performance than in letter fluency performance relative to healthy controls.[35] Neuroanatomically, category fluency relies on the medial temporal lobe regions, whereas letter fluency has been found to correlate with prefrontal lobe functioning.[36] Differences in the anatomical substrates for each verbal fluency task might explain the present results. Because of advanced medial temporal lobe atrophy, WML might not influence category fluency in the later stage of AD.

When diagnosis was not added, associations between the small PVH and low verbal fluency performance were shown in the present study. Several studies found that WML was particularly associated with a decline in mental processing speed, executive functions, but not with a decline in memory functions,[10,37–39] which could suggest that WML have an influence on frontal lobe functions. Memory decline is particularly related to medial temporal lobe atrophy, and might be less affected by WML.[17,40] The disruption of long associating fibers by PVH might be particularly deleterious for frontal lobe domain functions.[21] In the present results, small PVH contributed to cognitive decline in verbal fluency, but not in any other domains of cognitive function. It remains unclear why small PVH was correlated only with verbal fluency.

Our results are in line with several population-based studies[11–14] in which PVH and not are associated with different clinical conditions. It is also suggested that the pathology presenting PVH might impair cognitive functioning more easily than that affecting the subcortical area. Anatomically, the periventricular regions have a high density of long associating fibers, which connect the cortex with the subcortical nuclei and other distant brain territories, whereas the subcortical area has a high density of short-looped U fibers connecting adjacent gyri.[11] The mechanism underlying the present results requires further substantiation.

The main limitation of the present study was the rating system of WML. Regarding the semi-quantitative rating of white matter lesions used in our study, it could be argued that it is not sufficiently accurate, but this rating system has been shown to correlate well with quantitative volumetric measurements.[41] The present study showed that small amounts of WML were correlated with cognitive impairment. We assumed that greater degrees of WML correspond to different patterns of cognitive decline. WML could trigger or enhance neurodegenerative processes when the lesion load reaches a certain threshold.[19]

Because of the smaller sample size of aMCI patients, the statistical power of the study might have been insufficient to detect an association between cognitive deficit and small WML. Our sample size was also inadequate to examine the association of cognitive decline with the different locations of DWMH, which might have some importance. Some studies have shown that cognitive dysfunction differs according to where WML are present.[42] It would therefore be important to assess the specific roles of WML depending on their frontal, parietal or temporal locations.

In summary, the present study found that small PVH were significantly associated with cognitive decline, in particular with a deficit of verbal fluency, in aMCI patients. Furthermore, a category fluency deficit, not a letter fluency deficit, was found to show an interaction with small PVH. Further studies are required to confirm these results and to improve our understanding of the underlying mechanisms.

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Disclosure statement

The authors declare no conflict of interest.

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The Effect of Additional Training on Motor Outcomes at Discharge from Recovery Phase Rehabilitation Wards: A Survey from Multi-Center Stroke Data Bank in Japan

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Abstract

Objectives: The purpose of the present study was to examine the potential benefits of additional training in patients admitted to recovery phase rehabilitation ward using the data bank of post-stroke patient registry.

Subjects and Methods: Subjects were 2507 inpatients admitted to recovery phase rehabilitation wards between November 2004 and November 2010. Participants were retrospectively divided into four groups based upon chart review; patients who received no additional rehabilitation, patients who were added with self-initiated off hours training, patients who were added with off hours training by ward staff, patients who received both self-initiated training and training by ward staff. Parameters for assessing outcomes included length of stay, motor/cognitive subscales of functional independent measures (FIM) and motor benefit of FIM calculated by subtracting the score at admission from that at discharge.

Results: Participants were stratified into three groups depending on the motor FIM at admission (≦28, 29~56, 57≦) for comparison. Regarding outcome variables, significant inter-group differences were observed in all items examined within the subgroup who scored 28 or less and between 29 and 56. Meanwhile no such trends were observed in the group who scored 57 or more compared with those who scored less. In a decision tree created based upon Exhaustive Chi-squared Automatic Interaction Detection method, variables chosen were the motor FIM at admission (the first node) additional training (the second node), the cognitive FIM at admission(the third node).

Conclusions: Overall the results suggest that additional training can compensate for the shortage of regular rehabilitation implemented in recovery phase rehabilitation ward, thus may contribute to improved outcomes assessed by motor FIM at discharge.

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Introduction

Stroke is one of primary debilitating events that affect health status and functional capacity, and is reportedly ranked second or third cause of mortality or condition leading to functional impairments in most developed countries [1]. Japan is no exception that stroke is the first cause of conditions requiring care and is ranked the first in medical expenditure nationwide among the older population [2]. Recent advancement has made various therapeutic options including thrombolytic therapy, intravascular therapy or cerebral protective therapy available for stroke patients, however that does not undermine the significance of rehabilitation for functional recovery. It has been confirmed from previous randomized control trials (RCT) or systematic reviews that providing care in stroke units by multidisciplinary team comprising doctors, nurses, physiotherapist (PT), occupational therapist (OT) and speech therapist (ST) leads to improved clinical outcomes, such as long-term prognosis, activities of daily living at discharge, length of hospital stay [3,4]. To date, there had been a dearth of multi-center data base for rehabilitation medicine in Japan, which impeded implementation of studies supported by strong evidences. In order to establish rigorous evidences for the quality improvement and to provide rationales for the revision of reimbursement system in stroke rehabilitation, we have been establishing a data bank (DB) of post-stroke patients receiving rehabilitation since 2005, which was supported by a Grant-in-Aid issued from the

