an important component of daily life. There are several well-established visual memory tests, such as the Benton Visual Retention Test[10] and the Rey–Osterrieth Complex Figure Test,[11] that can be used to assess nonverbal visual memory. However, these tests are not reflective of situations and activities encountered in daily life, are time consuming, and have complex scoring systems.

Deficits in working memory functions (e.g., attention and executive function) caused by AD are thought to contribute to a range of significant problems such as impairments in performing everyday tasks (e.g., keeping track of conversations, walking while talking, and packing a bag). Thus, the attentional function would appear to be important for the early detection of cognitive decline, as this function decreases with the progression of cognitive decline.[12]

We developed a new short-term visual memory and attention test called the Spot the Difference for Cognitive Decline (SDCD) test. The SDCD test is a brief and simple test that uses pictures of familiar-looking sceneries. Examinees are asked to find the differences between two scenery pictures. This test can be used in clinical or community-based settings with a large population. In a previous study, it was reported that poor visual memory predicts the onset/progression of dementia.[13] The spot-the-difference task has been used as a cognitive test in previous studies,[14–16] although its usefulness for detecting cognitive impairment had not been described. These spot-the-difference tasks have often been used in memory function training for older adults with dementia in many countries, including Japan. However, the effects of this training have not been examined empirically. We hypothesized that the SDCD score would be associated with cognitive function, and this test would be able to identify community-dwelling older adults with cognitive impairment. The purpose of the present study, therefore, was to examine the accuracy of the SDCD test for the identification of cognitive impairment in community-dwelling older adults.

2. Methods

2.1. Participants

Participants for this study were recruited through advertisements in the local newspaper. A total of 443 Japanese people aged ≥65 years (mean age, 73.1 ± 5.3 years) responded. We included only community-dwelling older adults who were able to perform their activities of daily living independently. A screening interview was conducted to exclude participants with severe cardiac, pulmonary, or musculoskeletal disorders, as well as those using medications that affect attention (e.g., psychoactive drugs or drugs prescribed for sleep). Written informed consent was obtained from each participant in accordance with the guidelines of the Kyoto University Graduate School of Medicine, Kyoto, Japan and the Declaration of Helsinki, 1975. The study protocol was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

2.2. SDCD test protocol

The SDCD test uses two scenery pictures (Figs. 1 and 2) on A4 size papers. Fig. 1 is called the "first picture" and Fig. 2 the "second picture." There are 10 differences between the two pictures: the shape of the chimney smoke, shape of the doorknob, height of the fountain, shape of the mountain (seen between the house and the fountain), number of fruits on the tree, direction that the dog on the right is facing, shape of the leftmost flower, shape of the child's mouth, presence of a bird versus a butterfly, and presence of the father's backpack. First, the examinees are instructed to memorize

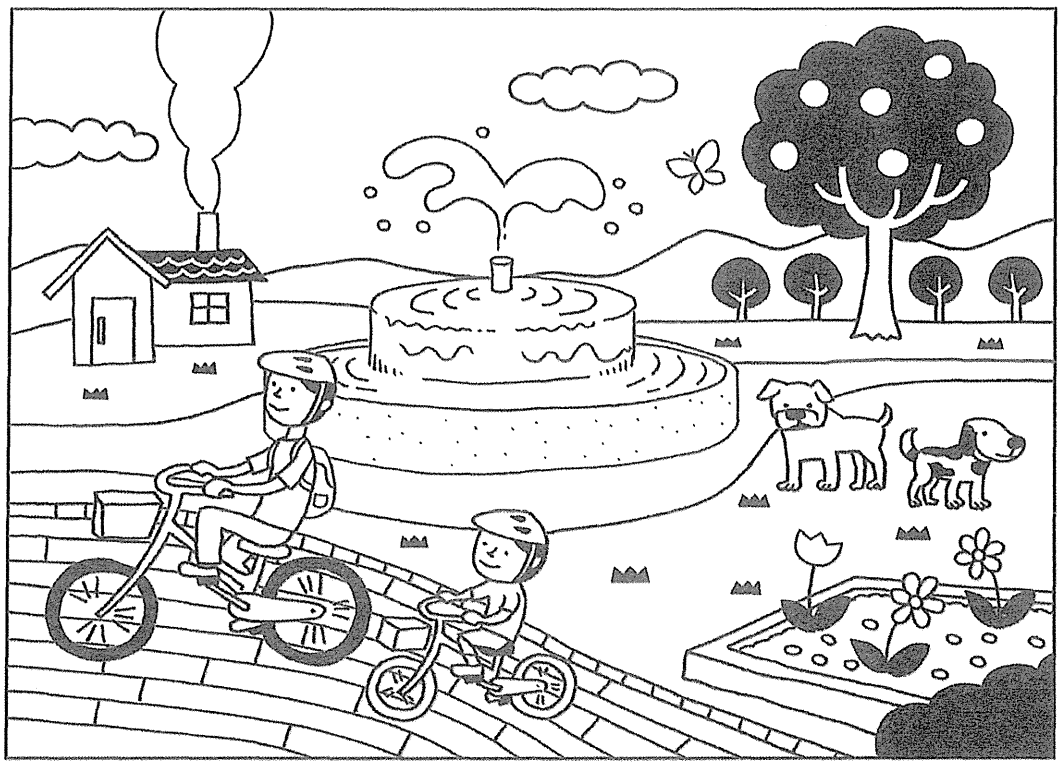

Fig. 1. First picture used in the Spot the Difference for Cognitive Decline test. The examinees were instructed to memorize the details of the picture, which was presented for 30 seconds.

Please cite this article in press as: Nishiguchi S, et al., Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline, Journal of Clinical Gerontology & Geriatrics (2014), http://dx.doi.org/10.1016/j.jcgg.2014.08.003

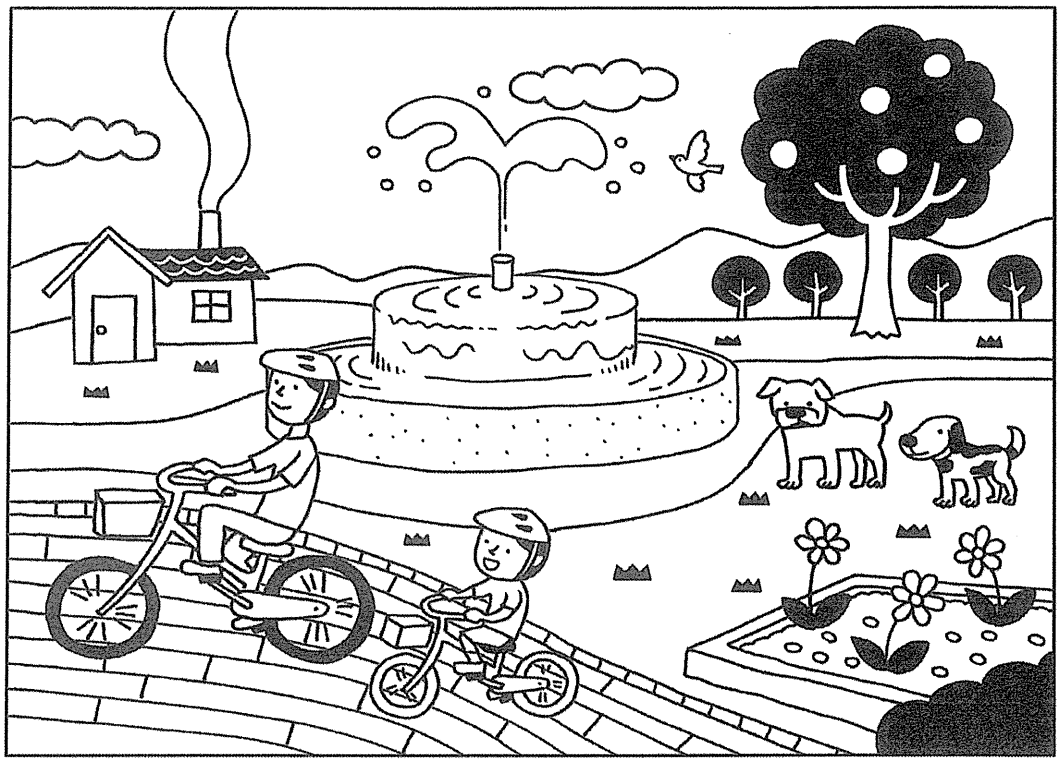

Fig. 2. Second picture in the Spot the Difference for Cognitive Decline test. This picture has 10 differences when compared with the first picture (Fig. 1). After studying the first picture for 30 seconds, the examinees were asked to find as many of the differences between the first and second pictures as they could within 1 minute.

the details of the first picture for 30 seconds. They are also told that there are "some" differences between the first and second pictures. The examiners do not inform the participants that there are 10 differences in total. After showing the first picture, the examiner takes the first picture away and shows the participants the second picture. The examinees are then asked to find the differences in the second picture, within 1 minute and without any hints. The number of the correct answers is then counted to determine the SDCD score. If the examinees' answers are close but not exactly correct (e.g., a flower type or increase in the fruit), these answers are marked as incorrect and not included in the SDCD score. In a sample of 21 participants, the SDCD had a high test–retest reliability [intertrial correlation coefficient (ICC) = 0.801; $p < 0.001$] between the two measurements with a 1-week interval.

2.3. Cognitive function

Participants' cognitive function was measured by two neuropsychological tests: the Mini-Mental State Examination (MMSE)[17] and the Scenery Picture Memory Test (SPMT).[18]

Global cognitive function was assessed using the MMSE, a standard test used in cognitive aging research for assessing mental status. Five areas of cognitive function—orientation, registration, attention and calculation, recall, and language—are tested. It has 11 questions in total and a maximum possible score of 30.

The SPMT is a simple memory test that assesses visual memory combined with verbal responses. This test uses a line drawing of a living room in a house on an A4-size paper, depicting 23 objects that are commonly observed in daily life. The examinee is instructed to look at the picture for 1 minute and remember the items. After this encoding period, participants are given a distractor task (a brief forward digit-span test). Participants are then asked to recall the objects in the picture without a time limit. Recall of the items usually takes approximately 2 minutes. The number of items recalled is the SPMT score. Higher scores indicate a better cognitive function.

2.4. Statistical analysis

We divided the participants into two groups (normal and cognitive impairment groups) based on the cutoff score of the MMSE (23/24). Differences between these two groups were statistically analyzed, using the unpaired t test for continuous variables and the χ^2 test for categorical variables. Differences between the SPMT and SDCD scores were examined using an analysis of variance. When a significant effect was found, the Tukey–Kramer *post hoc* test was used to examine the differences. In addition, the criterion-related validity was determined by evaluating the correlation between the SDCD score and the two neuropsychological tests using Spearman's rank correlation coefficient. Following this, we performed a multiple logistic regression analysis to determine whether the SDCD score was associated with cognitive impairment independently. For this analysis, the two groups (i.e., the normal group and the cognitive impairment group) were the dependent variables, and the SDCD score was the independent variable. We controlled age, gender, body mass index, medications, and the length of education. Furthermore, a receiver-operating characteristic (ROC) analysis was used to examine the power of the SDCD score and determine the optimal cutoff value of the SDCD score as a state variable. The area under the curve, sensitivity, and specificity of the SDCD score were calculated based on the ROC curve. The cutoff value for the SDCD score was determined based on the optimal sensitivity and specificity. Consequently, we performed a univariate logistic regression analysis to determine the correlation

Please cite this article in press as: Nishiguchi S, et al., Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline, Journal of Clinical Gerontology & Geriatrics (2014), http://dx.doi.org/10.1016/j.jcgg.2014.08.003

between the SDCD and the five subtests of the MMSE (orientation, registration, attention and calculation, recall, and language). For this analysis, the groups formed on the basis of the cutoff value of the SDCD were the dependent variables and each subtest of the MMSE was the independent variable.

