Table 4 Relationship between the Kihon Checklist Brazilian Portuguese version and the Edmonton Frail Scale score (n = 161)

Edmonton Frail Scale total score				
Kihon Checklist Domain Factors	Kendall's τ Coefficient	*P* value	Regression coefficient β R^2 = 0.387	*P*-value <0.001
Lifestyle	0.429	<0.001	0.073	0.788
Physical strength	0.367	<0.001	0.330	0.031
Nutrition	0.211	0.002	0.090	0.267
Eating	0.213	0.001	−0.005	0.966
Socialization	0.269	<0.001	0.075	0.433
Memory	0.285	<0.001	0.145	0.167
Mood	0.359	<0.001	0.196	0.014

Table 5 Differences of the Edmonton Frail Scale total score according to the frailty condition by Kihon Checklist cut-off points (n = 161)

Kihon Checklist Domains	Edmonton Frail Scale total score Non-frail Median (min–max), n	Frail Median (min–max), n	*P*-value
Lifestyle	3 (0–10), 157	6 (5–9), 4	0.015
Physical strength	2 (0–10), 138	4 (2–10), 23	<0.001
Nutrition	3 (0–10), 161	–	–
Eating	2 (0–10), 121	3 (0–10), 40	0.012
Socialization	3 (0–10), 113	5 (3–9), 48	0.002
Memory	2 (0–9), 77	3 (0–10), 84	<0.001
Mood	2 (0–9), 138	4 (1–10), 23	<0.001

Analyzed using Mann–Whitney *U*-test.

activities of daily living and also in instrumental activities of daily living, which is one of the principal factors for institutionalization and is also associated with mortality among older adults.[25,26] However, frailty is not unidimensional; the focus must be extended to include aspects such as cognition, mood and social support.[21] In the present study, we verified the contribution of the mood domain score of the KCL-PT to EFS total score (coefficient β = 0.196; P = 0.01). Evidence suggests that depression in the aged population is also associated with functional impairment and increased mortality.[27,28]

The EFS does not directly address the lifestyle, eating or socialization domains that are addressed by the KCL-PT. Those differences might explain the low regression coefficients of these domains with the EFS total score. It was intriguing that the nutrition and memory domains of the KCL-PT, which have corresponding domains in the EFS, did not present a significant regression coefficient for the EFS total score. However, when we analyzed just the specific domains, and not the total EFS total score, we verified a significant correlation between those domains (nutrition domain Kendall's τ coefficient = 0.483, P < 0.001 and memory domain, Kendall's τ coefficient =0.221, P = 0.002).

Although the KCL-PT domains presented a significant regression coefficient with EFS, the value could be considered low (R^2 = 0.387, P < 0.001). The EFS domains, such as general health state, social support, medication use and continence, that were not directly investigated by the KCL-PT could represent the remaining coefficient value that is unexplained by KCL-PT. Despite these differences, the essences of both frailty assessments were deemed similar because their total scores were significantly correlated, suggesting that the EFS was a suitable assessment of frailty for use in validating the Kihon Checklist in Brazil.

Although this is a pioneer study using the KCL in Brazil, we unfortunately could not compare our results with other Brazilian studies present in the literature. Despite this limitation, we believe that the quality of the KCL-PT was satisfactory in terms of internal consistency (Cronbach's α coefficient = 0.787), and the

KCL-PT is considered a valid frailty index for use with elderly Brazilian adults because its results correlated with those of the already-validated EFS. Therefore, we suggest the use of the KCL-PT to screen and monitor the elderly Brazilian population's frailty conditions.

Even though frailty confers morbidity, mortality and healthcare costs,[1,7] causing an increased strain on all healthcare systems and family structures, this type of syndrome can be avoided or delayed with identification and early intervention.[1] The awareness of this syndrome and its risks can be useful in supporting the care of frail elderly patients by healthcare workers, and thus can decrease patients' risks for adverse health outcomes.[29] Therefore, the ability to measure frailty is critical for this process at a healthcare policy level, as well as clinically, and information about frailty can support program planners by identifying the range of services that might be required, and the anticipated level of need for those services. Clinically, frailty stratification can help in planning interventions or predicting a patient's risk of death or need for institutional care.[30] The KCL-PT can be used to answer this emergent and emergency demand in screening the frailty of the elderly Brazilian population as a first step in facing and confronting frailty in this population.

The present study had several limitations, including the limited sample size and possible bias as a result of the choice of recruitment location. We suggest future studies that recruit a larger sample size, include different regions of Brazil and different institutional settings, such as communities for the elderly (urban and rural areas), nursing homes and other settings. Furthermore, additional studies to verify the association of the KCL-PT with other measures of health are necessary.

We successfully translated the KCL into Brazilian Portuguese and validated the instrument's application in an elderly Brazilian population. We encourage the application of the KCL-PT to investigate frailty in older adults with an aim of preventing or delaying functional dependence and other adverse health outcomes caused by the aging process. Given the simple 25 yes/no question structure of the KCL-PT, the checklist is suitable for clinical application, research and the needs of policy makers.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Effect of physical activity on memory function in older adults with mild Alzheimer's disease and mild cognitive impairment

Takanori Tanigawa,[1] Hajime Takechi,[2] Hidenori Arai,[1] Minoru Yamada,[1] Shu Nishiguchi[1] and Tomoki Aoyama[1]

[1]Department of Physical Therapy, Human Health Sciences, and [2]Department of Geriatric Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Aim: It is very important to maintain cognitive function in patients with mild cognitive disorder. The aim of the present study was to determine whether the amount of physical activity is associated with memory function in older adults with mild cognitive disorder.