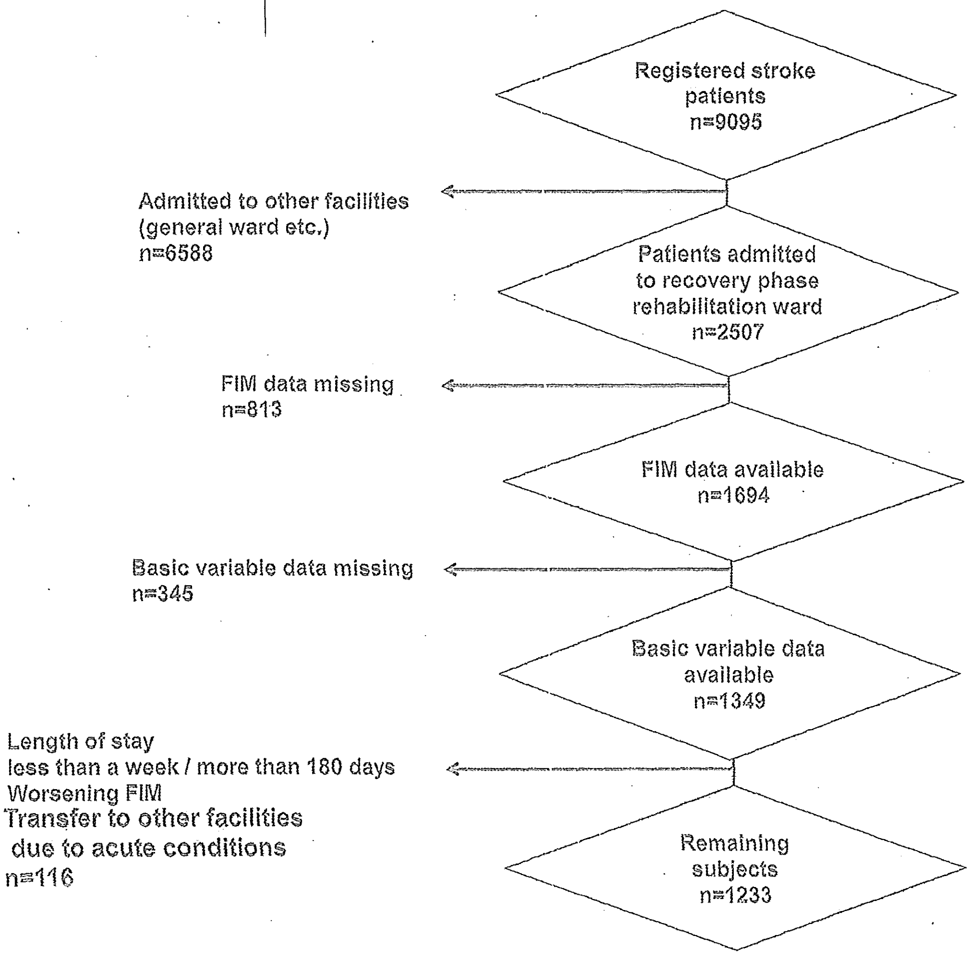

Figure 1. Flow chart showing selection procedure of participants.
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Ministry of Health, Labor and Welfare for the research project entitled "The development of data bank for stroke rehabilitation". By November 2011, we collected over 9000 cases from 30 institutions nationwide. In Japan recovery phase rehabilitation ward for patients took effect from the year 2000 and the 2006 revision for reimbursement enabled post stroke patients to receive a maximum of three hours rehabilitation per day by PT, OT and ST. This unique type of ward restricts intake of patient only to medical conditions such as stroke, spinal injuries, head trauma, hip fractures or disuse syndrome. In addition, there are specific regulations regarding the admission criteria, including term of admission. For example, stroke patients have to be admitted within two months after the onset of stroke with maximum length of stay limited until 150 days after the onset. Regarding the time of rehabilitation per day, only those who can tolerate three hours rehabilitation per day are eligible for the entry to rehabilitation programs according to the US Agency for Health Care Policy and Research [5], which is in contrast with the policy applied in Japan. On the other hand, there is a study implemented in a stroke unit that indicated the significance of "off hours" training enhanced by multidisciplinary team for improved activities of daily living (ADL) [1], which suggests a potential benefit of such off hours intervention particularly under the situation where there is a limitation in authorized volume of training. The "OFF hours" training comprises self-initiated training and training by ward staff. However, little attention to date has been paid to off hours intervention and its effect on functional prognosis [6,7]. As suggested in a recent meta-analysis, the importance of off hours training is a subject to be investigated through further research [8]. Although previous studies regarding off hours training focused on self-initiated training mainly led by patients themselves, there is also a necessity to evaluate additional training provided by ward staff. No studies so far had examined the effect of off hours training (self-initiated training, training by ward staff or both) in recovery phase rehabilitation wards uniquely introduced in Japan.

There is a difficulty in carrying out RCT in rehabilitation medicine. Therefore as an alternative method of investigation, well-designed comparative research with larger samples is considered significant [9]. However, there has been a concern about external validity in previous reports with such method since many of them either came from single institution or had not examined reproducibility in other samples of patients [9,10]. Thus in the present study, in order to endorse external validity, we obtained observational data from multiple sources and randomly assigned the individual data into two groups and examined

Table 1. Characteristics of participants stratified by motor subscales of FIM at admission.

		①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple comparison‡
Motor subscales of FIM at admission ≦28 (n = 427)							
		(n = 62)	(n = 7)	(n = 203)	(n = 155)		
Sex	Male	33(14.2%)	2(0.9%)	113(48.7%)	84(36.2%)	0.59	
	Female	29(14.9%)	5(2.6%)	90(46.2%)	71(36.4%)		
Type fo stroke	CI	38(14.7%)	3(1.2%)	132(51.2%)	85(32.9%)	0.02	
	CH	17(13.0)	2(1.5%)	50(38.2%)	62(47.3%)		
	SAH etc.	7(18.4%)	2(5.3%)	21(55.3%)	8(21.1%)		
Informal care resources	NIC	17(18.5%)	2(2.2%)	42(45.7%)	31(33.7%)	0.27	
	OIC	20(13.7%)	4(2.7%)	64(43.8%)	58(39.7%)		
	MTIC	19(10.6%)	1(0.6%)	94(52.5%)	65(36.3%)		
Age		74.5±9.9	73.0±8.0	75.3±9.2	69.4±11.8	<0.001	④<①③
Days after onset at admission		41.1±25.0	48.6±47.3	39.9±21.2	30.9±16.4	<0.001	④<①③
Motor subscales of FIM at admission 29~56 (n = 418)							
		(n = 63)	(n = 16)	(n = 71)	(n = 268)		
Sex	Male	50(18.9%)	13(4.9%)	43(16.2%)	159(60.0%)	0.01	
	Female	13(8.5%)	3(2.0%)	28(18.3%)	109(71.2%)		
Type of stroke	CI	27(10.2%)	11(4.1%)	58(21.8%)	170(63.9%)	<0.001	
	CH	31(13.9%)	2(0.9%)	11(8.9%)	79(64.2%)		
	SAH etc.	5(17.2%)	3(10.3%)	2(6.9%)	19(65.5%)		
Informal care resources	NIC	19(17.3%)	6(5.5%)	23(20.9%)	62(57.3%)	0.46	
	OIC	17(12.4%)	4(2.9%)	23(16.8%)	93(67.9%)		
	MTIC	26(15.7%)	6(3.6%)	23(13.9%)	111(66.9%)		
Age		71.8±9.5	68.1±9.7	75.1±10.7	66.6±12.8	<0.001	④<①③
Days after onset at admission		41.9±21.4	34.9±19.4	36.4±18.4	32.0±14.6	<0.001	④<①③
Motor subscales of FIM at admission 57≦ (n = 388)							
		(n = 45)	(n = 41)	(n = 22)	(n = 280)		
Sex	Male	23(9.3%)	31(12.6%)	13(5.3%)	180(72.9%)	0.12	
	Female	22(15.6%)	10(7.1%)	9(6.4%)	100(70.9%)		
Type of stroke	CI	28(11.2%)	16(6.4%)	16(6.4%)	190(76.0%)	0.003	

Table 1. Cont.