Data were analyzed using SPSS Statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

3. Results

Of the 443 participants, 30 (6.77%) were identified as having cognitive impairment based on an MMSE cutoff score of 23/24. Demographic characteristics of the participants are shown in Table 1. The normal group had a higher SDCD score (2.21 ± 1.38) than the cognitive impairment group (0.77 ± 0.86; $p < 0.001$). The normal group also had a higher SPMT score than the cognitive impairment group ($p < 0.001$). The education level of the normal group was also higher than that of the cognitive impairment group ($p = 0.002$). There were no significant differences in age, gender, body mass index, or the use of medication between the two groups.

The participants were reclassified into five groups according to their SDCD scores; differences in the MMSE and SPMT scores between the groups are shown in Figs. 3 and 4. There were significant differences in the MMSE scores ($F = 15.7$, $p < 0.001$) as well as in the SPMT scores ($F = 22.6$, $p < 0.001$) between the five groups. Results of the *post hoc* tests are shown in Figs. 3 and 4. In addition, the SDCD scores were moderately and positively correlated with the MMSE ($r = 0.333$) and SPMT ($r = 0.402$) scores ($p < 0.001$). These analyses indicated that a higher SDCD score was associated with higher cognitive function. In the logistic regression analysis, the SDCD score was significantly associated with cognitive impairment after adjusting for age, gender, body mass index, medications, and the length of education (odds ratio: 0.388; 95% confidence interval: 0.257–0.584; $p < 0.001$).

The ROC curve for the SDCD scores used for the identification of cognitive impairment was based on the MMSE cutoff score (23/24). The area under the curve was comparatively high for the SDCD scores (0.798, $p < 0.001$), and the cutoff value of the SDCD score was 1/2 (with ≥1 being considered normal) with a 70.5% sensitivity and 80.0% specificity. A univariate logistic regression analysis showed

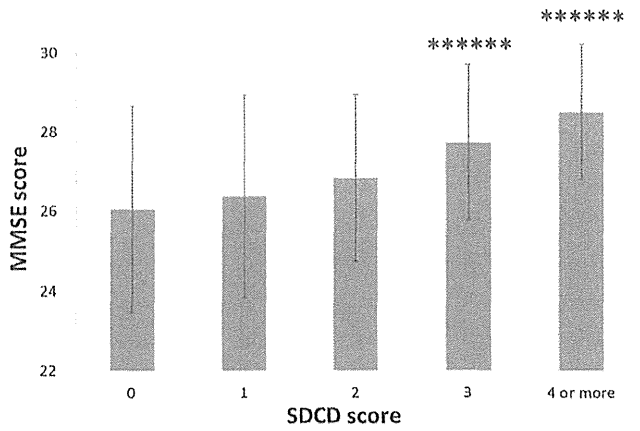

Fig. 3. Comparison of the MMSE scores between the groups formed based on the SDCD scores. There were significant differences in the MMSE scores across the five groups ($F = 15.7$, $p < 0.001$). * Significant difference from Group 0. ** Significant difference from Group 1. *** Significant difference from Group 2. MMSE = Mini-Mental State Examination; SDCD = Spot the Difference for Cognitive Decline.

that there were significant correlations between the SDCD scores and the four subtests of the MMSE ($p < 0.05$), except for the registration subtest (refer to Table 2).

4. Discussion

We examined a new type of short-term memory and attention test, the SDCD, which used a spot-the-difference task to identify cognitive impairment. In the present study, we showed that the SDCD test is a very quick and reliable screening tool for the identification of cognitive impairment in community-dwelling older adults.

The SDCD test is moderately and positively correlated with global cognitive and memory functions. The SDCD test includes a "memory" phase and a "recall and name the differences" phase. These phases require not only memory functions, but also other cognitive functions, such as attention. Some studies in the past have used similar spot-the-difference tasks as cognitive tests,[14,15] and only one previous study[16] has investigated brain activation in a test

Table 1
Characteristics of participants with and without cognitive impairment.[a]

	Normal ($n = 413$, MMSE ≥ 24, 27.4 ± 2.0)	Cognitive impairment ($n = 30$, MMSE < 24, 22.4 ± 1.1)	p
Age, y	72.9 ± 5.3	74.4 ± 5.3	0.160
Female	269 (65.3%)	20 (66.7%)	1.000
BMI, kg/m^2	22.7 ± 3.1	22.2 ± 2.8	0.384
Number of medications taken, n	2.53 ± 2.59	2.48 ± 2.46	0.237
Education			0.002**
<6 y	3 (0.7%)	0	
6–9 y	98 (23.7%)	17 (56.7%)	
10–12 y	212 (51.3%)	10 (33.3%)	
>12 y	100 (24.2%)	3 (10.0%)	
SDCD	2.21 ± 1.38	0.77 ± 0.86	<0.001**
SPMT	13.8 ± 3.5	10.1 ± 2.8	<0.001**

Data are presented as n (%) or mean ± SD.
* $p < 0.05$.
** $p < 0.01$.
BMI = body mass index; MMSE = Mini-Mental State Examination; SDCD = spot the difference for cognitive decline; SPMT = Scenery Picture Memory Test.
[a] Normal and cognitive impairment groups were defined according to the MMSE cutoff score of 23/24.

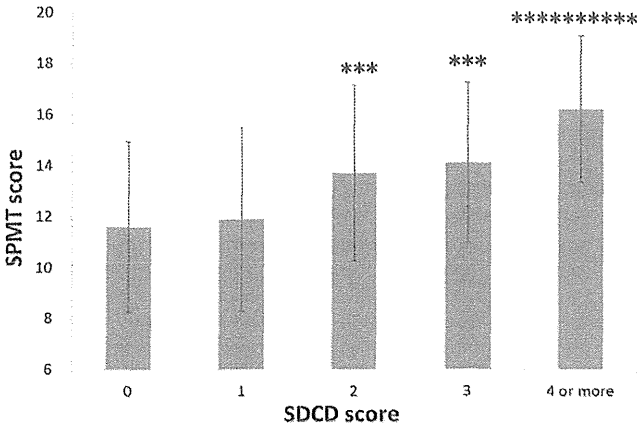

Figure 4. Comparison of the SPMT results between the groups formed based on the SDCD scores. There were significant differences in the MMSE scores across the groups ($F = 22.6$, $p < 0.001$). * Significant difference from Group 0. ** Significant difference from Group 1. *** Significant difference from Group 2. **** Significant difference from Group 3. MMSE = Mini-Mental State Examination; SDCD = Spot the Difference for Cognitive Decline; SPMT = Scenery Picture Memory Test.

Please cite this article in press as: Nishiguchi S, et al., Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline, Journal of Clinical Gerontology & Geriatrics (2014), http://dx.doi.org/10.1016/j.jcgg.2014.08.003

Table 2
Correlation between SDCD score and subtests of MMSE.[a]

Subtests (total score)	Subtest score	SDCD score < 2 (n = 146) n (%)	OR (95% CI)
Orientation (10)	≤8	20 (13.7)	Reference
	9	30 (20.5)	0.26 (0.11–0.62)**
	10	96 (65.8)	0.21 (0.10–0.46)**
Registration (3)	≤2	4 (2.7)	Reference
	3	142 (97.3)	0.61 (0.16–2.30)
Attention and calculation (5)	≤2	69 (47.3)	Reference
	3	10 (6.8)	1.10 (0.47–2.59)
	4	18 (12.3)	1.19 (0.61–2.34)
	5	49 (33.6)	0.57 (0.36–0.88)*
Recall (3)	≤1	22 (15.1)	Reference
	2	51 (34.9)	0.21 (0.09–0.50)**
	3	73 (50.0)	0.13 (0.06–0.31)**
Language (9)	≤7	14 (9.6)	Reference
	8	38 (26.0)	0.18 (0.06–0.59)**
	9	94 (64.4)	0.12 (0.04–0.36)**

* $p < 0.05$.
** $p < 0.01$.
CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio; SDCD = spot the difference for cognitive decline.
[a] For each univariate logistic regression analysis, SDCD scores <2 or ≥2 were the dependent variables and each subtest of the MMSE was the independent variable.

using a spot-the-difference task. Although the abovementioned test did not include a memory phase (unlike that included in the SDCD test), the results indicated that the brain areas related to visual information and attention was activated while carrying out the task. Our results indicated that the SDCD was associated with most of the subtests of the MMSE. Thus, the SDCD test appears to be associated not only with attention and memory, but also with global cognitive function. We need to minutely assess and investigate other cognitive functions (e.g., executive function and processing speed) and their association with the SDCD test in future studies.

The ROC curve for the SDCD score indicated that the SDCD test identified cognitive impairment with a high degree of accuracy. Previous studies have reported that some picture-based memory tests can reliably detect dementia.[18–20] These studies support the results of the present study. Moreover, the SDCD test is able to detect dementia in less time compared to other tests studied previously. Picture-based memory tests have some advantages over verbal memory tests. First, pictures are remembered better than words, a phenomenon known as the "picture superiority effect."[21] Previous studies showed that superiority of memory for pictorial material was often applied as a mnemonic aid for older adults.[22,23]_ENREF_17. Second, picture-based memory tests are not limited by the patient's level of education. Some verbal memory tests cannot be used for a population that has a low level of education.[19] Most of the verbal-based screening measures have not been validated in people with low education levels or illiterate individuals,[24,25] and it has been shown in previous studies that a low level of education can result in cognitively unimpaired people screening positive for dementia.[24] Furthermore, the SDCD test takes only approximately 2 minutes to assess short-term memory and attention functioning, in addition to its abovementioned merits. In the present study, the participants took approximately 10 minutes and approximately 5 minutes to complete the MMSE and the SPMT, respectively. The SDCD test appears as an easy game for patients, because of the simplicity of the differences, but it is actually quite a difficult cognitive task. It is possible that this characteristic makes the SDCD test fun for the participants to complete, thereby making its widespread use possible. Thus, we believe that the SDCD test can be used to identify cognitive impairment in older adults in a clinical or community-based setting.

The present study has several limitations. First, although we assessed global cognitive and memory functions with the MMSE and the SPMT, other cognitive functions, such as executive functions and processing speed, were not assessed in this study. We need to assess these cognitive functions and investigate their association with the SDCD test in future studies. Second, participants in the present study were community-dwelling older adults who had not received a diagnosis of dementia or MCI, and we did not confirm the test–retest reliability for older adults with dementia or MCI. In the future, we need to include older adults diagnosed with dementia to ascertain whether the SDCD test can discriminate between normal cognitive function and MCI in older adults.

5. Conclusion

We developed a new type of short-term memory and attention test that uses a spot-the-difference task for the identification of cognitive impairment. The present study indicates that the SDCD test can be an effective clinical tool for the identification of cognitive impairment in older adults.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to thank the volunteers for participating in this study. The authors acknowledge Masahiko Yonemitsu for drawing the pictures used in this study.

References

1. Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, et al. Vascular dementia and Alzheimer's disease: is there a difference? A comparison of symptoms by disease duration. *J Neuropsychiatry Clin Neurosci* 2000;**12**:305–15.
2. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;**366**:2112–7.
3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007;**3**:186–91.
4. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013;**28**:1109–24.
5. Amieva H, Letenneur L, Dartigues JF, Rouch-Leroyer I, Sourgen C, D'Alchée-Birée F, et al. Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement Geriatr Cogn Disord* 2004;**18**:87–93.
6. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, et al. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006;**63**:916–24.
7. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;**56**:303–8.
8. Baddeley AD. *Working memory*. Oxford: Oxford University Press; 1986.
9. Mayes AR. Learning and memory disorders and their assessment. *Neuropsychologia* 1986;**24**:25–39.
10. Benton AL. *Revised visual retention test*. 4th ed. New York: Psychological Corporation; 1974.
11. Lezak MD. *Neuropsychological assessment*. 3rd ed. New York: Oxford University Press; 1995.
12. Pettersson AF, Olsson E, Wahlund LO. Effect of divided attention on gait in subjects with and without cognitive impairment. *J Geriatr Psychiatry Neurol* 2007;**20**:58–62.
13. Kawas CH, Corrada MM, Brookmeyer R, Morrison A, Resnick SM, Zonderman AB, et al. Visual memory predicts Alzheimer's disease more than a decade before diagnosis. *Neurology* 2003;**60**:1089–93.
14. Dewar M, Alber J, Butler C, Cowan N, Della Sala S. Brief wakeful resting boosts new memories over the long term. *Psychol Sci* 2012;**23**:955–60.
15. Kreplin U, Fairclough SH. Activation of the rostromedial prefrontal cortex during the experience of positive emotion in the context of esthetic experience. An fNIRS study. *Front Hum Neurosci* 2013;**7**:879.