Methods: A total of 47 older adults with mild cognitive disorder were studied; 30 were diagnosed with mild Alzheimer's disease and 17 with mild cognitive impairment. The global cognitive function, memory function, physical performance and amount of physical activity were measured in these patients. We divided these patients according to their walking speed (<1 m/s or >1 m/s). A total of 26 elderly patients were classified as the slow walking group, whereas 21 were classified as the normal walking group.

Results: The normal walking group was younger and had significantly better scores than the slow walking group in physical performance. Stepwise multiple linear regression analysis showed that only the daily step counts were associated with the Scenery Picture Memory Test in patients of the slow walking group ($\beta = 0.471$, $P = 0.031$), but not other variables. No variable was significantly associated with the Scenery Picture Memory Test in the normal walking group.

Conclusions: Memory function was strongly associated with the amount of physical activity in patients with mild cognitive disorder who showed slow walking speed. The results show that lower physical activities could be a risk factor for cognitive decline, and that cognitive function in the elderly whose motor function and cognitive function are declining can be improved by increasing the amount of physical activity. **Geriatr Gerontol Int 2014; 14: 758–762.**

Keywords: memory function, mild cognitive disorder, older adults, physical activity, physical performance.

Introduction

Mild cognitive impairment (MCI) is a condition of objective cognitive impairment based on neuropsychological testing in the absence of clinically overt dementia.[1] This condition is of interest for identifying the prodromal and transitional stages of Alzheimer's disease (AD)[2,3] and other types of dementia. Indeed, a study shows that more than half of MCI cases progress to dementia within 5 years.[1] However, it is reported that the cognitive function of people with MCI can recover to normal.[4,5] Indeed, one study showed that 38.5% of older adults with MCI recovered to normal within 5 years.[6] Therefore, it is very important to prevent the deterioration of MCI to dementia. Because no consensus has been established regarding pharmacological intervention for MCI, non-pharmacological intervention is expected. Accordingly, we need to establish a way to prevent deterioration or even improve cognitive function in MCI patients.

Recently, it has attracted attention that increasing the amount of physical activity can prevent the decline of cognitive function. Many studies reported that global cognitive function is associated with the amount of physical activity. Furthermore, previous reports have shown that physical frailty is associated with an increased risk of developing AD and MCI,[8,9] and can predict a future cognitive decline in older adults.[10] Additionally, people with dementia have been shown to be

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Correspondence: Dr Tomoki Aoyama MD PhD, Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Email: aoyama.tomoki.4e@kyoto-u.ac.jp

frail because of their poor mobility and body composition.[11,12] Thus, cognitive function and physical frailty are interrelated.

Accordingly, the cognitive decline in frail elderly patients can cause further decline of cognitive function and motor function. Therefore, it is important to maintain and improve the cognitive function of the frail elderly with mild cognitive disorder.

Several studies have shown the relationship between cognitive decline that can be observed at the early stage of dementia and the amount of physical activity. However, no study has addressed whether the association between cognitive function and the amount of physical activity depends on the level of motor function in MCI or mild AD patients.

Therefore, the aim of the present study was to determine whether there is an association between memory function and the amount of physical activity in older adults with mild cognitive disorder, stratified by their motor function.

Methods

Participants

We recruited patients from the memory clinic of the Department of Geriatric Medicine in Kyoto University Hospital, Kyoto, Japan. The diagnosis of AD or MCI was made according to the following criteria: AD, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association;[13,14] and MCI, Petersen's criteria.[15] Of the 47 patients with cognitive disorder, 30 were classified as mild AD and 17 as MCI by the criteria. In the present study, we did not set the upper and lower limits of the Mini-Mental State Examination (MMSE) for the diagnosis of MCI. The exclusion criteria used in the present study were vascular dementia, dementia with Lewy bodies, lacunar infarcts, Fazekas grade 3 periventricular hyperintensity/deep white-matter hyperintensity,[16] severe cardiac, pulmonary or musculoskeletal disorders, or the presence of comorbidities associated with an increased risk of falls, such as Parkinson's disease and stroke.

Written informed consent for the trial was obtained from each participant or his/her family members in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975.

Walking speed

Comfortable 10-m walking time (walking time) is a simple test developed to screen basic mobility performance in frail older adults. It has been reported that the elderly with a walking score greater than 10.0 s can suffer an increased risk of falling.

Therefore, we divided the participants into two groups according to their walking speed (cut-off: 1 m/s); 26 of the older adults were classified as the normal walking group, whereas 21 of the older adults were classified as the slow walking group.

Cognitive function measures

Cognitive function was assessed by the MMSE and the Scenery Picture Memory Test (SPMT). MMSE is a global cognitive test that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. SPMT is a short and simple memory test assessing the visual memory encoded as scenery, combined with verbal answers. Briefly, it uses a line drawing scenery picture of a living room in a house where 23 objects commonly observed in daily life are drawn on an A4 piece of paper. The examinee is instructed to look at the picture for 1 min and remember the items. After this encoding period, we distracted participants by asking them to carry out a brief digits forward test. Participants were then asked to recall the objects in the picture without time limitation. This recall time usually takes less than 1 min. The number of items recalled is the score for SPMT. Higher scores indicate better cognitive function. We have previously shown that SPMT is a quick and effective screen for MCI.[17]

Physical performance measures

The participants were asked to carry out the three motor function tests that are widely used to identify the frail elderly. For each performance task, the participants carried out two trials, and the better performance of the two was used for the analysis. Physical performance assessments, such as walking time,[18] the Timed Up & Go (TUG) test,[19] the Functional Reach test,[20] the one-leg stand (OLS) test,[21] and the five chair stand test (5CS)[22] were carried out as previously described.