Motor subscales of FIM at admission ≤28 (n = 427)		①No additional training	②Self-initiated training	③Training by ward staff	④Dual training	p value[†]	multiple comparison[‡]
		(n = 62)	(n = 7)	(n = 203)	(n = 155)		
	CH	9(9.8%)	17(18.5%)	2(2.2%)	64(69.6%)		
	SAH etc.	8(17.4%)	8(17.4%)	4(8.7%)	26(56.5)		
Informal care	NIC	12(12.0%)	13(13.0%)	0(0.0%)	75(75.0%)	0.07	
resources	OIC	15(11.7%)	13(10.2%)	9(7.0%)	91(71.1%)		
	MTIC	16(10.6%)	13(8.6%)	12(7.9%)	110(72.8%)		
Age		72.0±11.1	61.7±15.5	70.9±18.2	64.2±13.7	<0.001	②④<①
Days after onset at admission		35.4±16.8	34.6±14.4	41.6±26.8	30.4±21.9	0.05	

note:SAH = Subarachnoidal hemorrhage; CI = Cerebral infarction; CH = Cerebral hemorrhage; NIC = No informal caregivers; OIC = One informal caregiver; MTIC = More than two informal caregivers.
[†]p value for one way analysis of variance.
[‡]multiple comparison: digits refer to group numbers (Tukey multiple comparison procedure).
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whether the equation model formulated in one group can also predict the outcomes in the other with statistical significance.

The purpose of the present study was to examine potential benefit of off-hours rehabilitation involving self-initiated training by patients themselves, and training by ward staff in patients admitted to recovery phase rehabilitation wards using the DB of post-stroke patients registered during the term of observation.

Subjects and Methods

The present study was a secondary analysis of the DB of post-stroke patients registered between November 2004 and November 2010. Subjects were 2507 inpatients admitted to recovery phase rehabilitation wards out of 9095 patients registered in post-stroke DB. The DB was managed by the Japan Association of Rehabilitation Database (JARD) and the data was provided after the research protocol was approved by the institutional review board. Thus the data is not publicly available but only those who obtained the approval were authorized access to the DB. Of the subjects, those whose essential data (age, sex, FIM, record of self-initiated off hours training) were either absent or missing in more than 40% of inpatients, length of stay being either less than 7 days or more than 180 days, venue of rehabilitation changed due to acute medical conditions, FIM scores at discharge deteriorated were excluded, eventually 1233 inpatients were subjected to analyses (Fig. 1). Variables included age, sex and type of stroke as basic information. The followings were also included; number of days after admission, number of informal caregivers (none, single person, more than 2 people), total volume of PT and OT counted by Formal Therapy Unit (FTU) and FTU per day were also calculated (1FTU is equivalent to 20 minute Formal Therapy). Parameters for assessing outcomes included length of stay, motor FIM/cognitive FIM and motor benefit of FIM calculated by subtracting the score at admission from that at discharge. Participants were retrospectively divided into four groups based upon chart records; patients who received no additional rehabilitation (no additional training), patients who were added with self-initiated off hours training (self-initiated training), patients who were added with off hours training by ward staff (training by ward staff), patients who received both self-initiated off hours training and training by ward staff (dual additional training) and their outcomes assessed by parameters aforementioned were compared.

Statistical Analysis

Age, length of stay, number of days after the onset of stroke until discharge, FTU, FTU/day, motor FIM, cognitive FIM and motor benefit of FIM of the four intervention groups were compared using analysis of variance followed by Tukey's post-hoc test.It is known that improvement of ADLs during admission can be higher in patients whose physical independence at admission is intermediate compared with patients who have either low or high physical independence, thus exhibits reverse U-shaped trend [11]. Therefore, subjects were divided equally into three subgroups based on the motor FIM at admission for group comparison. Categorical data (sex, types of stroke and presence of informal caregivers) of the four groups were compared using chi-square test. In order to clarify contributing factors to motor FIM at discharge after possible confounding factors (presence of informal caregivers, motor FIM at admission and cognitive FIM at admission) having been adjusted, a decision tree analysis was carried out, making measured variables at admission that indicated significant intergroup differences by univariate analysis explanatory variables. In the present study Exhaustive Chi-Squared Automatic Interaction Detection (ECHAID) was adopted for the analysis. ECHAID is a

Table 2. Outcome parameters of participants at discharge stratified by motor subscales of FIM at admission.

Motor subscales of FIM at admission ≦28 (n=427)

	①No additional training (n=62)	②Self-initiated traning (n=7)	③Training by ward staff (n=203)	④Dual training (n=155)	p value†	multiple comparison‡
Length of stay	111.3±46.2	105.0±61.4	95.7±43.9	124.9±31.2	<0.001	①④>③
FTU*	358.8±184.0	308.7±252.9	275.3±179.2	474.4±221.4	<0.001	④>①>③
FTU/day*	3.2±1.0	3.2±1.8	2.8±1.2	3.8±1.4	<0.001	④>①③
Motor FIM at admission	17.9±5.0	16.9±3.9	16.3±4.2	20.2±4.9	<0.001	④>①③
Cognitive FIM at admission	11.4±6.4	15.0±8.6	11.9±6.4	17.9±8.3	<0.001	④>①③
Motor FIM at discharge	31.7±16.3	50.6±22.3	33.0±18.4	52.1±21.4	<0.001	④>①③
Cognitive FIM at discharge	15.0±7.7	21.7±8.5	15.9±6.4	24.6±8.3	<0.001	④>①③
Motor benefit of FIM	13.8±12.8	33.7±22.3	16.7±17.0	31.9±19.7	<0.001	④>①③, ②>①

Motor subscales of FIM at admission 29~56 (n=418)

	①No additional training (n=63)	②Self-initiated traning (n=16)	③Training by ward staff (n=71)	④Dual training (n=268)	p value†	multiple comparison‡
Length of stay	111.2±47.8	100.4±33.1	88.4±38.1	104.1±37.6	0.01	①④>③
FTU*	398.5±222.4	379.4±171.2	248.3±144.3	405.1±242.7	<0.01	①④>③
FTU/day*	3.5±1.0	3.8±0.8	2.8±1.1	3.7±1.5	<0.01	①②④>③
Motor FIM at admission	42.3±8.6	49.5±6.9	39.9±7.5	43.5±8.0	<0.01	②>①③④, ④>③
Cognitive FIM at admission	22.1±7.3	24.5±7.5	19.6±5.9	24.7±7.1	<0.01	④>①③, ②>③
Motor FIM at discharge	61.3±15.7	75.2±7.0	61.0±11.3	72.7±11.5	<0.01	②④>①③
Cognitive FIM at discharge	24.7±7.1	30.0±5.8	22.4±5.8	29.3±5.7	<0.01	②④>①③
Motor benefit of FIM	19.0±11.6	25.7±8.1	21.1±11.6	29.1±11.3	<0.01	④>①③