Please cite this article in press as: Nishiguchi S, et al., Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline, Journal of Clinical Gerontology & Geriatrics (2014), http://dx.doi.org/10.1016/j.jcgg.2014.08.003

16. Fukuba E, Kitagaki H, Wada A, Uchida K, Hara S, Hayashi T, et al. Brain activation during the spot the differences game. *Magn Reson Med Sci* 2009;8: 23–32.
17. Folstein MF, Folstein SE, McHugh PR. Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.
18. Takechi H, Dodge HH. Scenery picture memory test: a new type of quick and effective screening test to detect early stage Alzheimer's disease patients. *Geriatr Gerontol Int* 2010;**10**:183–90.
19. Carnero-Pardo C, Espejo-Martinez B, Lopez-Alcalde S, Espinosa-Garcia M, Saez-Zea C, Vilchez-Carrillo R, et al. Effectiveness and costs of phototest in dementia and cognitive impairment screening. *BMC Neurol* 2011;**11**:92.
20. Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 2002;**73**:126–33.
21. Park DC, Puglisi JT, Sovacool M. Memory for pictures, words, and spatial location in older adults: evidence for pictorial superiority. *J Gerontol* 1983;**38**: 582–8.
22. Cavanaugh JC, Grady JG, Perlmutter M. Forgetting and use of memory aids in 20 to 70 year olds everyday life. *Int J Aging Hum Dev* 1983;**17**:113–22.
23. McDowd J, Botwinick J. Rote and gist memory in relation to type of information, sensory mode, and age. *J Genet Psychol* 1984;**145**:167–78.
24. Prince M. Methodological issues for population-based research into dementia in developing countries. A position paper from the 10/66 Dementia Research Group. *Int J Geriatr Psychiatry* 2000;**15**:21–30.
25. Chandra V, Ganguli M, Ratcliff G, Pandav R, Sharma S, Belle S, et al. Practical issues in cognitive screening of elderly illiterate populations in developing countries. The Indo-US Cross-National Dementia Epidemiology Study. *Aging (Milano)* 1998;**10**:349–57.

Please cite this article in press as: Nishiguchi S, et al., Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline, Journal of Clinical Gerontology & Geriatrics (2014), http://dx.doi.org/10.1016/j.jcgg.2014.08.003

Journal of Clinical Gerontology & Geriatrics 5 (2014) 18–22

Contents lists available at ScienceDirect

Journal of Clinical Gerontology & Geriatrics

journal homepage: www.e-jcgg.com

Original article

Effect of physical activity at midlife on skeletal muscle mass in old age in community-dwelling older women: A cross-sectional study

Shu Nishiguchi, MSc [a,b,*], Minoru Yamada, PhD [a], Yuu Kajiwara, MSc [c], Takuya Sonoda, MSc [d], Kazuya Yoshimura, MSc [e], Hiroki Kayama [a], Takanori Tanigawa [a], Taiki Yukutake [a], Tomoki Aoyama, MD PhD [a]

[a] Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[b] Japan Society for the Promotion of Science, Tokyo, Japan
[c] Japanese Red Cross, Fukuoka Hospital, Fukuoka, Japan
[d] Department of Health and Welfare, Health Affairs Policy Division, Kyoto Prefecture, Kyoto, Japan
[e] Possible Medical Science Co. Ltd, Osaka, Japan

ARTICLE INFO

Article history:
Received 8 May 2013
Received in revised form
24 August 2013
Accepted 10 September 2013
Available online 12 December 2013

Keywords:
Community-dwelling older adults
Midlife physical activity
Physical performance
Skeletal muscle mass

ABSTRACT

Background/Purpose: Measures to prevent the development of muscle mass decline should be initiated from midlife. However, the impact of physical activity at midlife on muscle mass in old age remains uncertain. The aim of this cross-sectional study was to determine whether physical activity at midlife influences muscle mass and physical performance in old age.
Methods: A total of 272 Japanese women aged 65 years and older were enrolled in the study. Information about physical activity levels at midlife and in old age were collected using a retrospective questionnaire. We calculated the skeletal muscle mass index in old age and recorded the participants' walking speed and hand grip strength in old age. We then classified the participants into four groups according to their physical activity levels at midlife and in old age and conducted multiple linear regression analysis to determine whether the physical activity levels at midlife and in old age were associated with skeletal muscle mass index and physical performance in old age.
Results: The participants in the groups that were physically inactive at midlife had a significantly lower skeletal muscle mass index in old age than those who were physically active at midlife ($p < 0.01$). Participants in the groups that were physically inactive in old age also had significantly slower walking speeds at old age than those who were physically active ($p < 0.01$). These associations remained significant after adjustment for age and body mass index.
Conclusion: Physical activity at midlife may be associated with a higher muscle mass in old age and physical activity in old age may be associated with higher walking speeds in old age.

1. Introduction

Muscle mass declines at approximately 1–2% per year after the age of 50 years.[1] Longitudinal studies have shown a clear decline in muscle mass, strength, and power beginning at approximately 35 years of age.[2] The age-related loss of skeletal muscle mass induces an increased risk of falls and fractures, physical disability, mobility disorders, and mortality.[3,4] To promote healthy aging, it is therefore important to develop ways of preventing muscle mass decline.

The beneficial effect of physical activity in preventing adverse health outcomes is widely endorsed. There is growing evidence that older adults who engage in physical activity are more likely to experience better physical function and have a longer active life expectancy than sedentary older adults.[5–7] Physical activity also has a positive impact on preventing muscle mass decline.[8] Physical activity is one of the most important modifiable factors associated with the risk of chronic morbidity and high mortality in the general population.

Recent studies have shown an association between physical activity at midlife and functional and health status in old age. The level of physical activity at midlife was related to better physical

* Corresponding author. Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: nishiguchi.shu.82s@st.kyoto-u.ac.jp (S. Nishiguchi).

2210-8335/$ – see front matter
http://dx.doi.org/10.1016/j.jcgg.2013.09.002

health and functioning and lower mortality risk.[9–12] Previous studies have also investigated the effects of midlife physical activity on different components of mobility[13–15] and the risk of institutionalization.[16] The benefits of physical activity at midlife appear to result from the maintenance of muscle strength,[13] cognitive function,[17] and other functions in old age. Furthermore, muscle mass in old age also appears to benefit from physical activity at midlife. Although it is important to prevent the development of muscle mass decline in old age and midlife, the effect of physical activity at midlife on muscle mass in old age remains uncertain.

The aim of this cross-sectional observational study was to determine whether physical activity at midlife was associated with muscle mass and physical performance in old age. We hypothesized that physical activity at midlife might prevent the decrease in muscle mass in old age.

2. Methods

2.1. Participants

Participants were recruited through a local press release requesting healthy community-dwelling volunteers. A total of 272 Japanese women aged 65 years and older (mean ± SD age 73.6 ± 5.5 years) living in the city of Kyoto enrolled in the study. Participants were interviewed and excluded if they met any of the following criteria: severe cognitive impairment; severe cardiac, pulmonary, or musculoskeletal disorders; and comorbidities associated with a greater risk of falls, such as Parkinson's disease and stroke. Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine.

2.2. Assessment of physical activity

A questionnaire[13] was used to collect retrospective information about physical activity levels during midlife and old age. In the present study, we defined midlife as the period between the ages of 40 and 65 years. The questions were: 'How much physical activity did you have during midlife?' and 'How much physical activity do you have these days?' Similar to the approach used in the previous study, there were three response categories: no regular physical activity (0); regular physical activity (1); and regular sports (2). Regular physical activity/sports were defined based on a previous study[18] as activities/sports engaged in at a frequency of more than once a week. We defined light walking or moderate exercise (equivalent to less than approximately 4.0 metabolic equivalents) as physical activity and moderate or vigorous physical activities (equivalent to more than approximately 4.0 metabolic equivalents) as sports; these definitions were based on the International Physical Activity Questionnaire.[19] For each of the midlife and old age physical activity levels, Category 0 was defined as 'inactive' and Categories 1 and 2 (combined) were defined as 'active' in the analyses.

2.3. Skeletal muscle mass index

A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co. Ltd, Seoul, Korea) was used to perform bioelectrical impedance analysis.[20] This system also uses an electrical current at multiple frequencies (5, 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water. The participants stood on two metallic electrodes and held metallic grip electrodes. Using segmental body composition, muscle mass was determined and used for further analysis. The skeletal muscle mass index (SMI) was calculated by dividing the muscle mass by height squared in meters (kg/m^2). This index has been used in several epidemiological studies.[4]

2.4. Measurements of physical performance

The following two measurements for the assessment of mobility and physical strength were made for each participant in the presence of experienced physiotherapists: (1) 10 m or 4 m walking test[21]; and (2) the hand grip strength (HGS) test.[22]

In the walking test, participants were asked to walk 10 m or 4 m at their normal walking speed. Walking time was calculated using a stopwatch to record the time taken to cover the central 10 m or 4 m of the walkway (2 m at the start and finish were used for acceleration and deceleration). Using the better walking time of two trials, the participants' walking speed (m/s) was calculated to obtain values for analyses.

In the HGS test, participants used a hand-held dynamometer with the arm held to the side of the body. The participants squeezed the dynamometer with maximum isometric effort. No other body movement was allowed. The HGS score was defined as the better performance of two trials.

2.5. Assessment of sarcopenia

For the present study we adopted the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP).[23] The EWGSOP recommended defining sarcopenia as the presence of both low muscle function (slow walking speed equal to or less than 0.8 m/s; or low HGS equal to or less than 20 kg) and low muscle mass. For assessing low appendicular muscle mass, we divided the SMIs of the participants into quartiles and defined the first quartile as the cutoff for low appendicular muscle mass (SMI 5.55 kg/m^2).

2.6. Statistical analysis

Before analysis, we classified the participants into four groups according to physical activity levels in midlife and old age: Group I, physically inactive at both midlife and old age; Group II, physically active at midlife, but not at old age; Group III, physically inactive at midlife, but active at old age; and Group IV, physically active at both midlife and old age (Fig. 1).

Differences in the demographic variables among the four groups were examined using analysis of variance (ANOVA). When a significant effect was found, differences were determined with the Tukey–Kramer's post-hoc test. In addition, we entered four

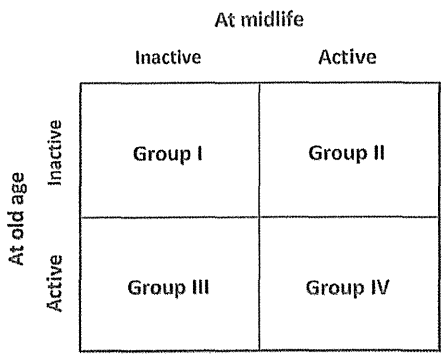

Fig. 1. Classification of participants in the four groups according to the midlife and old age physical activity levels: (Group I = physically inactive at both midlife and old age; Group II = physically active at midlife, but not at old age; Group III = physically inactive at midlife, but active at old age; Group IV = physically active at both midlife and old age).

dummy-coded groups, with Group IV as the reference group in models with independent variables; unadjusted and adjusted multiple linear regression analysis were conducted to determine whether physical activity levels in midlife and old age were associated with SMI and physical performance in old age. In the adjusted analyses, age and body mass index were entered as control variables.