Physical activity measures

In physical activity, a valid, accurate and reliable pedometer, the Yamax Power walker EX-510, was used to measure the free-living step counts.[23] The participants were instructed to wear the pedometer in their pocket on the side of their dominant leg for 14 consecutive days except when bathing, sleeping or carrying out water-based activities. This pedometer has a 30-day data storage capacity. We calculated the averages of their daily step counts for 2 weeks.

Table 1 Comparison of demographic characteristics and measurements with the overall group, normal walking group, and slow walking group

	All (= 47)	Normal walking (= 26)	Slow walking (= 21)	*P*-value
Age (years)	76.9 ± 7.0	74.7 ± 7.2	79.6 ± 5.9	0.016*
Female sex, *n* (%)	28 (59.6%)	17 (65.4%)	11 (52.4%)	0.38
BMI	21.7 ± 3.7	22.1 ± 3.7	21.1 ± 3.8	0.36
Loneliness	5 (10.6%)	2 (7.7%)	3 (14.3%)	0.64
Donepezil treatment	41 (87.2%)	24 (92.3%)	17 (81.0%)	0.39
MMSE	23.4 ± 3.6	23.0 ± 3.1	24.0 ± 4.2	0.37
SPMT	6.5 ± 4.7	6.7 ± 5.1	6.1 ± 4.4	0.68
Physical activity	4371.9 ± 3605.9	5264.0 ± 3476.9	3267.4 ± 3532.5	0.06
10 m walking time	9.9 ± 2.3	8.2 ± 1.0	12.3 ± 1.6	<0.001***
TUG time	9.5 ± 2.7	7.9 ± 1.4	11.4 ± 2.6	<0.001***
OLS	11.9 ± 15.8	16.9 ± 19.3	5.8 ± 6.1	0.01*
5CS	11.1 ± 3.5	10.0 ± 2.2	12.4 ± 4.2	0.016*

5CS, five chair stand test; BMI, body mass index; MMSE, Mini-Mental State examination; OLS, one leg standing; SPMT, Scenery Picture Memory Test; TUG, Timed Up & Go test. *$P < 0.05$ ***$P < 0.001$.

Statistical analysis

The *t*-test and χ^2-test were used to compare the data between the normal and slow walking groups. Multiple linear regression analysis using a stepwise method was carried out to investigate whether physical activity, age, sex, body mass index, TUG, OLS and 5CS were independently associated with SPMT. The data were analyzed using SPSS software Windows version 20.0 (SPSS, Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant for all analyses.

Results

The demographic characteristics of the overall, normal and slow walking groups are summarized in Table 1. A total of 26 patients were classified as the normal walking group, and 21 patients as the slow walking group. There were no significant differences in sex, body mass index, loneliness, donepezil treatment, SPMT or physical activity between the two groups ($P > 0.05$). The normal walking group was younger (normal walking group 74.7 ± 7.2, slow walking group 79.6 ± 5.9, $P = 0.016$), and had significantly better scores than the slow walking group in TUG (normal walking group 7.9 ± 1.4 s, slow walking group 11.4 ± 2.6 s, $P < 0.001$), OLS (normal walking group 24.3 ± 24.3 s, slow walking group 5.8 ± 6.1 s, $P = 0.006$), 5CS (normal walking group 10.0 ± 2.2 s, slow walking group 12.4 ± 4.2 s, $P = 0.016$; Table 1). In the slow walking group, physical activity was significantly correlated with SPMT ($r = 0.471$, $P = 0.031$), as shown in Figure 1, but this correlation was absent in the normal walking group. In addition, there was a correlation between SPMT and physical activity after adjusted by age and sex in the slow walking group ($r = 0.493$, $P = 0.032$).

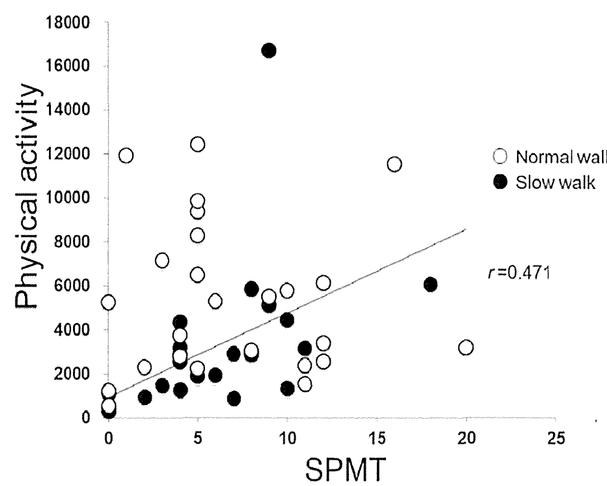

Figure 1 Relationship between physical activity and the Scenery Picture Memory Test (SPMT) in the normal walking and slow walking groups. In the slow walking group, physical activity was correlated significantly with SPMT ($r = 0.471$, $P = 0.031$).