Motor subscales of FIM at admission 57≦ (n=388)

	①No additional training (n=45)	②Self-initiated traning (n=41)	③Training by ward staff (n=22)	④Dual training (n=280)	p value†	multiple comparison‡
Length of stay	89.3±46.9	69.4±42.4	75.5±33.2	74.6±39.2	0.10	
FTU*	320.7±210.5	251.0±176.3	175.6±78.7	296.0±207.6	0.02	①④>③
FTU/day*	3.5±1.1	3.6±1.0	2.4±0.7	3.9±1.6	<0.01	①②④>③
Motor FIM at admission	71.4±10.3	76.7±9.8	67.3±9.7	70.8±9.2	<0.01	②>③④
Cognitive FIM at admission	27.4±6.3	29.0±5.7	19.8±6.3	29.2±5.9	<0.01	①②④>③

Table 2. Cont.

Motor subscales of FIM at admission ≦28 (n = 427)	①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple comparison‡
	(n = 62)	(n = 7)	(n = 203)	(n = 155)		
Motor FIM at discharge	82±7	86.0±6	81.2±7.9	82.2±6.8	0.07	②>①③④
Cognitive FIM at discharge	29±5.4	31.0±4.2	23.9±5.5	31.6±4.5	<0.01	①②④>③, ④>①
Motor benefit of FIM	10.6±7.8	9.3±7.9	13.9±8.5	11.4±7.5	0.13	

*FTU: Formal Therapy Unit: One unit is equivalent of 20minute rehabilitation.
†p value for one way analysis of variance.
‡multiple comparison: digits refer to group numbers (Tukey multiple comparison procedure).
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commonly used algorithm of classification tree analysis that employed multi-contingency tables of Chi-squared significant test to identify optimal splits [12]. In order to avoid over fitting, we specified the growing depth of 3 with the parent node having at least 100 subjects and a child node at least 50 subjects. Gains and index charts were constructed to identify the nodes with a relatively high probability. The statistics of misclassification risk was used to assess the prediction results. Primary outcomes to evaluate the effectiveness of additional training was motor FIM at discharge. Motor FIM on admission, the motor FIM at discharge were automatically divided into three ordinal scales (lower tertile; ≦55, mid tertile; 56–79, upper tertile; 80≦) in order for the calculations to fit into the decision tree created. To ensure the validity of the analysis, split-sample validation method was adopted in the present study. In brief, subjects were randomly divided into two groups. Decision trees analysis was carried out in one group and whether the equation obtained in the study group can be applicable in another group (validation group) was examined. All the analyses were carried out using a statistical software package (SPSS version 19.0 for Windows, Chicago IL, USA) and a p value of <0.05 was adopted to show statistical significances. All the personal data were coded deleting any information related to personal identification in order to secure anonymity of the study and the study protocol was approved by the ethical committee of the Japan Society for Rehabilitation Medicine.

Results

1. Group Comparison

Table 1 compares variables of subjects stratified into three groups depending on the motor FIM at admission (≦28, 29~56, ≥57). Subjects who scored 28 or less showed significant inter-group differences in the type of stroke, age and the interval between the onset and admission. A post-hoc analysis indicated that dual training group was younger and had shorter interval between the onset and admission relative to self-initiated training group and training by ward staff group. Subjects who scored between 29 and 56 showed similar trend in variables examined with those with lower tertile. Meanwhile in subjects who scored 57 or more on the motor FIM at admission, types of stroke and age showed inter-group differences with self-initiated training group and dual additional training group being younger relative to no additional training group.

Table 2 shows comparison of variables stratified by the motor FIM at admission. Significant inter-group differences were observed in all items examined within the subgroup who scored 28 or less. A post-hoc analysis revealed that dual training group showed better outcomes compared with training by ward staff group, and dual training group were superior to no additional training group in all parameters apart from the length of stay. Inter-group differences were also observed in a subgroup whose motor FIM at admission were between 29 and 56, and a post-hoc analysis indicated similar results showing that dual training group had better outcomes than training by ward staff group.Meanwhile no such trends were observed by post-hoc analysis in the group who scored 57 or more (upper tertile) compared with those who scored less.

2. Decision Tree Analysis using ECHAID

Figure 2 shows a decision tree created based upon ECHAID method. Overall risk estimate for the model in the study group was 0.32, while that in the validation group was 0.31, therefore the analysis was considered appropriate. The variables chosen in the decision tree were the motor FIM at admission,additional trainings,the cognitive FIM at admission. The motor FIM at admission were chosen in the first node, therefore considered most influential on the motor FIM at discharge. For those who scored 56 or less on the motor FIM at admission, no additional training group, training by ward staff and dual training group, self-initiated training group were divided. Meanwhile better cognitive FIM at admission (>28) emerged as a variable to determine improved motor FIM at discharge in those who scored 57 or more on the motor FIM at admission.

Discussion

The main purpose of the present study was to clarify the effect of additional training other than formal therapy by qualified therapists (PT, OT, ST) on motor FIM at discharge in post-stroke patients. The study utilized multi-center DB of stroke patients and the samples were randomly assigned to either study or validation group. Decision tree analyses were carried out and risk estimates for both groups were compared with an aim to examine whether the model obtained in the study group can be extrapolated in the validation group as well. To date most of studies using decision tree analysis adopt cross validation, which uses random sample out of all subjects for examining validity of the analysis implemented [13,14]. The limitation about this method is that sampled subjects for validation are included in actual analysis for creating decision tree, and therefore not quite independent. The present analysis was a result from over 1000 cases and was validated by equal number of subjects. Therefore the decision tree created can be considered to exceed in external validity compared with results obtained from conventional methods. The results indicated that in both groups whose motor FIM at admission were either less than 28 or between 29 and 56, those who received both self-initiated training and training by ward staff showed better cognitive and motor FIM at discharge. Furthermore, the decision tree analysis, after adjusting for other possible factors that might affect motor FIM at discharge, also confirmed that implementations of additional training were beneficial in terms of improved outcomes at discharge for those whose motor FIM at admission were below 56. In principle, a factor that appears in the first node has the strongest explanatory power in the decision tree analysis. Thus it was the motor FIM at admission that was most strongly related to the motor FIM at discharge, followed by the implementation of additional training for those in the lower and mid tertile groups of baseline motor FIM. Meanwhile in the upper tertile group, cognitive profiles at admission were more strongly related to the outcomes at discharge than the implementation of additional training. In the upper tertile group, whose overall functional impairment was relatively mild compared with other groups, cognitive capacity affecting attention or concentration to the training assigned may have stronger impact on the efficacy of training than the volume of training. Overall the results suggest that implementation of self-initiated training together with training by ward staff or at least self-initiated training alone might contribute to improved outcomes assessed by motor FIM at discharge, albeit actual contents of off-hours rehabilitation were