Statistical analyses were carried out using the SPSS version 20.0 software package (SPSS, Chicago, IL, USA), with $p < 0.05$ accepted as significant.

3. Results

Table 1 shows the characteristics of the study population. The number (%) of participants in Groups I, II, III, and IV was 57 (21.0), 25 (9.2), 84 (30.9), and 106 (38.9), respectively. Participants in Group IV (SMI 6.35 ± 0.87 kg/m^2, walking speed 1.41 ± 0.26 m/s) (physically active at both midlife and old age) had significantly higher SMIs than those in Groups I (5.85 ± 0.92 kg/m^2, $p < 0.01$) and III (6.00 ± 1.08 kg/m^2, $p < 0.05$) (physically inactive at midlife) and faster walking speeds than those in Groups I (1.30 ± 0.25 m/s, $p < 0.05$) and II (1.27 ± 0.27 m/s, $p < 0.05$) (physically inactive at old age) (Table 1). There was no other significant difference among the four groups. A total of 38 (14.0%) participants had sarcopenia: 10 of 57 (17.5%), 3 of 25 (12.0%), 16 of 84 (16.7%), and 9 of 106 (8.5%) participants in Groups I, II, III, and IV, respectively.

In the unadjusted multiple linear regression analysis with Group IV as the reference, older adults within Groups I and III showed a significantly lower SMI ($p < 0.01$) and older adults in Groups I and II showed a significantly slower walking speed ($p < 0.01$) (Table 2). Thus participants who were physically inactive at midlife (Groups I and III) had a significantly lower SMI and participants who were physically inactive in old age (Groups I and II) had a significantly slower walking speed. These associations remained significant after adjustment for age and body mass index ($p < 0.05$) (Table 2). However, no group showed significant associations with HGS in the unadjusted and adjusted analysis.

4. Discussion

This is the first cross-sectional study to attempt to clarify the relationship between physical activity levels at midlife and skeletal muscle mass in old age. This study showed that older adults who were physically active at midlife might have a higher skeletal muscle mass in old age than those that were not physically active at midlife. A previous study reported that the rate of lean mass loss was about three times less than the rate of decline in leg strength.[24] Our results for the relationship between physical activity at midlife and skeletal muscle mass appear to be consistent with the previous study. In addition, the previous study reported that the exercise-induced increase in muscle mass was typically less than that expected for the concomitant increase in strength.[25] Therefore physical activity at midlife may be important and beneficial for preventing muscle mass decline in old age.

Muscle mass is controlled by catabolic and anabolic factors. A previous cohort study showed that regular physical activity was associated with low levels of catabolic markers such as interleukin-6.[26] In addition to its effects on catabolic factors, an increase in physical activity was associated with a high level of insulin-like growth factor-1, one of the most important factors linked to intensifying muscle mass in premenopausal women.[27] These results suggest that continuous regular physical activity prevents catabolic effects and promotes anabolic effects. However, there are no longitudinal reports that have reported an association between these factors and muscle mass from midlife to old age. On the basis of our preliminary results regarding the relationship between physical activity at midlife and skeletal muscle mass, further studies are required to confirm the benefits of physical activity from midlife for the prevention of muscle mass decline.

Our study also showed that adults physically active in old age might have a faster walking speed than those who were not physically active in old age. In addition, physical activity at midlife and in old age was not associated with grip strength in old age. Hughes et al[28] reported longitudinal changes in muscle mass, physical activity, and muscle strength and found that muscle mass decline explained only 5% of the decline in strength. Further, the changes in strength were no different between people of middle and old age who reported taking regular exercise in the past compared with those who had not exercised regularly in the past. These are the reasons why the relationship between physical activity and physical performance has different trends from that between physical activity and skeletal muscle mass. Furthermore, we observed significantly lower SMIs in Group III participants and slower walking speeds in Group II participants compared with Group IV, although there was no difference in muscle mass and physical performance between Groups II and III. These results seem to indicate that physical activity at midlife and old age may affect skeletal muscle mass and physical performance in old age. However, a previous longitudinal prospective study of the association between physical activity at midlife and walking speed[29] reported

Table 1
Demographic differences according to physical activity levels at midlife and old age.

	Total (n = 272)	Physical activity levels at midlife and old age					
		Group I (n = 57)	Group II (n = 25)	Group III (n = 84)	Group IV (n = 106)	p	*Post-hoc*
Age (y), mean ± SD	73.6 ± 5.5	74.1 ± 6.2	75.0 ± 5.2	74.0 ± 5.5	72.7 ± 4.9	0.146	—
Height (cm), mean ± SD	151.2 ± 5.4	151.1 ± 5.2	153.9 ± 5.4	150.9 ± 4.8	150.7 ± 5.9	0.088	—
Weight (kg), mean ± SD	49.7 ± 7.5	48.8 ± 6.9	51.7 ± 8.4	49.5 ± 7.6	49.9 ± 7.3	0.459	—
BMI (kg/m^2), mean ± SD	21.7 ± 2.9	21.4 ± 2.7	21.7 ± 2.8	21.7 ± 3.0	22.0 ± 2.8	0.653	—
SMI (kg/m^2), mean ± SD	6.11 ± 0.92	5.85 ± 0.92	6.14 ± 0.82	6.00 ± 1.08	6.35 ± 0.87	0.004	*,**
Walking speed (m/s), mean ± SD	1.35 ± 0.25	1.30 ± 0.25	1.27 ± 0.27	1.34 ± 0.23	1.41 ± 0.26	0.010	†,‡
HGS (kg), mean ± SD	22.1 ± 6.7	21.3 ± 3.5	21.4 ± 7.5	22.2 ± 10.2	22.5 ± 6.8	0.672	—
Sarcopenia, n (%)	38 (14.0)	10 (17.5)	3 (12.0)	16 (16.7)	9 (8.5)		

Group I = physically inactive at both midlife and old age; Group II = physically active at midlife, but not at old age; Group III = physically inactive at midlife, but active at old age; Group IV = physically active at both midlife and old age; BMI = body mass index; HGS = hand grip strength; SMI = skeletal muscle mass index.
*Significant difference between Group IV and Group I ($p < 0.01$).
**Significant difference between Group IV and Group III ($p < 0.05$).
†Significant difference between Group IV and Group I ($p < 0.05$).
‡Significant difference between Group IV and Group II ($p < 0.05$).

Table 2
Association of physical activity status with skeletal muscle index and physical performance in old age.

Dependent variable	Unadjusted model			Adjusted model		
	β	95% CI	Adjusted R^2 value	β	95% CI	Adjusted R^2 value
SMI			0.05			0.35
Group I	−0.22	−0.80 to −0.21**		−0.16	−0.61 to −0.11**	
Group II	−0.06	−0.62 to 0.21		−0.03	−0.48 to 0.24	
Group III	−0.18	−0.61 to −0.09**		−0.15	−0.50 to −0.07**	
Group IV	Reference			Reference		
Walking speed			0.05			0.17
Group I	−0.18	−0.19 to −0.03**		−0.17	−0.19 to −0.03**	
Group II	−0.18	−0.28 to −0.05**		−0.14	−0.24 to −0.02*	
Group III	−0.12	−0.14 to 0.01		−0.09	−0.12 to 0.02	
Group IV	Reference			Reference		
HGS			0.01			0.07
Group I	−0.08	−3.47 to 0.93		−0.06	−3.16 to 1.30	
Group II	−0.06	−4.51 to 1.66		−0.03	−3.93 to 2.30	
Group III	−0.02	−2.23 to 1.69		−0.01	−1.84 to 2.05	
Group IV	Reference			Reference		

Note: In the adjusted analysis, age and BMI were entered as control variables. Group I = physically inactive at both midlife and old age; Group II = physically active at midlife, but not at old age; Group III = physically inactive at midlife, but active at old age; Group IV = physically active at both midlife and old age; β = standard regression coefficient; CI = confidence interval; HGS = hand grip strength; SMI = skeletal muscle mass index.
*$p < 0.05$.
**$p < 0.01$.

results which were different from the present study. This may in part be because: (1) our assessment of physical activity was retrospective; (2) our questionnaire was not a particularly detailed assessment of physical activity as it did not contain items addressing the continuance and intensity of physical activity; and (3) the present study was cross-sectional. These may be the main reasons why our results differ from previous studies. In future studies, details regarding the level of physical activity at midlife and in old age must be collected to better understand how physical activity at midlife affects physical performance.

Many research groups have recently defined sarcopenia as the coexistence of low muscle mass and low physical performance.[23,30,31] The evidence-based clinical effect of physical activity on the prevention of sarcopenia has also been reported from multiple points of view.[8] The present study showed the relationship between physical activity at midlife and skeletal muscle mass as well as between physical activity in old age and physical performance, and suggested that continued physical activity from midlife to old age might be one of the important factors for the prevention of sarcopenia in old age. The benefits of constant physical activity for various health improvements are well known. Additional studies are required to determine the benefits of physical activity over the life course, not only in terms of various health improvements, but also for the prevention of sarcopenia.

There were several limitations to the present study. Firstly, this study was cross-sectional and we included no information on the effect of continuous regular physical activity from midlife to old age in the questionnaire. A longitudinal prospective study is therefore needed to confirm these results and extend the present study. Secondly, our assessment of physical activity at midlife and old age was conducted using a very simple questionnaire and was based on the participants' ability to recall information. Thirdly, the findings in the present study should be considered as preliminary due to the relatively small sample size, which may introduce some error of inference, reduce the power of the analysis, and limit generalization. Finally, we did not collect any information about comorbidity or current treatment with drugs for our participants.

In conclusion, the results of our study suggest that physical activity at midlife may be associated with high muscle mass in old age and that physical activity in old age may be associated with a fast walking speed in old age. The present study seems to be a fundamental study to determine the benefits of physical activity over the life course for the prevention of sarcopenia.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

We thank the students of Human Health Sciences at Kyoto University for their help with data collection.

References

1. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *J Cachexia Sarcopenia Muscle* 2010;1:129–33.
2. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* 2000;88:1321–6.
3. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging* 2008;12:433–50.
4. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol* 2004;159:413–21.
5. Keysor JJ. Does late-life physical activity or exercise prevent or minimize disablement? A critical review of the scientific evidence. *Am J Prev Med* 2003;25:129–36.
6. Leveille SG, Guralnik JM, Ferrucci L, Langlois JA. Aging successfully until death in old age: opportunities for increasing active life expectancy. *Am J Epidemiol* 1999;149:654–64.
7. Ferrucci L, Izmirlian G, Leveille S, Phillips CL, Corti MC, Brock DB, et al. Smoking, physical activity, and active life expectancy. *Am J Epidemiol* 1999;149:645–53.
8. Pillard F, Laoudj-Chenivesse D, Carnac G, Mercier J, Rami J, Riviere D, et al. Physical activity and sarcopenia. *Clin Geriatr Med* 2011;27:449–70.
9. Balboa-Castillo T, Guallar-Castillon P, Leon-Munoz LM, Graciani A, Lopez-Garcia E, Rodriguez-Artalejo F. Physical activity and mortality related to obesity and functional status in older adults in Spain. *Am J Prev Med* 2011;40:39–46.

10. Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. Physical activity at midlife in relation to successful survival in women at age 70 years or older. *Arch Intern Med* 2010;**170**:194–201.
11. Bäckmand HM, Kaprio J, Kujala UM, Sarna S. Physical activity, mood and the functioning of daily living. A longitudinal study among former elite athletes and referents in middle and old age. *Arch Gerontol Geriatr* 2009;**48**:1–9.
12. Willis BL, Gao A, Leonard D, Defina LF, Berry JD. Midlife fitness and the development of chronic conditions in later life. *Arch Intern Med* 2012;**172**: 1333–40.
13. Tikkanen P, Nykänen I, Lönnroos E, Sipilä S, Sulkava R, Hartikainen S. Physical activity at age of 20–64 years and mobility and muscle strength in old age: a community-based study. *J Gerontol A Biol Sci Med Sci* 2012;**67**:905–10.
14. Patel KV, Coppin AK, Manini TM, Lauretani F, Bandinelli S, Ferrucci L, et al. Midlife physical activity and mobility in older age: The InCHIANTI study. *Am J Prev Med* 2006;**31**:217–24.
15. Willcox BJ, He Q, Chen R, Yano K, Masaki KH, Grove JS, et al. Midlife risk factors and healthy survival in men. *JAMA* 2006;**296**:2343–50.
16. von Bonsdorff MB, Rantanen T, Leinonen R, Kujala UM, Törmäkangas T, Mänty M, et al. Physical activity history and end-of-life hospital and long-term care. *J Gerontol A Biol Sci Med Sci* 2009;**64**:778–84.
17. Middleton LE, Barnes DE, Lui LY, Yaffe K. Physical activity over the life course and its association with cognitive performance and impairment in old age. *J Am Geriatr Soc* 2010;**58**:1322–6.
18. Abe T, Kawakami Y, Bemben MG, Fukunaga T. Comparison of age-related, site-specific muscle loss between young and old active and inactive Japanese women. *J Geriatr Phys Ther* 2011;**34**:168–73.
19. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;**35**:1381–95.
20. Gibson AL, Holmes JC, Desautels RL, Edmonds LB, Nuudi L. Ability of new octapolar bioimpedance spectroscopy analyzers to predict 4-component-model percentage body fat in Hispanic, black, and white adults. *Am J Clin Nutr* 2008;**87**:332–8.
21. Lopopolo RB, Greco M, Sullivan D, Craik RL, Mangione KK. Effect of therapeutic exercise on gait speed in community-dwelling elderly people: a meta-analysis. *Phys Ther* 2006;**86**:520–40.
22. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;**40**:423–9.
23. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;**39**: 412–23.
24. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sc* 2006;**61**: 1059–64.
25. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol* 1988;**64**:1038–44.
26. Hamer M, Sabia S, Batty GD, Shipley MJ, Tabák AG, Singh-Manoux A, et al. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. *Circulation* 2012;**126**: 928–33.
27. Ardawi MS, Rouzi AA, Qari MH. Physical activity in relation to serum sclerostin, insulin-like growth factor-1, and bone turnover markers in healthy premenopausal women: a cross-sectional and a longitudinal study. *J Clin Endocrinol Metab* 2012;**97**:3691–9.
28. Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, et al. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. *J Gerontol A Biol Sci Med Sci* 2001;**56**: B209–17.
29. Brach JS, FitzGerald S, Newman AB, Kelsey S, Kuller L, VanSwearingen JM, et al. Physical activity and functional status in community-dwelling older women: a 14-year prospective study. *Arch Intern Med* 2003;**163**:2565–71.
30. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011;**12**:403–9.
31. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. *J Am Med Dir Assoc* 2011;**12**:249–56.

JAMDA 16 (2015) 120–124

JAMDA

journal homepage: www.jamda.com

Original Study

Differential Association of Frailty With Cognitive Decline and Sarcopenia in Community-Dwelling Older Adults

Shu Nishiguchi RPT, MSc[a,b,*], Minoru Yamada RPT, PhD[c], Naoto Fukutani RPT, MSc[a], Daiki Adachi RPT[a], Yuto Tashiro RPT[a], Takayuki Hotta RPT[a], Saori Morino RPT[a], Hidehiko Shirooka RPT[a], Yuma Nozaki RPT[a], Hinako Hirata RPT[a], Moe Yamaguchi RPT[a], Hidenori Arai MD, PhD[a], Tadao Tsuboyama MD, PhD[a], Tomoki Aoyama MD, PhD[a]

[a] *Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[b] *Japan Society for the Promotion of Science, Tokyo, Japan*
[c] *Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tokyo, Japan*

Keywords:
Frailty
cognitive decline
sarcopenia
community-dwelling older adults

A B S T R A C T

Objectives: Frailty in older adults is a serious problem because of various adverse health outcomes in many countries with aging populations, such as Japan. The purpose of this study was to determine whether frailty and pre-frailty are associated with cognitive decline and sarcopenia in community-dwelling older adults.
Design: This is a cross-sectional study.
Setting: Japan.
Participants: The participants were 273 Japanese community-dwelling older women aged 65 years and older.
Measurements: We used the frailty criteria developed by the Cardiovascular Health Study to define physical frailty. We divided the cohort into nonfrail, prefrail, and frail according to frailty scores. Cognitive decline and memory decline were defined by using the Mini-Mental State Examination and Scenery Picture Memory Test, respectively. Sarcopenia was defined according to the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia.
Results: In the multivariate logistic regression analysis by using non-frail participants as the reference, pre-frail elderly individuals were significantly more likely to have sarcopenia than non-frail elderly individuals [odds ratio (OR): 2.77, 95% confidence interval (CI): 1.05–9.26], but not cognitive decline or memory decline. Frail elderly individuals were significantly more likely to have cognitive decline (OR: 5.76, 95% CI: 1.20–27.6), memory decline (OR: 5.53, 95% CI: 1.64–18.7) and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0) than non-frail elderly individuals.
Conclusions: Sarcopenia was associated with pre-frailty and frailty, whereas cognitive decline was associated only with frailty.

Frailty in older adults is a serious concern in countries with aging populations, such as Japan. In general, frailty is defined as a vulnerable state that places older adults at high risk for adverse health outcomes, such as falls, hospitalization, and mortality.[1,2] Using the frailty criteria developed by the Cardiovascular Health Study, the overall prevalence of frailty in community-dwelling adults aged 65 or older in the United States has been found to range from 7% to 12% and was greater in women than in men.[1] In Japanese, the prevalence of frailty in community-dwelling adults aged 65 or older was 11.3%, and it increased with aging.[3] Frail older adults are considered to have a substantially increased risk of disability, dependency, and need for long-term care insurance. Therefore, prevention and early detection of frailty is important for addressing age-related health care issues.

The causes of frailty are not clearly defined, but it has been suggested that age-related physical changes are the main causes of frailty.[4] Sarcopenia, defined as progressive loss of skeletal muscle mass, strength, and physical function, is regarded as a key component of physical frailty.[5,6] The Interventions on Frailty Working Group assessed various methods for screening, recruiting, evaluating, and

The authors declare no conflicts of interest.

* Address correspondence to Shu Nishiguchi, RPT, MSc, Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: nishiguchi.shu.82s@st.kyoto-u.ac.jp (S. Nishiguchi).

http://dx.doi.org/10.1016/j.jamda.2014.07.010
1525-8610/

retaining frail elderly individuals in clinical trials.[7] They reported that most researchers focused on the following domains when identifying physical frailty: mobility, such as lower-extremity performance and gait abnormalities; muscle weakness; poor exercise tolerance; unstable balance; and factors related to body composition, such as weight loss, malnutrition, and muscle loss.[7] Age-dependent loss of skeletal muscle mass is a multifactorial process; contributing factors include physical inactivity, malnutrition, oxidative stress, changes in endocrine function, and increases in inflammatory cytokines.[5] Thus, the domains of frailty overlap with the factors related to sarcopenia, and both frailty and sarcopenia mutually result in adverse health outcomes.[5,6]

Of note, some definitions of frailty include cognitive function and dementia.[4,8] Several cross-sectional studies have reported an association between physical frailty and cognitive function.[1,7,9,10] In addition, longitudinal studies have revealed that a higher level of physical frailty is associated with increased risk of incident Alzheimer's disease (AD)[11] and mild cognitive impairment.[12] It has been indicated that frailty is associated with AD pathology[13] and its biological mechanisms.[14] However, not all dementia patients become frail; therefore, the association between frailty and cognitive impairment warrants further study.

Frailty is associated with sarcopenia and cognitive decline. Furthermore, frailty has been considered to include other aspects, such as psychosocial issues and comorbidities.[15] However, it is unclear whether the associations between frailty and cognitive decline as well as between frailty and sarcopenia are different according to the level of frailty. Therefore, the purpose of this study was to determine whether frailty and prefrailty are associated with cognitive decline and sarcopenia in community-dwelling older adults.

Methods

Participants

Participants for this study were recruited through the local press; 273 Japanese women aged 65 years and older (mean age 73.0 ± 5.4 years) responded. We included community-dwelling older adults who were independent in activities of daily living. Participants were interviewed and excluded if they met any of the following criteria: severe cardiac, pulmonary, or musculoskeletal disorders; severe neurologic disorders, such as Parkinson disease and stroke; and participation in Japan's long-term care service. The following data were collected from each participant: age, height, weight, and number of medications being consumed.

Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

Assessment of Frailty

We measured physical frailty domains determined in a previous study.[3] As in that study, we considered the frailty phenotype to be characterized by limitations in the following 5 domains by using frailty criteria developed by the Cardiovascular Health Study[1]: slowness, weakness, exhaustion, low activity, and shrinking. To measure slowness, each participant's 10-m normal walking speed (m/s) was calculated, and a slow walk was defined as <1.0 m/s. To measure weakness, low grip strength was established according to a sex-specific cutoff of the average grip strength in each arm (women: <17 kg). Exhaustion was assessed via self-report by using the Geriatric Depression Scale[16] (ie, exhaustion was defined as a negative ["no"] answer to the question "do you feel full of energy?)" We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" If a participant answered "no" to both of these questions, then we considered their physical activity to be low. Shrinking was established according to self-reports of weight loss in response to the following question: "In the past 2 years, have you lost more than 5% of your body weight irrespective of intent to lose weight?" If a participant answered "yes" to this question, then we considered them to have shrunk. We calculated the number of affected domains and classified participants as follows: prefrailty = 1 or 2, frailty ≥3.[1]

Measurement of Cognitive Function

Participants' cognitive function was measured by using 2 neuropsychological tests: the Mini-Mental State Examination (MMSE)[17] and the Scenery Picture Memory Test (SPMT).[18]

Global cognitive function was assessed by using the MMSE, a standard test in cognitive aging research to assess mental status. The MMSE tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. It has 11 questions and a possible maximum score of 30. We divided the participants into a normal or a cognitive decline group based on a cut-off of 23/24 as the MMSE score.[19]

The SPMT is a simple memory test that assesses visual memory combined with verbal responses. This test uses a line drawing of a living room in a house with 23 objects commonly observed in daily life on an A4 piece of paper. The examinee is instructed to look at the picture for 1 minute and remember the items. After this encoding period, participants are distracted by completing a brief digits forward test. Participants are then asked to recall the objects in the picture without a time limitation. The recall usually takes approximately 2 minutes. The number of items recalled is the score for the SPMT. We divided the participants into a normal or memory decline group based on a cut-off of 9/10 as the SPMT score.[18]

Definition of Sarcopenia

We defined sarcopenia by using the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia, which assesses the presence of both low muscle function (low physical performance or low muscle strength) and low muscle mass.[20] A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co, Ltd, Seoul, Korea) was used to perform bioelectrical impedance analysis.[21] This system uses electrical current at multiple frequencies (5, 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water. Participants stood on 2 metallic electrodes and held metallic grip electrodes. Using segmental body composition, appendicular skeletal muscle mass was determined and used for further analysis. Skeletal muscle mass index (SMI) was calculated by dividing muscle mass by height squared in meters (kg/m^2). This index has been used in several epidemiological studies.[22,23] If a participant had both low muscle function (slow walking speed, ≤0.8 m/s; low grip strength for women, ≤18 kg) and low SMI (low muscle mass for women, ≤5.7 kg/m^2), then they were defined as having sarcopenia.[20]