Stepwise multiple linear regression analysis showed that no item was significantly associated with SPMT in the normal walking group, whereas only physical activity ($\beta = 0.471$, $P = 0.031$) was significantly associated with SPMT in the slow walking group (Table 2).

Discussion

The present study showed that memory function is strongly associated with the amount of physical activity

Table 2 Stepwise multiple regression analysis for Scenery Picture Memory Test

	Normal walking		Slow walking	
	β estimates	*P*-value	β estimates	*P*-value
Daily step counts	–	–	0.471	0.031*
Age	–	–	–	–
Sex	–	–	–	–
BMI	–	–	–	–
TUG time	–	–	–	–
OLS	–	–	–	–
5CS	–	–	–	–

Note: 5CS, five chair stand test; BMI, body mass index; OLS, one leg standing; TUG, Timed Up & Go test. *$P < 0.05$.

only in the slow walking group with mild cognitive disorder. The present results show that lower physical activity could be a risk factor for cognitive decline in the elderly, and would strengthen the evidence to show the relationship between the amount of physical activity and cognitive function, as previously reported.[24] Additionally, the present study might show that the cognitive function of the elderly whose motor function and cognitive function are declining can be improved by increasing the amount of physical activity.

Physical activity might have an impact on cognitive function. The reasons why the SPMT, not MMSE, showed a correlation with physical activity might be explained as following. First, SPMT has been developed to screen mild cognitive disorder, whereas the MMSE is usually used for a broad range of cognitive impairment from normal to severe dementia. Because we only included patients with mild cognitive disorder, SPMT might be better to detect small correlated changes with other functions than MMSE. Second, SPMT shows good correlation not only with memory tests, but also with frontal function tests including word fluency test (Takechi *et al.* unpubl. observation). We speculate that efficient reminding of many objects from the scene requires the frontal function. Third, SPMT uses a line drawing scenery picture of a living room familiar to the elderly. It has been reported that aerobic exercise induces beneficial changes in brain structure and function that are correlated with improvements in cognition,[25,26] even in AD patients.[27,28] Physical activity, such as walking in and out of doors, might concomitantly give the patients visual stimulation. Because SPMT uses a picture of a living room familiar to the elderly, the degree of visual stimulation in daily living might have affected the results of SPMT. Thus, physical activity and the capacity to remember a visual scene might have shown a correlation. We suggest that increasing the amount of physical activity might result in beneficial biological changes to the brain structure and function or in beneficial physical changes to mobility and body composition. Therefore, increasing the step counts in a day could help to maintain and improve the cognitive function of older adults with mild cognitive disorder.

In the normal walking group with mild cognitive disorder, we found no significant association between memory function and the other variables. Other studies also show a lack of association of cognitive function with the amount of physical activity in older adults with similar ages to those in the present study.[7,29] Therefore, we need to consider effective strategies for patients with higher physical function.

There were several limitations of the present study. First, our limited sample size might introduce some error of inference, reduce the power of the analysis and limit generalization. Second, the present study was a cross-sectional study. Therefore, the relationship between the memory function and physical activity needs further investigation, such as an increase in physical activity levels for a certain period can improve the scores of SPMT, MMSE and other cognitive tests. Third, the definition of the normal walking group depended only on walking time in the present study. We might have to measure a frailty index, such as the Edmonton frail scale[30] or the Fried frailty assessment,[31] if we can extend our results to the frail elderly. Fourth, we used the SPMT, a visual memory test, as a cognitive test. However, we did not measure other factors, such as visual function and attention, that might have affected the present results. Therefore, it might be impossible to evaluate properly the relationship between physical activity and memory function. Thus, the results of the present study should be interpreted with caution.

In conclusion, the present study shows that cognition is associated with higher levels of physical activity only in patients with mild cognitive disorder who showed a slow walking speed. Our results suggest that increasing the amount of physical activity might prevent the deterioration of cognitive function. Further investigation, such as a prospective study, is required to confirm our results.

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Disclosure statement

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Original Article

Arterial Stiffness Determined According to the Cardio-Ankle Vascular Index (CAVI) is Associated with Mild Cognitive Decline in Community-Dwelling Elderly Subjects

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

[1]Department of Physical Therapy, Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan
[2]Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Aims: The purpose of this study was to determine the cross-sectional relationship between the cognitive function and cardio-ankle vascular index (CAVI) in Japanese community-dwelling elderly subjects.

Methods: A total of 179 Japanese community-dwelling elderly subjects were recruited for this study. The age, height, weight, gender and past medical history (cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia) of each participant was recorded. In addition, the degree of arterial stiffness was determined according to the CAVI, while the cognitive function was assessed using the Mini-Mental State Examination (MMSE). After dividing the cohort into two groups according to the MMSE score (≤ 26, >26), we used a multiple regression analysis to assign the level of the cognitive function as a dependent variable.

Results: The data were statistically analyzed for the 174 participants (84 men and 90 women) who completed the data collection process without omissions. A multivariate logistic regression analysis showed that a higher weight (Odds Ratio [OR]: 1.05, 95% Confidence Interval [95% CI]: 1.00-1.11, $p=0.03$), male gender (OR: 3.13, 95% CI: 1.05-9.34, $p=0.04$) and lower CAVI (OR: 0.68, 95% CI: 0.48-0.96, $p=0.03$) were significantly correlated with a higher MMSE score. We also found significant correlations between the MMSE and weight (OR: 1.11, 95% CI: 1.03-1.19, $p=0.01$) and CAVI (OR: 0.57, 95% CI: 0.33-0.98, $p=0.04$) in elderly men only using a gender-specific analysis.