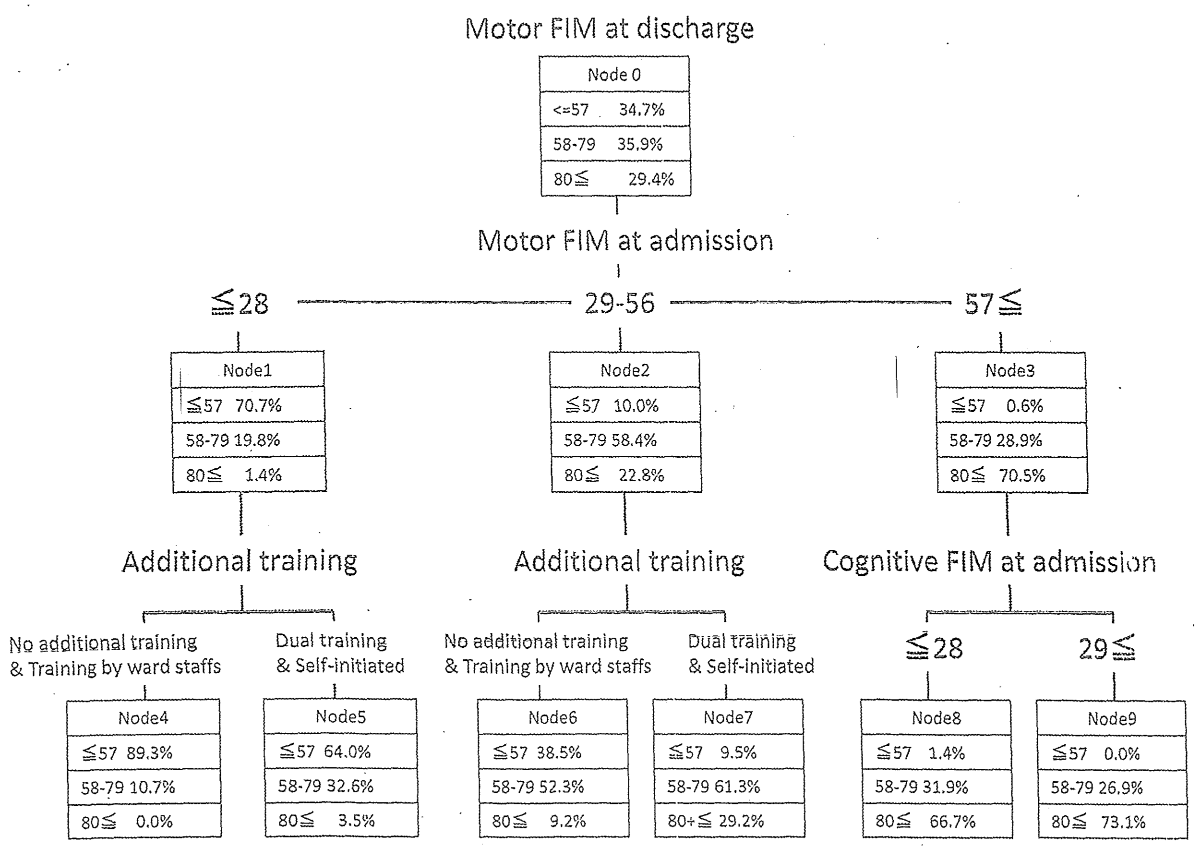

Figure 2. Decision tree for Functional Independence Measure among 1233 stroke patients (Validation Group).
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not available to obtain from the DB. However, given small sample size of patients who implemented self-initiated training, the present results must be interpreted with caution. A previous study by Galvin et al [15].employing a randomized controlled trial (RCT) on the effect of self-initiated training confirmed the improvement of ADLs or easing stress experienced by family. Another report also stressed the efficacy of self-initiated training assisted by patients' family for improved physical functions of lower extremities and ADLs [7]. A systematic review by Meheroz et al [6]. have demonstrated that off hours repeated use of upper extremities may contribute to improved functions. Previous studies including RCT [15–17] that investigated the effect of self-initiated training targeted particular conditions such as first onset, no episode of dementia or restricted severity of hemiparesis, therefore the findings can be applied to conditions meeting inclusion criterion. Meanwhile the results obtained in the present study can be applied to patients with broad conditions of stroke. Regarding the effect of training by ward staff, Indredavik et al [18] stated that one of the advantages of stroke unit compared with general ward is the preventive approaches of secondary complications or disuse syndromes by staff nurses. Studies of stroke unit have shown that multidisciplinary interventions might lead to beneficial outcomes. Likewise, the present study suggested the importance of close collaborations of multidisciplinary staffs by having demonstrated that the implementation of either both self-initiated training and additional training by ward staff or self-initiated training alone was found to be beneficial for improving motor outcomes in post stroke patients admitted to recovery phase rehabilitation ward although the findings cannot directly be applied to any ward accommodating post stroke patients. Possibly due to insufficient availability of physiotherapist, average total time of regular rehabilitation per day in the present study was approximately 70 minutes, which figures fall far short of upper limit of 90 minutes. Additional training can compensate for the shortage, which therefore must have worked effectively for the improvement of motor function as suggested in previous reports [1,19].

Even though every possible confounding factors had been considered in the present analyses, so-called reverse causality of having chosen subjects who were expected to improve cannot completely be eliminated, which serves as a limitation of the present study. Further analyses adopting propensity score, instrumental variables or RCT would be necessary to control reverse causality. Due to restriction of data availability, actual amount of time and intensity of self-initiated training and training by ward staff were not considered. Comparison of efficacy betweenthe two off hours training groups favored self-initiated training. Elevated motivation of patients themselves, leading to proactive participation to the training, may explain the observed difference although such possible reason remains a speculation under the absence of detailed information about off hours training. Despite external validity of this multi-center study having been warranted, given that many institutions participated in the DB registration had specialists of rehabilitation medicine, and had elevated motivation represented by relatively higher implementation rate of training by ward staff, the present results need to be interpreted with caution. Nonetheless, we believe that the present multi-center study using stroke DB suggested the significance of additional (self-initiated, by ward staff or both) training at least for patients whose ADLs at admission are classified as more than moderately impaired.

Author Contributions

Conceived and designed the experiments: NS DM SJ MS KK. Performed the experiments: NS DM SJ MS. Analyzed the data: NS YS. Contributed reagents/materials/analysis tools: NS. Wrote the paper: NS YS. Supervised the entire experiments: MK.