Statistical Analysis

Prior to the analysis, we classified participants into the following 3 groups according to their frailty score: nonfrailty, prefrailty, and frailty. Differences in the demographic variables, MMSE, SPMT, and

Table 1
Demographic Differences According to Frailty Scores

	Total (n = 273)	Frailty Level			*P* for Trend	Post-hoc
		Nonfrailty (n = 89)	Prefrailty (n = 155)	Frailty (n = 57)		
Age (y)	73.0 ± 5.4	73.1 ± 4.6	72.3 ± 5.6	76.6 ± 5.1	<.001†	a, b
BMI (kg/m^2)	22.5 ± 3.2	22.2 ± 3.0	22.7 ± 3.3	21.9 ± 3.8	.291	—
Medications	2.32 ± 2.24	2.18 ± 2.35	2.23 ± 2.10	3.27 ± 2.55	.072	—
Walking speed (m/s)	1.40 ± 0.20	1.43 ± 0.18	1.41 ± 0.20	1.21 ± 0.20	<.001†	a, b
Grip strength (kg)	22.4 ± 4.0	23.4 ± 3.4	22.6 ± 3.8	18.3 ± 4.1	<.001†	a, b
Cognitive decline (n)	18 (6.56%)	4 (4.49%)	9 (5.81%)	5 (8.77%)	.047*	
Memory decline (n)	20 (7.33%)	6 (6.74%)	4 (2.58%)	10 (17.5%)	<.001†	
Sarcopenia (n)	22 (8.06%)	2 (2.25%)	9 (5.81%)	11 (19.3%)	<.001†	

AWGS, Asian Working Group for Sarcopenia; BMI, body mass index.
Nonfrailty was defined as frailty score of 0, prefrailty was score 1 or 2, frailty was score 3 or greater.
Cognitive decline was defined as the cut-off of MMSE score (23/24).
Memory decline was defined as the cut-off of SPMT score (9/10).
Sarcopenia was defined by using the AWGS-recommended diagnostic algorithm.
a, significant difference between frailty and nonfrailty ($P < .01$).
b, significant difference between score frailty and prefrailty ($P < .01$).
*$P < .05$.
†$P < .01$.

SMI among the 3 groups were examined by using the analysis of variance. When a significant effect was found, differences were determined with the Tukey-Kramer post-hoc test. Differences in the prevalence of cognitive decline, memory decline, and sarcopenia among the 3 groups were evaluated by using the χ^2 test. In addition, multivariate logistic regression analyses, adjusted for age, body mass index, and medications, were performed to determine whether physical frailty was associated with cognitive decline, memory decline, or sarcopenia. For this analysis, cognitive decline, memory decline, and sarcopenia were dependent variables, whereas the 3 frailty groups (dummy coded with non-frailty group as the reference group) were independent variables. Subsequent multivariate logistic regression analyses were performed to determine the independent association between each level of frailty and the risk of cognitive decline or sarcopenia. In these subsequent analyses (adjusted for age and medications), the frailty groups were the dependent variables, and cognitive decline and sarcopenia were independent variables. Odds ratios (ORs) with 95% confidence intervals (CI) were presented. Statistical analyses were carried out by using SPSS Statistics for Windows, version 20.0 (SPSS Inc, Chicago, IL), with a significance threshold of 0.05.

Results

Demographic data for participants stratified by frailty group are shown in Table 1. There were 89 participants (32.6%) in the nonfrailty group, 155 participants (56.8%) in the prefrailty group, and 29 participants (10.6%) in the frailty group. Analysis of variance showed that there were significant differences in age, walking speed, and grip strength among the 3 groups (Table 1). In the χ^2 test, there were

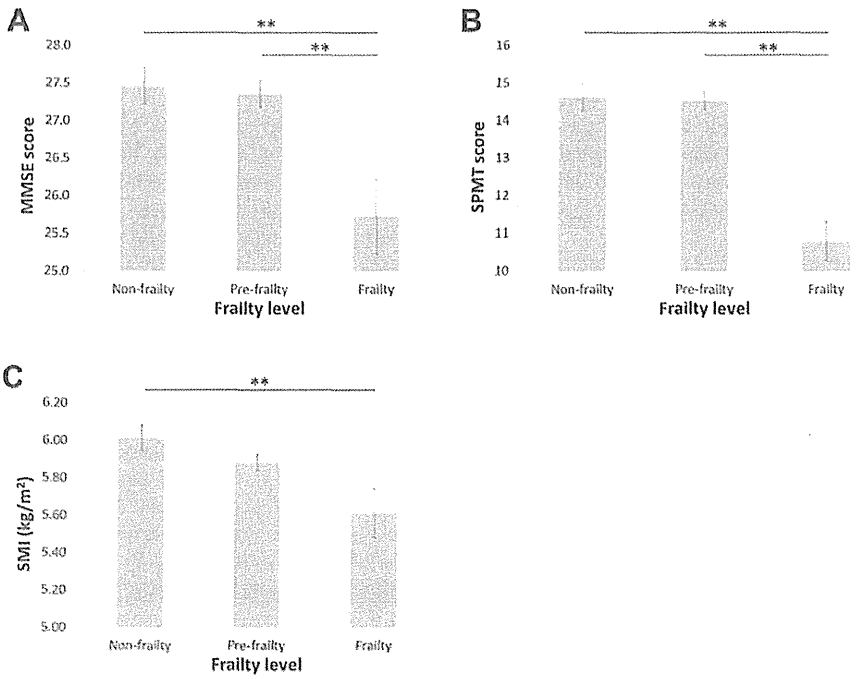

Fig. 1. Comparison of the MMSE, SPMT, and SMI between the groups according to the level of frailty. (A) There were significant differences in the MMSE scores between the 3 groups ($F = 6.78$, $P = .001$). (B) There were significant differences in the SPMT scores between the 3 groups ($F = 18.5$, $P < .001$). (C) There were significant differences in the SMI between the 3 groups ($F = 5.17$, $P = .006$). *$P < .05$, **$P < .01$.

Table 2
Relationship Between the Level of Frailty and Cognitive Decline, Memory Decline, and Sarcopenia

Frailty Level	Cognitive Decline		Memory Decline		Sarcopenia	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Nonfrailty	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Prefrailty	1.79 (0.47–6.84)	.394	0.37 (0.10–1.36)	.134	2.77 (1.05–9.26)	.044*
Frailty	5.76 (1.20–27.6)	.029*	5.53 (1.64–18.7)	.006†	19.1 (3.73–98.0)	<.001†

The analyses for cognitive decline and memory decline were adjusted for age, BMI, and medications.
The analysis for sarcopenia was adjusted for age and medications.
*$P < .05$.
†$P < .01$.

significant differences in the prevalence of cognitive decline, memory decline, and sarcopenia (Table 1). In addition, the frailty group had significantly lower MMSE ($F = 6.78$, $P = .001$, Figure 1, a) and SPMT ($F = 18.5$, $P < .001$, Figure 1, b) than the nonfrailty and prefrailty groups, and lower SMI ($F = 5.17$, $P = .006$, Figure 1, c) than the nonfrailty group.

Eighteen participants (6.6%) had cognitive decline, 20 participants (7.3%) had memory decline, and 23 participants (8.4%) had sarcopenia. In the multivariate logistic regression analysis after adjustment for age, body mass index, and medications, by using nonfrailty group as the reference, the prefrailty group was significantly more likely to have sarcopenia (OR: 2.77, 95% CI: 1.05–9.26, $P = .044$) but not cognitive decline or memory decline (Table 2). The frailty group was significantly more likely to have cognitive decline (OR: 5.76, 95% CI: 1.20–27.6, $P = .029$), memory decline (OR: 5.53, 95% CI: 1.64–18.7, $P = .006$), and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0, $P < .001$) (Table 2).

In the logistic regression analysis in which the frailty groups were the dependent variables and cognitive decline and sarcopenia were independent variables, cognitive decline was independently only associated with a frailty score of ≥3 (OR: 3.73, 95% CI: 1.23–11.4, $P = .020$), whereas sarcopenia was independently associated with both prefrailty (score ≥1; OR: 5.33, 95% CI: 1.22–23.3, $P = .026$) and frailty (score ≥3; OR: 13.1, 95% CI: 4.98–34.2, $P < .001$). These associations remained significant after adjustment for age and medications (Table 3).

Discussion

The results of this study showed that frailty (defined as frailty score ≥3) was associated with cognitive decline, memory decline, and sarcopenia, and that prefrailty (frailty score = 1 or 2) was associated with only sarcopenia. It is a new and interesting finding that there were differences in the association between physical frailty and cognitive decline, memory decline, and sarcopenia according to level of frailty.

In this study, we showed that frailty, but not prefrailty, was associated with cognitive decline and memory decline. Our results also showed that frailty and prefrailty were associated with sarcopenia, in contrast to cognitive and memory decline. In Japanese, multicenter, population-based studies, the prevalence of dementia was not high among those aged 65–74 years (less than 10%), but was higher among those aged 75 years and older.[24] The prevalence of sarcopenia exhibited the same tendency, with the prevalence rising among those aged 75 years and older.[25,26] Thus, older adults (particularly those 75 and older) are prone to both cognitive impairment and sarcopenia. However, low physical performance, low physical strength, and the decrease of muscle mass, which overlap with both sarcopenia and frailty, can be found from middle age.[27–29] Thus, as shown in the results of this study, it is possible that sarcopenia is associated with frailty at an earlier stage than is cognitive impairment, and that sarcopenia is affected more by frailty than is cognitive impairment.

A recent study investigated the association of physical frailty and pre-frailty with dementia and cognitive impairment.[30] In that study, physically frail older adults were over 4 times more likely to have AD, and 8 times more likely to have cognitive impairment than robust older adults were. Prefrail older adults showed an increased risk for dementia in the aforementioned study, but some estimates were not statistically significant in the fully adjusted models.[30] The results of that study were consistent with our study. Previous studies indicated that frailty is associated with AD pathology[13] and biological mechanisms,[14] such as diffuse neuritic plaques, oxidative stress, and inflammation. It is also possible that frailty and AD share common lifestyle risk factors, such as physical inactivity and smoking, that lead to their pathophysiology, which contributes simultaneously to physical frailty and AD.[13] On the other hand, it has been indicated that comorbidities caused by cognitive impairment were also associated with frailty in patients with AD or mild cognitive impairment.[31] Thus, it is likely that these associations interact with one another, leaving the causal association between physical frailty and cognitive decline unclear. Further studies are required to understand these associations.

Definitions of frailty and sarcopenia overlap, and sarcopenia is considered one of the core symptoms of physical frailty.[5,6] The causal mechanisms underlying sarcopenia can be oxidative stress, dysregulation of inflammatory cytokines and hormones, malnutrition,

Table 3
Independent Relationship Between Each Level of Frailty and Cognitive Decline or Sarcopenia

Domains	Univariate Analysis						Multivariate Analysis					
	Frailty Score						Frailty Score					
	≤1		≤2		≤3		≤1		≤2		≤3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Cognitive decline	1.76 (0.56–5.51)	.331	1.43 (0.54–3.84)	.473	3.73 (1.23–11.4)	.020*	2.48 (0.68–9.07)	.168	1.63 (0.56–4.72)	.371	4.61 (1.27–16.8)	.020*
Sarcopenia	5.33 (1.22–23.3)	.026*	9.07 (3.22–25.5)	<.001†	13.1 (4.98–34.2)	<.001†	5.47 (1.21–24.6)	.027*	8.75 (3.00–25.5)	<.001†	10.0 (3.40–29.6)	<.001†

The multivariate analyses were adjusted for age and medications.
*$P < .05$.
†$P < .01$.

physical inactivity, and muscle apoptosis, all of which have been hypothesized to contribute to frailty through interactive pathways.[32,33] Recently, the definition of sarcopenia has been the coexistence of low muscle mass and low physical performance,[5,20,34] which are contained in frailty domains. Thus, the association of sarcopenia with even prefrailty seems reasonable. Overlapping intervention strategies (eg, nutritional supplementation and exercise) may be required to prevent both frailty and sarcopenia.