Conclusions: We found that the elderly subjects with a high CAVI exhibited a worse cognitive function even after adjusting for age, height, weight and gender. This finding therefore indicates the usefulness of the CAVI in the early detection of dementia.

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Key words: Cognitive function, Arterial stiffness, Community-dwelling elderly

Introduction

Dementia can drastically influence daily life and is currently one of the most common diseases in the elderly. The World Health Organization estimated that 35 million people worldwide suffered from dementia in 2012, and people with dementia have been shown to be frail due to their poor mobility and body composition. Approximately 48% of people with Alzheimer's disease (AD), the most common form of dementia, are estimated to live in Asia, and this percentage will grow to 59% by 2050[1)]. The transitional stage between normal aging and AD is called mild cognitive impairment (MCI), and more than half of MCI cases progress to dementia within five years[2, 3)]. Therefore, preventing cognitive decline is crucial.

Address for correspondence: Hidenori Arai, Department of Human Health Sciences, Kyoto University Graduate School of Medicine, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
E-mail: harai@kuhp.kyoto-u.ac.jp
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Identifying risk factors that can predict cognitive decline will help to prevent such decline. Although many studies have attempted to address this issue, evidence supporting the role of modifiable risk factors remains limited[4-6]. Meanwhile, vascular risk factors have received attention in recent years[7, 8]. High blood pressure[9], dyslipidemia[9], obesity[10] and diabetes mellitus[10] have been proposed to be risk factors for cognitive decline. Among these factors, arterial stiffness, specifically, is a comparatively easy-to-modify risk factor. It has been reported that systemic atherosclerosis plays a role in the cognitive function and is directly linked to the pathology of Alzheimer's disease[11]. In one European study, it was found that functional changes in the arterial system may be involved in the onset of dementia[12].

Arterial stiffness is one of the most easily measured vascular risk factors in community-dwelling elderly subjects due to its noninvasive nature. The brachial-ankle pulse wave velocity (baPWV) is widely used for this purpose. In a cross-sectional study of 370 middle-aged Korean participants, the baPWV was found to be significantly correlated with the cognitive function[13]. In addition, in a Japanese study, a high baPWV was shown to be a risk factor for a poor cognitive function in 352 community-dwelling elderly subjects[5]. However, there are several problems associated with the measurement of baPWV, as the value of the parameter depends on the blood pressure (BP) at the time of measurement[14]. Therefore, it is difficult to evaluate arterial stiffness in patients treated with antihypertensive medications or those with masked hypertension. In contrast, the cardio-ankle vascular index (CAVI) is a novel BP-independent parameter of arterial stiffness[15, 16]. This parameter is adjusted for the PWV according to the systolic and diastolic blood pressure and blood density and is therefore a theoretically BP-independent index. Clinicians can ensure the validity of arterial stiffness measurements using this parameter. However, no studies have so far evaluated the relationship between the cognitive function and arterial stiffness using the CAVI. In addition, few studies have evaluated this relationship in community-dwelling elderly patients.

The purpose of this study, therefore, was to determine the cross-sectional relationship between the cognitive function and the CAVI in Japanese community-dwelling elderly subjects.

Methods

Participants

Participants were recruited for this study through local press requesting healthy community-dwelling volunteers, resulting in a total of 179 Japanese participants 65 years of age or older and currently living in the community. Interviews were then performed to exclude participants based on the following exclusion criteria: severe cardiac, pulmonary or musculoskeletal disorders; comorbidities associated with a greater risk of falls, such as Parkinson's disease and stroke; and the use of psychotropic drugs. Written informed consent was obtained from each participant for the trial in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995. The study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

Measurements

Demographic Data

Age, height, weight, gender, past medical history (cardiovascular disease, hypertension, diabetes mellitus, 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 and university) were recorded as demographic data. All data were collected at the onset of data collection. We surveyed age and gender from the participant directly and measured the height and weight using standardized height and weight scales.

CAVI

The CAVI was determined using the VaSera-1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan). The procedure has been detailed previously[15, 16]. Briefly, after the participants had rested for five minutes in a sitting position, they were placed in a supine position. Then, cuffs were wrapped around both brachia and ankles to detect the brachial and ankle pulse waves. Electrocardiograms and heart sounds were monitored. The PWV from the heart to the ankle was calculated by measuring the length from the aortic valve to the ankle and dividing by time, which was determined according to the heart sounds and the rise of the brachial and ankle pulse waves. Blood pressure was also measured at the brachial artery. Finally, scale conversion was performed using the following formula:

$$CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2\} + b \text{ (no unit)}$$

ρ: blood density, Ps: systolic blood pressure, Pd; diastolic blood pressure, ΔP: Ps-Pd, PWV: pulse wave velocity, a and b: constants.