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ORIGINAL ARTICLE

Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40 to 79 years-of-age

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Aim: The age-dependent loss of skeletal muscle mass is highly concerning in diverse aging populations. However, age-dependent changes in muscle mass and the visceral fat area have not been well documented in Asian populations. The aim of the present study was to evaluate the age-dependent changes in skeletal muscle mass and the visceral fat area in Japanese adults from 40 to 79 years-of-age.

Methods: This was a cross-sectional study. Healthy men (n = 16 379) and women (n = 21 660) aged 40–79 years participated in the present study. The skeletal muscle mass and visceral fat area were measured in the study participants by bioelectrical impedance. The muscle mass data were converted into the skeletal muscle mass index (SMI) by dividing the weight by the height squared (kg/m^2).

Results: The SMI showed an age-dependent decrease in both sexes. Between 40 and 79 years, the total SMI decreased by 10.8% in men and by 6.4% in women. The arm SMI decreased by 12.6% in men and 4.1% in women, and the leg SMI decreased by 10.1% in men and by 7.1% in women in the same period. In contrast, the visceral fat area showed an age-dependent increase in both sexes. The visceral fat area increased by 42.9% in men and by 65.3% in women. The multiple regression analysis showed that the SMI was negatively associated with visceral obesity in both sexes.

Conclusions: In Japanese adults, sex-specific changes in skeletal muscle mass are more prominent in the arm than in the leg. Furthermore, the age-dependent increases in visceral adipose tissue might lead to loss of skeletal muscle mass. **Geriatr Gerontol Int 2014; 14 (Suppl. 1): 8–14.**

Keywords: age-dependent, Japanese, skeletal muscle mass, visceral fat area.

Introduction

Sarcopenia is an age-dependent loss of skeletal muscle mass, and is a serious medical concern in older populations.[1,2] Sarcopenia is characterized by an impaired state of health associated with mobility disorders, an increased risk of falls and fractures, an impaired ability to carry out activities of daily living, disabilities, and a loss of independence.[3–5]

Previous epidemiological studies of sarcopenia in several countries have shown a disease prevalence of 5–40% in older men and 7–70% in older women.[6–18] In general, the prevalence of sarcopenia is approximately 25% in older men and 20% in older women. Notably, previous work from this laboratory has shown that sarcopenia is highly prevalent among Japanese adults aged 80 years and older.[18] Because older adults have a greater potential for health problems than young adults, it is very important to begin prevention of sarcopenia early, possibly before the age of 65 years. Two previous studies from the USA and Europe have shown that the age-dependent loss of skeletal muscle mass starts at approximately 50 years-of-age, and that skeletal muscle mass declines by 6.6–23.3% until 79 years-of-age.[19,20] However, age-dependent changes in muscle mass in Asians are not well documented.

Visceral adiposity, which is the basis of metabolic syndrome and cardiovascular disease, is aggravated with age.[21] The visceral adipose tissue produces many inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6,[22] and expression of these inflammatory cytokines can lead to increased skeletal muscle breakdown.[23] Furthermore, previous studies have shown that increased visceral fat area is associated with decreased skeletal muscle mass in a

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small sample of older adults.[24] However, the association of skeletal muscle mass with age-dependent changes in visceral fat in a large population has not previously been shown.

The primary aim of the present study was to evaluate the age-dependent changes in skeletal muscle mass and visceral fat area using a large cross-sectional cohort of Japanese adults between 40 and 79 years-of-age. We also evaluated sex differences in skeletal muscle loss in the arms and legs. The secondary aim of the present study was to evaluate the association between the skeletal muscle mass and visceral fat area.

Methods

Participants

Participants were recruited by advertisements at several fitness and community centers. The participants in the present study were limited to visitors to these centers in the Kyoto, Osaka, and Hyogo prefectures in Japan. The inclusion criteria were an age of 40–79 years, living in the community and the ability to walk independently (including with a cane). The exclusion criteria were a certification of frailty status by the long-term care insurance service in Japan and artificial implants, such as cardiac pacemakers and replacement joints, which would interfere with accurate bioimpedance measurements. An interview was also used to identify those with the following exclusion criteria: severe cognitive impairment; severe cardiac, pulmonary, or musculoskeletal disorders; and comorbidities associated with greater risk of falls, such as Parkinson's disease or stroke. Because the purpose of the present study was to address physiological age-dependent changes in body composition, we excluded frail elderly and adults with those comorbidities. The present study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

Healthy men (n = 16 379) and women (n = 21 660) aged 40–79 years participated in the present study. The male participants were divided into eight groups according to age: 40–44 (n = 3697), 45–49 (n = 3151), 50–54 (n = 2202), 55–59 (n = 1952), 60–64 (n = 2274), 65–69 (n = 1683), 70–74 (n = 1030), and 75–79 (n = 390) years. The female participants were similarly divided into eight groups according to age: 40–44 (n = 3828), 45–49 (n = 3686), 50–54 (n = 3597), 55–59 (n = 3002), 60–64 (n = 3490), 65–69 (n = 2314), 70–74 (n = 1269), and 75–79 (n = 474) years.

Skeletal muscle mass index and visceral fat area

A bioelectrical impedance data acquisition system (Inbody 720; Biospace, Seoul, Korea) was used to determine bioelectrical impedance.[25] This system uses an electrical current at different frequencies (5, 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water in the body. The study participants stood on two metallic electrodes and held metallic grip electrodes. Using segmental body composition and muscle mass, a value for the appendicular skeletal muscle mass was determined and used for further analysis. The muscle mass was converted into the skeletal muscle mass index (SMI) by dividing the weight by the height squared (kg/m^2). This index has been used in several epidemiological studies.[6,26] Additionally, the SMI of the arms and legs was calculated. The visceral fat area was determined by evaluating a transverse cross-section of the fourth and fifth abdominal lumbar area.

Statistical analysis

Differences in the total SMI, arm SMI, leg SMI, and visceral fat area among the eight age groups were examined using an analysis of variance. Multiple regression models were applied to determine the relationship between the visceral fat area and the SMI, adjusted for age and weight in each sex. The data were managed and analyzed using SPSS (Windows version 18.0; SPSS, Chicago, IL, USA). A P-value of <0.05 was considered to show statistical significance for all analyses.

Results

The mean age of the study participants was 54.5 ± 9.9 years, and 21 660 (56.9%) of the participants were women. The total SMI showed an age-dependent decrease in both sexes (men, $F = 251.1$, $P < 0.001$; women, $F = 135.6$, $P < 0.001$; Table 1). The percentage change in the total SMI at 40–44 years showed an age-dependent decrease in both sexes (Fig. 1, Table 1). In those aged over 65 years, the percentage change in the total SMI was greater in men than in women. In addition, the 20th percentile of total SMI in men and women aged 65–79 years was 7.02 kg/m^2 and 5.61 kg/m^2, respectively (Table 2).