During recent years, the definition of frailty has been changing. Frailty has been considered to include other aspects, for instance social aspects and comorbidities.[15] In addition to these aspects, poor cognition needs to be included in the definition of frailty, as shown in previous studies[4,8] and by this study. Furthermore, this study indicated that poor cognition was associated with frailty and that sarcopenia was associated even with prefrailty. The results indicate that we need to understand the consecutive mechanism as well as the association of prefrailty and frailty with cognitive decline, sarcopenia, and other adverse health outcomes. Interventions may need to be tailored to the level of frailty to effectively prevent various functional declines. Future studies should investigate these intervention strategies.

There were several limitations to this study. First, the cross-sectional design prevented us from establishing causal associations between frailty and cognitive decline or sarcopenia. Second, the findings in this study should be considered preliminary owing to the relatively small sample size, which may introduce some error of inference, reduce the power of analysis, and limit generalization. Third, the design of this study was not a population sampling, and participants in this study were independent in activities of daily living. This may lead to an underestimation of the prevalence of frailty, cognitive decline, and sarcopenia, as the participants were relatively healthy elderly persons.

In conclusion, our results indicate that there were differences in the association between physical frailty and cognitive decline, memory decline, and sarcopenia according to the level of frailty. Cognitive decline and memory decline were associated with frailty. Sarcopenia was associated with prefrailty and frailty. Further studies are required to understand these associations including biological mechanisms.

Acknowledgments

The authors thank the students of the Department of Human Health Sciences at Kyoto University for their help with data collection.

References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
2. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381:752–762.
3. Shimada H, Makizako H, Doi T, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc 2013;14:518–524.
4. Pel-Littel RE, Schuurmans MJ, Emmelot-Vonk MH, Verhaar HJ. Frailty: Defining and measuring of a concept. J Nutr Health Aging 2009;13:390–394.
5. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–423.
6. Xue QL, Bandeen-Roche K, Varadhan R, et al. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 2008;63:984–990.
7. Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. J Am Geriatr Soc 2004;52:625–634.
8. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
9. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–263.
10. Mitnitski AB, Song X, Rockwood K. The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. J Gerontol A Biol Sci Med Sci 2004;59:M627–M632.
11. Buchman AS, Boyle PA, Wilson RS, et al. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483–489.
12. Boyle PA, Buchman AS, Wilson RS, et al. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc 2010;58:248–255.
13. Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology 2008;71:499–504.
14. Mulero J, Zafrilla P, Martinez-Cacha A. Oxidative stress, frailty and cognitive decline. J Nutr Health Aging 2011;15:756–760.
15. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: A call to action. J Am Med Dir Assoc 2013;14:392–397.
16. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982;17:37–49.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
18. Takechi H, Dodge HH. Scenery Picture Memory Test: A new type of quick and effective screening test to detect early stage Alzheimer's disease patients. Geriatr Gerontol Int 2010;10:183–190.
19. Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York: Oxford University Press; 2004.
20. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: Consensus report of the asian working group for sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
21. Gibson AL, Holmes JC, Desautels RL, et al. Ability of new octapolar bioimpedance spectroscopy analyzers to predict 4-component-model percentage body fat in Hispanic, black, and white adults. Am J Clin Nutr 2008;87:332–338.
22. Janssen I, Baumgartner RN, Ross R, et al. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol 2004;159:413–421.
23. Janssen I. Influence of sarcopenia on the development of physical disability: The Cardiovascular Health Study. J Am Geriatr Soc 2006;54:56–62.
24. Ikejima C, Hisanaga A, Meguro K, et al. Multicentre population-based dementia prevalence survey in Japan: A preliminary report. Psychogeriatrics 2012;12:120–123.
25. Akune T, Muraki S, Oka H, et al. Exercise habits during middle age are associated with lower prevalence of sarcopenia: The ROAD study. Osteoporos Int 2014;25:1081–1088.
26. Yamada M, Nishiguchi S, Fukutani N, et al. Prevalence of sarcopenia in community-dwelling Japanese older adults. J Am Med Dir Assoc 2013;14:911–915.
27. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. J Appl Physiol (1985) 2003;95:1851–1860.
28. Speakman JR, Westerterp KR. Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 years of age. Am J Clin Nutr 2010;92:826–834.
29. Yamada M, Moriguch Y, Mitani T, et al. Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40 to 79 years-of-age. Geriatr Gerontol Int 2014;14:8–14.
30. Kulmala J, Nykänen I, Mänty M, Hartikainen S. Association between Frailty and Dementia: A population-based study. Gerontology 2014;60:16–21.
31. Ní Mhaolain AM, Gallagher D, Crosby L, et al. Correlates of frailty in Alzheimer's disease and mild cognitive impairment. Age Ageing 2011;40:630–633.
32. Marcell TJ. Sarcopenia: Causes, consequences, and preventions. J Gerontol A Biol Sci Med Sci 2003;58:M911–M916.
33. Dirks AJ, Hofer T, Marzetti E, et al. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. Ageing Res Rev 2006;5:179–195.
34. Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: An international consensus. J Am Med Dir Assoc 2011;12:403–409.

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: October 31, 2014
Published online: December 20, 2014

Original Article

Arterial Stiffness Predicts Cognitive Decline in Japanese Community-dwelling Elderly Subjects: A One-year Follow-up Study

Taiki Yukutake[1], Minoru Yamada[1,2], Naoto Fukutani[1], Shu Nishiguchi[1,3], Hiroki Kayama[1], Takanori Tanigawa[1], Daiki Adachi[1], Takayuki Hotta[1], Saori Morino[1], Yuto Tashiro[1], Tomoki Aoyama[1] and Hidenori Arai[1]

[1]Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2]Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tokyo, Japan
[3]Japan Society for the Promotion of Science, Tokyo, Japan

Aim: The purpose of this study was to determine whether arterial stiffness can be used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects.
Methods: A total of 103 Japanese community-dwelling elderly patients joined this study. Information regarding the age, height, weight, gender and past medical history of each participant was obtained. Additionally, arterial stiffness was determined according to the cardio-ankle vascular index (CAVI), and the cognitive function was assessed with the Mini-Mental State Examination (MMSE). One year later, we performed the MMSE in the same subjects. After dividing the cohort according to the 80th percentile of the CAVI (normal and arterial stiffness [AS] groups), we examined whether the degree of cognitive decline, as determined using the pre- and post-MMSE, was significantly different based on the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE scores.
Results: Of the 103 subjects who participated in the pre-data collection, 74 (38 men and 36 women, 73.4±4.0 years) joined the post-data collection. We found a significant difference in the change in the post-MMSE scores between the normal and AS groups (pre-MMSE: normal group [27.4±2.1] and AS group [26.9±2.4] and post-MMSE: normal group [27.2±2.1] and AS group [25.5±2.3], $F=5.95$, $p=0.02$). For each domain of the MMSE, the changes in MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) and MMSE-language ($F=4.32$, $p=0.04$) were significantly different according to an ANCOVA.
Conclusions: We found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects regardless of the initial level of the global cognitive function. This finding indicates the potential use of the degree of arterial stiffness as an indicator for preventing or delaying the onset of dementia in the elderly.

J Atheroscler Thromb, 2014; 21:000-000.

Key words: Arterial stiffness, Cognitive impairment, Elderly, Dementia

Introduction

Dementia is a serious issue, especially in community-dwelling elderly subjects[1]. Thirty-five million people worldwide suffered from dementia in 2012 according to the World Health Organization. Approximately 48% of patients with Alzheimer's disease (AD), the most common form of dementia, are estimated to live in Asia, and this percentage is expected to increase to 59% by 2050[2]. Elderly people with dementia are typically frail due to their poor mobility and body composition, and the transitional stage between normal aging and AD, called mild cognitive impairment (MCI), results in frailty[3], depression[4], lower levels of physical activity[1] and higher mortality[5]. Preventing cognitive decline is therefore crucial.

Of risk factors for cognitive decline, cardiovascular risk factors have received more attention in recent

Address for correspondence: Hidenori Arai, Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
E-mail: harai@kuhp.kyoto-u.ac.jp
Received: July 31, 2014
Accepted for publication: October 31, 2014

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: October 31, 2014
Published online: December 20, 2014

years[6, 7]. High blood pressure[8], dyslipidemia[8], obesity[9] and diabetes mellitus[9] have been proposed to be risk factors for cognitive decline. Among these factors, arterial stiffness is a comparatively easy-to-modify risk factor in community-dwelling elderly subjects. Madden *et al.* reported that three months of aerobic training reduces the degree of multifactorial arterial stiffness without generating any significant improvements in aerobic fitness, weight, BMI, waist-to-hip ratio or blood pressure in community-dwelling older individuals[10]. Additionally, previous studies have demonstrated the effectiveness of antihypertensive agents in improving arterial stiffness in both short- and long-term trials[11]. Community-dwelling elderly can improve their arterial stiffness; therefore, focusing on treating arterial stiffness may be effective for preventing cognitive decline.

Most older adults with MCI live in the community, and more than half of MCI cases progress to dementia within five years[12]. Therefore, a desired goal is the early detection of cognitive decline, especially in the community-dwelling elderly. When evaluating the degree of arterial stiffness in community-dwelling elderly subjects, the most important property is the ease of measurement. Arterial stiffness is one of the most easily measured vascular risk factors in community-dwelling elderly patients due to its non-invasive nature; therefore, it can be used as a predictor of cognitive decline in this population. Previous studies have also shown arterial stiffness to be a predictor of cognitive decline. However, the subjects in these studies were not elderly individuals living in the community[13, 14]. Additionally, other authors have reported that they were unable to validate arterial stiffness as an independent risk factor for cognitive decline, as measured according to the global cognitive function using the Mini-Mental State Examination (MMSE)[15-17]. Yamamoto *et al.* reported a relationship between the cognitive function and arterial stiffness determined according to the CAVI in community dwelling elderly[18], although the mean age was approximately 80 years, which is a bit high considering the mean age of community-dwelling elderly individuals in Japan. It may be more important to focus on healthier and younger older adults when discussing community-dwelling elderly[19]. The efficacy of arterial stiffness as a predictor of cognitive decline, especially in community-dwelling elderly patients, is less well investigated[4].

The purpose of this study therefore was to address whether the degree of arterial stiffness can be used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects. We used the CAVI to assess arterial stiffness, as this parameter was found to significantly correlate with cognitive decline in a cross-sectional study[18, 19].

Methods

Participants

Participants were recruited for this study through local press that requested healthy community-dwelling volunteers 65 years of age or older, and data collection was performed on two occasions: November 2012 (pre-data collection) and November 2013 (post-data collection). Interviews were conducted to exclude participants from both data collections based on the following exclusion criteria: severe cardiac, pulmonary or musculoskeletal disorders; comorbidities associated with a higher risk of falls, such as Parkinson's disease or stroke; and the use of psychotropic drugs. Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995 during both data collection periods. The study protocol was approved by the ethics committee of Kyoto University Graduate School of Medicine.

Measurements—*Pre-data Collection*

Demographic Data

Each patient's age, height, weight, gender, past medical history (cardiovascular disease, hypertension, diabetes mellitus and hyperlipidemia), smoking status (number of cigarettes smoked per day and total number of years smoked) and educational background (elementary school, junior high school, high school, career college or university) were obtained as demographic data. All data were collected at the first data collection time point. We directly asked about each participant's age and gender and measured their height and weight using standardized height and weight scales.