The validity, reproducibility and blood pressure-independent nature of this experiment have been well

Table 1. Differences in each variable between the MMSE high/low score groups

	All (n=174)			Men (n=84)			Women (n=90)		
	Low MMSE (≤26) n=56	High MMSE (>26) n=118	p	Low MMSE (≤26) n=30	High MMSE (>26) n=54	p	Low MMSE (≤26) n=26	High MMSE (>26) n=64	p
MMSE	24.6±1.3	28.7±1.1	<0.01**	24.8±1.0	28.8±1.1	<0.01**	24.5±1.5	28.6±1.1	<0.01**
Age, year	74.2±4.6	73.4±4.3	0.26	73.8±5.2	73.8±4.2	0.94	74.5±3.7	73.0±4.4	0.12
Height, cm	155.5±8.7	156.1±8.1	0.65	162.2±5.3	162.8±6.0	0.64	147.8±4.6	150.5±4.7	0.02*
Weight, kg	54.0±8.8	57.3±9.7	0.03*	57.6±9.3	63.6±8.7	0.01*	49.9±6.1	52.0±7.1	0.19
Gender, male	30 (53.6%)	54 (45.8%)	0.21	–	–	–	–	–	–
Mean CAVI	9.61±1.30	9.13±1.16	0.02*	9.97±1.52	9.38±0.87	0.03*	9.19±0.85	9.03±0.93	0.47
Cardiovascular disease	8 (14.3%)	8 (6.8%)	0.16	6 (20.0%)	4 (7.4%)	0.16	2 (7.7%)	4 (6.3%)	1.00
Hypertension	21 (37.5%)	50 (42.4%)	0.62	13 (43.3%)	23 (42.6%)	1.00	8 (30.8%)	27 (42.2%)	0.35
Diabetes mellitus	6 (10.7%)	14 (11.9%)	1.00	2 (6.7%)	8 (14.9%)	0.47	4 (15.4%)	6 (9.4%)	0.47
Hyperlipidemia	8 (14.3%)	18 (15.3%)	1.00	4 (13.3%)	5 (9.6%)	0.72	4 (15.4%)	13 (20.3%)	0.77
Brinkman index	0 (0-762.5)	0 (0-356.3)	0.70	0 (0-787.5)	0 (0-637.5)	0.50	0 (0-612.5)	0 (0-2.25)	0.23
Educational background			n.s.			n.s.			n.s.
Elementary school	2 (3.6%)	1 (0.8%)		2 (6.7%)	1 (1.9%)		0 (0.0%)	0 (0.0%)	
Junior high school	26 (46.4%)	28 (23.7%)		16 (53.3%)	15 (27.8%)		10 (38.5%)	13 (20.3%)	
High school	26 (46.4%)	69 (58.5%)		11 (36.7%)	30 (55.6%)		15 (57.7%)	39 (60.9%)	
Career college	0 (0.0%)	7 (5.9%)		0 (0.0%)	1 (1.9%)		0 (0.0%)	6 (9.4%)	
University	2 (3.6%)	13 (11.0%)		1 (3.3%)	7 (13.0%)		1 (3.8%)	6 (9.4%)	

Mean CAVI = the mean value of the right and left CAVI scores; Mean ± SD values are shown for age, height, weight and mean CAVI; n (%) is shown for gender, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia and educational background; Median (25% quartile-75% quartile) is shown for the Brinkman index; n.s.: not significant.
*: $p<0.05$, **: $p<0.01$

documented by several studies[15, 16]. The measurements were obtained once, and the mean value of the right and left CAVI scores for each patient was used for the analysis[17].

Cognitive Function Measurement

The cognitive function was assessed using the Mini-Mental State Examination (MMSE)[18]. The MMSE is a short screening test that consists of five areas of possible cognitive impairment: orientation; registration; attention and calculation; and language. The scores ranged from 0 to 30, with a higher score indicating a better cognitive performance. We tested the participants individually based on the generalized method and used 26/27 as the cutoff score, according to Spering CC *et al.*[19].

Statistical Analysis

The participants were divided into two groups based on the MMSE score: ≤26 or >26. This cutoff of 26/27 has been shown to be a better balanced score of estimates of diagnostic accuracy for educated individuals[19]. Because our participants were community-dwelling and highly educated and all lived independently, we adopted this 26/27 cutoff.

We statistically analyzed the differences between the two groups using the unpaired t-test for age, height, weight and the mean CAVI on both sides, 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 multivariate logistic regression model was performed to investigate whether the CAVI was independently associated with the MMSE score. We assigned a high MMSE score as the dependent variable adjusted for age, height, weight and gender. A value of $p<0.05$ was considered to be statistically significant for all analyses.

Results

In total, there were 179 elderly participants (85 men and 94 women) in this study. Of the 179 patients, 84 men and 90 women completed the data collection without omissions, for a total of 174 data points.

We assigned 56 elderly subjects (30 men and 26 women) into the low MMSE group and 118 elderly subjects (54 men and 64 women) into the high MMSE group. **Table 1** shows the differences in each variable between the two groups. While there were no significant differences in age, height, gender or past medical history, a higher weight was associated with a higher MMSE score ($p=0.03$). In addition, the low MMSE group had significantly higher CAVI values than the high MMSE group (**Fig. 1**, the low group: 9.61 ± 1.30, the high group: 9.13 ± 1.16, $p=0.02$).