To compare the age-dependent changes in muscle mass in the upper and lower limbs in this cohort, we analyzed the arm and leg SMI. The arm SMI showed an age-dependent decrease in both sexes (men, $F = 132.1$, $P < 0.001$; women, $F = 24.1$, $P < 0.001$; Table 1). The percentage change in the arm SMI using the 40–44 years group as a reference also showed an age-dependent decrease in both sexes (Fig. 2, Table 1).

Similarly to the arm SMI, the leg SMI also showed an age-dependent decrease in both sexes (men, $F = 273.2$, $P < 0.001$; women, $F = 192.2$, $P < 0.001$; Table 1). The percentage change in the leg SMI also showed an

Table 1 Participant characteristics by age half decade

		Overall Men (n = 16 379) Women (n = 21 660)			40–44 years Men (n = 3697) Women (n = 3828)			45–49 years Men (n = 3151) Women (n = 3686)			50–54 years Men (n = 2202) Women (n = 3597)			55–59 Men (n = 1952) Women (n = 3002)		
		Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years
Total SMI (kg/m²)	Men	7.97	0.73	–	8.20	0.78	–	8.11	0.66	–1.0	8.11	0.67	–1.1	7.98	0.64	–2.7
	Women	6.26	0.64	–	6.41	0.67	–	6.39	0.64	–0.3	6.33	0.64	–1.3	6.23	0.59	–2.8
Arm SMI (kg/m²)	Men	2.08	0.28	–	2.14	0.31	–	2.11	0.26	–1.4	2.11	0.26	–1.2	2.08	0.24	–3.0
	Women	1.47	0.22	–	1.49	0.24	–	1.49	0.23	–0.5	1.47	0.22	–1.4	1.46	0.21	–2.3
Leg SMI (kg/m²)	Men	7.98	0.73	–	6.06	0.51	–	6.00	0.46	–0.9	5.99	0.46	–1.1	5.91	0.45	–2.5
	Women	6.26	0.64	–	4.92	0.48	–	4.91	0.45	–0.3	4.85	0.46	–1.3	4.77	0.42	–3.0
Visceral fat area (cm²)	Men	100.6	29.2	–	88.4	28.8	–	91.9	27.1	4.0	98.9	28.8	11.9	103.5	25.7	17.1
	Women	84.7	27.4	–	68.0	25.3	–	72.1	23.9	6.0	79.3	23.6	16.5	89.4	23.0	31.5

		60–64 years Men (n = 2274) Women (n = 3490)			65–69 years Men (n = 1683) Women (n = 2314)			70–74 years Men (n = 1030) Women (n = 1269)			75–79 years Men (n = 390) Women (n = 474)			ANOVA	
		Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	F-value	P-value
Total SMI (kg/m²)	Men	7.84	0.68	–4.3	7.64	0.67	–6.9	7.59	0.66	–7.4	7.32	0.62	–10.8	251.1	<0.001
	Women	6.14	0.61	–4.2	6.08	0.60	–5.2	6.09	0.55	–5.1	6.00	0.60	–6.4	135.6	<0.001
Arm SMI (kg/m²)	Men	2.05	0.25	–4.4	1.99	0.25	–6.9	1.96	0.24	–8.5	1.87	0.26	–12.6	132.1	<0.001
	Women	1.45	0.22	–3.1	1.44	0.21	–3.6	1.46	0.20	–2.5	1.43	0.21	–4.1	24.1	<0.001
Leg SMI (kg/m²)	Men	5.80	0.48	–4.3	5.64	0.46	–6.9	5.64	0.51	–7.0	5.45	0.45	–10.1	273.2	<0.001
	Women	4.69	0.43	–4.6	4.64	0.44	–5.7	4.63	0.41	–5.9	4.57	0.45	–7.1	192.2	<0.001
Visceral fat area (cm²)	Men	108.3	26.2	22.5	113.0	25.7	27.8	122.3	25.1	38.3	126.4	25.2	42.9	376.9	<0.001
	Women	94.0	23.3	38.2	101.6	23.0	49.4	108.5	24.1	59.5	112.4	29.3	65.3	966.7	<0.001

Percentage change of 40–44 years = (absolute change value / 40–44 years value) × 100. SMI, skeletal muscle mass index.

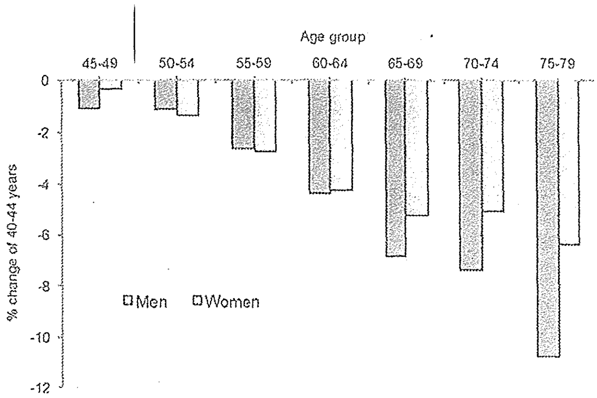

Figure 1 The percentage of change in the total skeletal muscle mass index in each sex and each age group, using 40–44 years-of-age as a reference.

Table 2 20th percentile of total skeletal muscle mass index (kg/m²) in both sexes

Age group (years)	20th percentile of SMI Men	Women
65–69	7.06	5.61
70–74	7.09	5.63
75–79	6.83	5.54
65–79	7.02	5.61

SMI, skeletal muscle mass index.

age-dependent decrease in both sexes (Fig. 2, Table 1). The age-dependent changes in the leg SMI were similar in men and women. However, the age-dependent changes in the arm SMI were greater in men than in women.

Next, we examined the age-dependent changes in visceral obesity. The visceral fat area showed an age-dependent increase in both sexes (men, $F = 376.9$, $P < 0.001$; women, $F = 966.7$, $P < 0.001$; Table 1). The percentage change from 40–44 years in the visceral fat area showed an age-dependent increase in both sexes (Fig. 3, Table 1).

To examine the association between skeletal muscle mass and visceral obesity, we carried out a multiple regression analysis using the SMI as an outcome. We found that the visceral fat area, age, and weight were significant and independent determinants of the SMI in both men ($\beta = -0.586$) and women ($\beta = -0.627$; Table 3). Therefore, the age-dependent change in the SMI was negatively associated with the visceral-fat area in both sexes.