Arterial Stiffness

The degree of arterial stiffness was determined based on the CAVI using the VaSera-1500 device (Fukuda Denshi Co., Ltd., Tokyo, Japan). The details of this procedure have been described previously[20, 21]. After the participants had rested for five minutes in the sitting position, we obtained these measurements as previously described. Higher CAVI values indicate a higher degree of arterial stiffness. The measurements were obtained once, and the mean values of the right and left CAVI scores for each patient were used for the analysis[19].

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: October 31, 2014
Published online: December 20, 2014

Table 1. Baseline characteristics and post-MMSE scores in the study population

	All (n=74)		
	Normal group n=59	AS group n=15	p
Demographic data			
Age, year	72.8±3.8	76.1±3.6	<0.01
BMI, kg/m^2	23.2±2.6	23.2±3.2	0.99
Gender, male	28 (47.5%)	10 (66.7%)	0.25
Mean CAVI	8.83±0.61	10.6±0.51	<0.01
Cognitive function			
Pre-MMSE	27.4±2.1	26.9±2.4	0.40
Post-MMSE	27.2±2.0	25.5±2.3	<0.01
Pre-MMSE (orientation)	9.6±0.6	9.7±0.5	0.89
Post-MMSE (orientation)	9.7±0.7	9.7±0.5	0.89
Pre-MMSE (registration)	2.9±0.4	3.0±0.0	0.53
Post-MMSE (registration)	2.9±0.3	3.0±0.0	0.49
Pre-MMSE (attention and calculation)	3.2±1.7	2.9±1.8	0.55
Post-MMSE (attention and calculation)	3.4±1.7	2.3±1.5	0.03
Pre-MMSE (recall)	2.6±0.6	2.4±0.8	0.30
Post-MMSE (recall)	2.5±0.6	2.4±0.7	0.69
Pre-MMSE (language)	8.9±0.3	8.9±0.4	0.73
Post-MMSE (language)	8.7±0.5	8.2±1.3	0.15
Comorbidities			
Cardiovascular disease	6 (10.2%)	4 (26.7%)	0.11
Hypertension	23 (39.0%)	8 (53.3%)	0.39
Diabetes mellitus	5 (8.5%)	4 (26.7%)	0.08
Hyperlipidemia	9 (15.3%)	2 (13.3%)	1.00
Brinkman index	0 (0-800)	0 (0-400)	0.63
Educational background			n.s.
Elementary school	0 (0.0%)	1 (6.7%)	
Junior high school	16 (27.1%)	4 (26.7%)	
High school	35 (59.3%)	9 (60.0%)	
Career college	3 (5.1%)	0 (0.0%)	
University	5 (8.5%)	1 (6.7%)	

Mean CAVI = mean value of the right and left CAVI scores. The mean ± SD is shown for age, BMI, mean CAVI and pre- and post MMSE. n (%) is shown for gender, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia and educational background. The median (25% quartile-75% quartile) is shown for the Brinkman index. AS: arterial stiffness; n.s.: not significant.

Cognitive Function Measurements

The cognitive function was assessed using the Mini-Mental State Examination (MMSE)[22]. The MMSE is a short screening test that consists of the following five areas for detecting cognitive impairment: orientation, registration, attention and calculation, recall and language. The scores range from 0 to 30, with higher scores indicating better cognitive performance. The MMSE was performed at both the pre- and post-data collection time points.

Measurements—*Post-data Collection*

Cognitive Function Measurements

One year later, the cognitive function was also assessed using the MMSE[22]. We performed the MMSE using the same inclusion and exclusion criteria as that used at the pre-data collection time point.

Statistical Analysis

The patients were divided into two groups based on the 80th percentile of the CAVI values: the normal and arterial stiffness [AS] groups. We analyzed the differences between these two groups using the unpaired

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: October 31, 2014
Published online: December 20, 2014

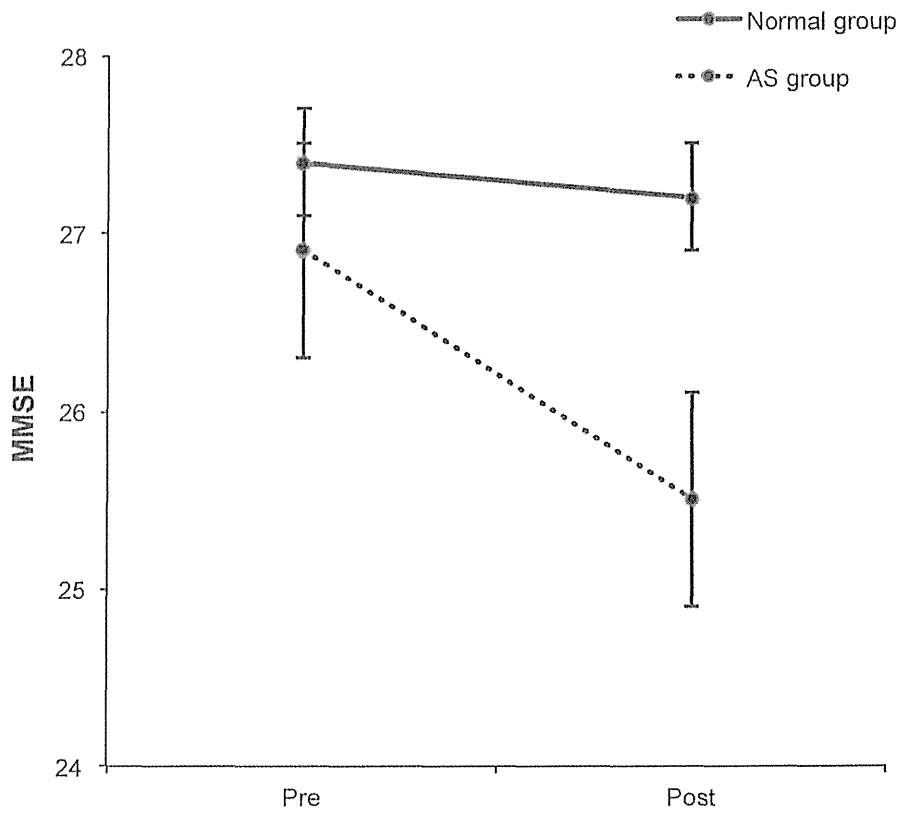

Fig. 1. Two-way analysis of variance showing the differences in the changes in the post-MMSE scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.95$, $p=0.02$).

t-test for age, body mass index (BMI), mean CAVI values on both sides and the pre- and post-MMSE scores (total score and scores for each domain), the χ^2 test for gender, past medical history and educational background and the Mann Whitney *U*-test for the Brinkman index (number of cigarettes smoked per day × total number of years smoked). A repeated measures two-way analysis of covariance (ANCOVA) was used to analyze whether the degree of cognitive decline determined according to the pre- and post-MMSE scores (total score and scores for each domain) differed significantly according to the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE score. A p value of <0.05 was considered to be statistically significant for all analyses.

Results

In total, 74 individuals (38 men and 36 women, 73.4±4.0 years) participated in both data collection events. Of these individuals, none were excluded. We assigned 59 elderly individuals (28 men and 31 women) to the normal group and 15 (10 men and five women) to the AS group. **Table 1** shows the differences in each variable between the two groups. While there were no significant differences in BMI, gender, pre-MMSE, educational background or past medical history, we found significant differences in age ($p<0.01$) and the mean CAVI values ($p<0.01$). Additionally, the normal group had a significantly higher total post-MMSE scores (normal group: 27.2±2.1, AS group: 25.5±2.3, $p<0.01$) and higher post-MMSE scores for the attention-and-calculation domain (normal group: 3.4±1.7, AS group: 2.3±1.5, $p=0.03$) than the AS group.

The ANCOVA adjusted for age, BMI, gender and pre-MMSE showed a significant difference in the changes in the post-MMSE scores between the normal and AS groups ($F=5.95$, $p=0.02$) (**Fig. 1**), indicating that elderly individuals with a higher degree of arterial

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: October 31, 2014
Published online: December 20, 2014

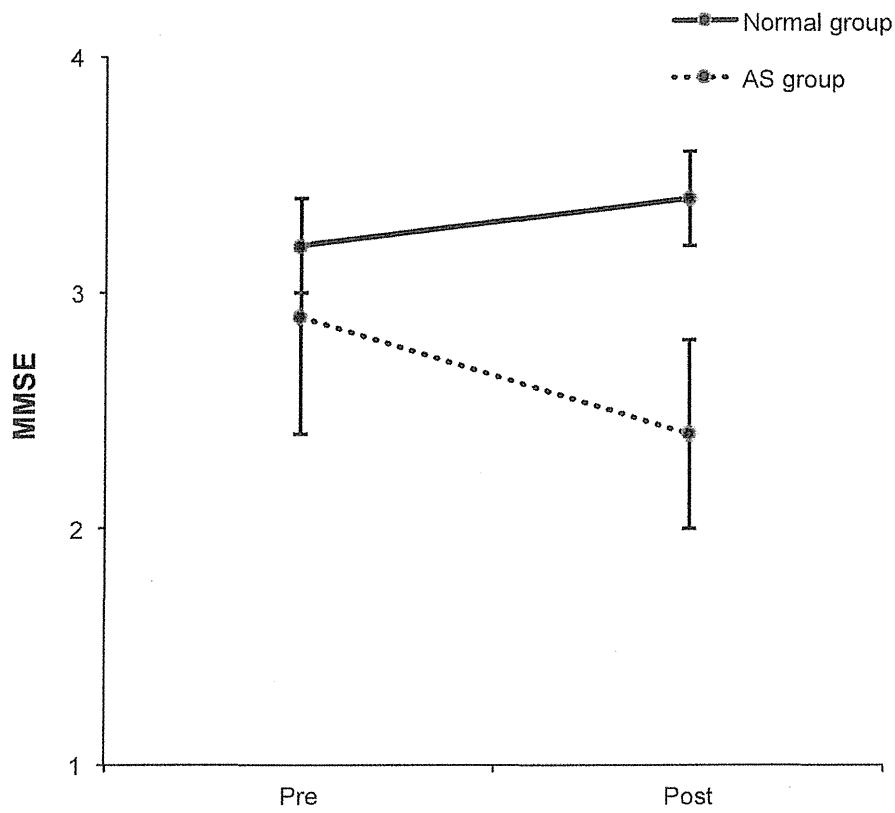

Fig. 2. Two-way analysis of variance showing the differences in the changes in the post-MMSE (attention and calculation) scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.11$, $p=0.03$).

stiffness may experience greater levels of cognitive decline, even after adjusting for age, BMI, gender and the pre-MMSE score. Additionally, the changes in the MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) (**Fig. 2**) and MMSE-language ($F=4.32$, $p=0.04$) (**Fig. 3**) domains were shown to be significantly different according to the ANCOVA. The other areas did not show any differences between the two groups (orientation; $F=0.27$, $p=0.60$: registration; $F=2.69$, $p=0.11$, recall; $F=0.16$, $p=0.69$).

Discussion

In this study, we analyzed whether the degree of cognitive decline differs significantly according to the severity of arterial stiffness, adjusted for age, BMI, gender and the cognitive function at baseline and at the one-year follow-up. Consequently, we found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects, regardless of the initial level of the global cognitive function. Previous studies have demonstrated that arterial stiffness has a predictive effect on cognitive decline in the non-community-dwelling elderly[13-15, 18]; however, few reports have found arterial stiffness to be a predictor of cognitive decline in this group.

There are hypotheses regarding pathways linking arterial stiffness and cognitive decline, wherein augmented pressure pulses penetrate and damage small cerebral vessels in the global brain[23]. Brain lesions, such as ischemic lesions and white matter abnormalities resulting from augmented pressure, are thought to cause cognitive decline, thereby leading to dementia[24]. The augmented pressure caused by arterial stiffness independently predicts cognitive performance[25], and many previously published studies evaluating the association between arterial stiffness and the cognitive function have discussed the causal relationship with this phenomenon[14, 17, 18, 23].

Several studies have examined whether the sever-