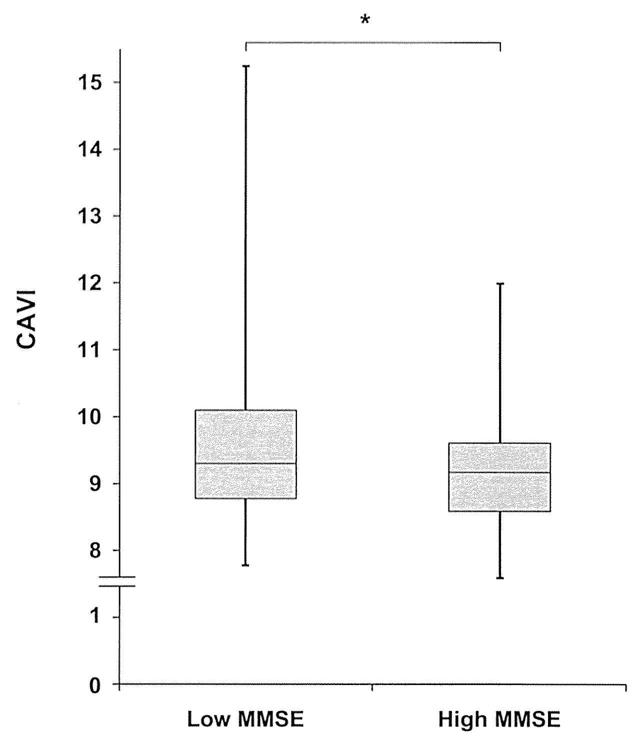

Fig. 1. Differences in the mean CAVI values between the high and low MMSE groups.

We statistically analyzed the differences between the two groups using the unpaired t-test for the mean CAVI on both sides.
*: $p=0.02$

The multivariate logistic regression analysis showed that a higher weight (odds ratio [OR]: 1.05, 95% confidence interval [95% CI]: 1.00-1.11, $p=0.03$), female gender (OR: 3.13, 95% CI: 1.05-9.34, $p=0.04$) and lower CAVI (OR: 0.68, 95% CI: 0.48-0.96, $p=0.03$) were significantly correlated with a higher MMSE score (**Table 2**), indicating that elderly subjects with a higher CAVI have a lower cognitive function, even after adjustment for age, height, weight and gender. In the multivariate logistic regression analysis of each gender, we found a significant correlation between the MMSE score and weight (OR: 1.11, 95% CI: 1.03-1.19, $p=0.01$) and CAVI (OR: 0.57, 95% CI: 0.33-0.98, $p=0.04$) in the elderly men only (**Table 2**).

Discussion

We analyzed the relationship between the cogni-

Table 2. Multivariate logistic regression model to determine the association with a high MMSE score

	All (n=174)		Male (n=84)		Female (n=90)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, year	1.00 (0.92-1.09)	1.00	1.08 (0.95-1.12)	0.25	0.96 (0.85-1.09)	0.51
Height, cm	1.04 (0.97-1.12)	0.27	0.97 (0.88-1.08)	0.60	1.13 (1.00-1.28)	0.05
Weight, kg	1.05 (1.00-1.11)	0.03*	1.11 (1.03-1.19)	0.01*	1.01 (0.94-1.09)	0.82
Gender	-	0.04*	-	-	-	-
men	1 [Reference]	-	-	-	-	-
women	3.13 (1.05-9.34)	-	-	-	-	-
Mean CAVI	0.68 (0.48-0.96)	0.03*	0.57 (0.33-0.98)	0.04*	0.73 (0.44-1.23)	0.24

Mean CAVI = the mean value of the right and left CAVI scores; OR = Odds Ratio, 95% CI = 95% confidence interval.
*: $p<0.05$

tive function and the CAVI in Japanese community-dwelling elderly subjects. In this study, we found a negative correlation between the CAVI and the cognitive function, even after adjusting for age, height, weight and gender. Many studies have demonstrated a relationship between arterial stiffness and a decreased cognitive function[5, 12, 13]; however, there are no reports using the novel index of arterial stiffness, the CAVI, in community-dwelling elderly subjects.

Several mechanisms may potentially explain why arterial stiffness is associated with the cognitive function. First, the development of dementia is associated with organic brain lesions, such as ischemic lesions and white matter abnormalities[20]. Because stiff blood vessels lose their capacity to buffer pulse pressure, the pulsatile flow is increased, causing damage to the fragile small vessels in the brain[21]. This phenomenon has been demonstrated in animal studies, in which locally induced isolated alterations in pressure pulsatility have been shown to have major effects on the cerebral microvascular structure and function[22]. Pase *et al.*[23] reported that the augmented pressure caused by arterial stiffness independently predicts the cognitive function. In addition, some studies have shown evidence that asymptomatic cerebral microvascular lesions caused by augmented pressure are associated with an increased risk of AD[24, 25]. Our major finding indicating a correlation between the CAVI and the cognitive function is consistent with the results of these previous reports. However, this relationship was found only in elderly men in a gender-specific analysis; therefore, cognition may be more strongly affected by arterial stiffness in men than in women. Larger studies should address the effects of the CAVI on the cognitive function in elderly women.

The peculiarity of the CAVI is that it indicates BP-independent arterial stiffness, unlike the baPWV. Therefore, it is conceivable that the CAVI is a useful parameter in patients who are subject to variation in BP at various times due to masked hypertension or the use of antihypertensive medications. Masked hypertension is defined as a normal BP in the clinic or office (<140/90 mmHg) with an elevated BP out of the clinic (ambulatory daytime BP or home BP> 135/85 mmHg)[26]. This phenomenon can occur in up to 8-38% of the general population and is observed at all ages[27]. In addition, antihypertensive medication use has recently increased. Men have seen the greatest increase in antihypertensive medication use (47.5%, 1988-1994 versus 57.9%, 1999-2002) among hypertensive adults[28]. Moreover, Takaki *et al.* demonstrated the superiority of the CAVI to the baPWV in measurement sensitivity[29]. They found that the CAVI was better correlated with the parameters of left ventricular diastolic indices, low-density lipoprotein cholesterol and angina pectoris than the baPWV.