Discussion

The current cross-sectional study was carried out to evaluate the SMI in Japanese adults aged between 40 and 79 years. Our data show that the SMI decreased age-dependently in both sexes. Notably, regarding the age-dependent decreases in the total SMI and in those aged over 65 years, the percentage change in the total SMI was greater in men than in women. From 40 to 79 years, the total SMI decreased by 10.8% in men and by 6.4% in women. Previous epidemiological studies of body composition have shown that between 40 and 79 years, the fat-free mass decreases by 6.6–23.3% in both sexes.[19,20] The age-dependent increases in inflammatory cytokines, such as IL-6 and TNF-α, can result in increased skeletal muscle breakdown.[23] In contrast, the age-dependent decrease in anabolic hormones, such as testosterone, growth hormone, and insulin-like growth factor-1 (IGF-1), might lead to a loss of skeletal muscle

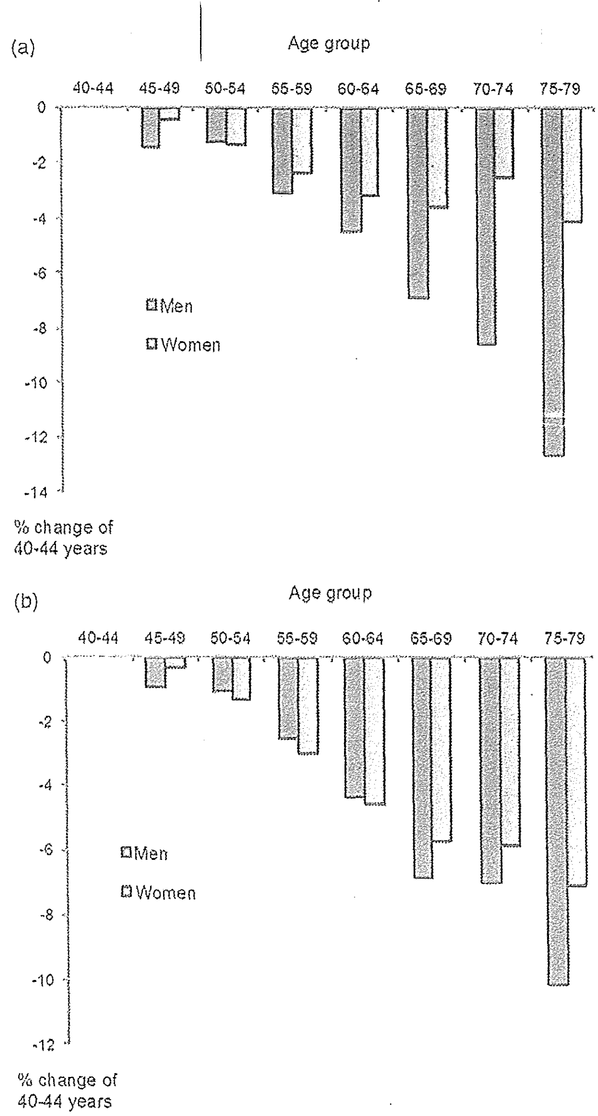

Figure 2 The percentage of change in the (a) arm and (b) leg skeletal muscle mass index (SMI) in each sex and each age group using 40–44 years-of-age as a reference.

mass.[27,28] In addition, there is also an age-dependent decrease in the amount of physical activity and energy intake. These behavioral changes can enhance the age-dependent reduction in skeletal muscle mass.

Interestingly, in those aged over 65 years, age-dependent decreases in total SMI were greater in men than in women. Furthermore, this age-dependent sex difference was more prominent in the arm than in the leg. From 40 to 79 years, the arm SMI decreased by 12.6% in men and by 4.1% in women. This is consistent to the previous studies in Japanese older adults. Kitamura *et al.* reported that the arm lean tissue mass was 5.97 ± 0.75 and 5.01 ± 0.67 in men, and 3.56 ± 0.54 and 3.24 in women aged in their 40s and 70s, respectively.[29] Based on their data, the percentage change in the arm lean tissue mass in men is –16.0% and is –8.9% in women. However, there is no sex difference in the percentage change in the leg lean tissue mass. The mechanism of this sex difference in the arm and leg lean tissue mass change is not clear. In general, older Japanese women frequently use the upper limbs, such as when washing and cooking. However, older Japanese men usually do not carry out such work. Therefore, it is possible that these behavioral differences lead to greater age-dependent decreases in the arm SMI in men than in women. As another possibility, Baumgartner reported that the sex hormone signal is an important factor for muscle mass in men, but not in women; however, physical activity is an important factor for muscle mass in both sexes.[30] Furthermore, previous studies have shown that 20% of men older than 60 years, 30% of men older than 70 years, and 50% of men older than 80 years have serum testosterone levels below the normal range.[31] Thus, it is also possible that the sex hormone-dependent changes in muscle mass are greater in men than in women. Therefore, age-dependent gender differences in the SMI might be influenced by daily activity or alterations in sex hormone levels.

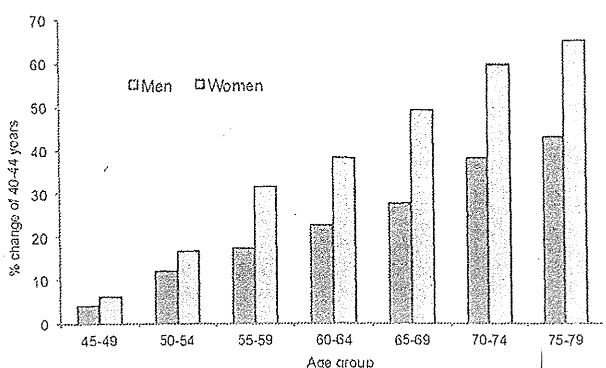

Figure 3 The percentage of change in the visceral fat area in each sex and each age group using 40–44 years-of-age as a reference.

The present data show that aging is associated with a progressive increase in visceral fat area in both sexes. From 40 to 79 years of age, the visceral fat area increased by 42.9% in men and by 65.3% in women. Furthermore, the SMI was negatively associated with the visceral fat area when adjusted for age and body weight in both sexes. The visceral adipose tissue produces many catabolic factors, such as TNF-α and IL-6.[22] Therefore, the age-dependent increases in both visceral adipose tissue and inflammatory cytokines might lead to a loss of skeletal muscle mass. Recently, sarcopenic obesity has been defined as both low muscle mass and high adipose tissue in older adults, and the health-related risk is higher in sarcopenic obesity than in sarcopenia.[32] The current data show that the age-dependent changes in body composition can accelerate sarcopenic obesity. These results suggest that it is very important to begin prevention of sarcopenia and sarcopenic obesity as early as possible.

According to our analysis of this cohort, we found that the 20th percentile of total SMI in men and women aged 65–79 years was 7.02 kg/m² and 5.61 kg/m², respectively. These values were slightly higher than those determined by the young adult mean in our database (men 6.75 kg/m²; women 5.07 kg/m²).[18] That these values were lower than the 20th percentile of total SMI

Table 3 Multiple regression analysis for the association with skeletal muscle mass index in both sexes

Independent variables	Men Adjusted R^2 value = 0.781** standard regression value	Women Adjusted R^2 value = 0.627** standard regression value
Visceral fat area (cm²)	–0.586**	–0.627**
Age (year)	0.212**	0.252**
Weight (kg)	1.180**	1.169**

**$P < 0.01$.