When evaluating arterial stiffness in community-dwelling elderly subjects, the most important properties of an instrument for assessment are ease of measurement and validation. The clinical advantage of our study is the indication of a significant relationship between arterial stiffness and the cognitive function in community-dwelling elderly subjects based on the use of a better arterial stiffness index, the CAVI. In order to early detect cognitive decline, clinicians should conduct screening exams for community-dwelling elderly patients. This is why we adopted the 26/27 cutoff point for our patients, all of whom lived independently and were highly educated. This index has the potential to be used to detect cognitive decline earlier in community-dwelling elderly subjects due to its validity and noninvasive nature.

This study is associated with several limitations. First, because this study is a cross-sectional study, the cause-effect relationship between the CAVI and the cognitive function is unknown. Second, we were unable to perform neuroimaging procedures. The participants may have had asymptomatic brain lesions that we could not fully investigate. In addition, we did not distinguish between the types of dementia. Different types of dementia may affect the results. Further investigations, such as prospective studies, are required to confirm the findings of the present study.

Conclusion

This is the first study to determine the relationship between the cognitive function and the CAVI in community-dwelling elderly subjects. We found a significant relationship between a higher CAVI and mild cognitive decline. This finding indicates the usefulness of the CAVI in the early detection of dementia.

Conflicts of Interest

None.

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Chronic kidney disease (CKD) is an independent risk factor for long-term care insurance (LTCI) need certification among older Japanese adults: A two-year prospective cohort study

Minoru Yamada *, Hidenori Arai, Shu Nishiguchi, Yuu Kajiwara, Kazuya Yoshimura, Takuya Sonoda, Taiki Yukutake, Hiroki Kayama, Takanori Tanigawa, Tomoki Aoyama

Department of Human Health Sciences, Kyoto University Graduate School of Medicine, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

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ABSTRACT

CKD is associated with impairments in health status, physical function, and frailty. The aim of the current prospective cohort study was to determine whether CKD predicted new LTCI need certification among community-dwelling older Japanese adults. This was a prospective cohort study. We analyzed the cohort data from a prospective study, The Japan Multicenter Aging Cohort for Care Prevention (J-MACC). We followed 8063 elderly adults for 2 years, and we analyzed the relationship between CKD and LTCI need. The outcome studied was new certification for LTCI service need during a 2-year period. We measured serum creatinine (the estimated glomerular filtration rate; eGFR), serum albumin, frailty checklist scores, and body mass index. During the 2-year follow-up, 536 subjects (6.6%) were newly certified as needing LTCI services. We stratified the cohort according to eGFR quartile and performed multivariate analyses using an eGFR value of 71.4–83.6 ml/min/1.73 m^2 as a reference. We found that subjects with eGFR values <60.0 ml/min/1.73 m^2 had a significantly elevated risk of LTCI service need (adjusted hazard ratio: 1.44 [95% CI 1.12–1.86]). Our results indicate that CKD is independently associated with new LTCI service need certification and is an important marker of frailty in older adults.

1. Introduction

Frailty in older adults is a serious problem in countries with aging populations, such as Japan. In general, frailty is defined as a vulnerable state that places older adults at high risk of adverse health outcomes, such as falls, hospitalization, and mortality (Wiswell et al., 2001).

Age is a major risk factor for CKD, which is a growing health problem in Japan. The prevalence of CKD in the adult Japanese population is estimated to be 13% (Imai et al., 2009). In addition, the number of patients with end-stage renal disease (ESRD) has increased by approximately 7% per year in Japan (Akiba et al., 2000). CKD is associated with impairments in health status and physical function, as well as frailty (Brogan, Haber, & Kutner, 2000; Kurella et al., 2004; Kurella, Yaffe, Shlipak, Wenger, & Chertow, 2005). CKD is also associated with oxidative stress, chronic inflammation, insulin resistance, vascular calcification, and osteoporosis (Ensrud et al., 2007; Landau et al., 2011; Shanahan, 2005). Furthermore, a decreased creatinine clearance <60 ml/min/1.73 m^2 has been shown to predict incident falls among community-dwelling older women (Gallagher, Rapuri, & Smith, 2007). Thus, CKD poses a considerable medical and public health challenge, particularly in the older population.

Japan implemented a LTCI system in April 2000 to help manage a rapidly aging population. Prior to 2000, long-term care services were provided under a tax-based social welfare system for seniors with limited economic resources and family support (Campbell & Ikegami, 2000). However, since the implementation of LTCI, the services of this program have been provided to elderly adults who are certified as requiring support or care according to their care needs and certification assessment (Tsutsui & Muramatsu, 2005).

The aim of the current prospective cohort study, therefore, was to determine whether CKD was a risk factor for LTCI need among community-dwelling older Japanese adults.

2. Methods

2.1. Subjects

We analyzed the cohort data from a prospective study entitled J-MACC. This cohort study investigated the factors associated with LTCI need in community-dwelling Japanese

* Corresponding author. Tel.: +81 75 751 3964; fax: +81 75 751 3909.
E-mail address: yamada@hs.med.kyoto-u.ac.jp (M. Yamada).

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adults aged 65 years or older. We recruited community-dwelling older adults who were independent in terms of the activities of daily living (ADL) in 2009. The exclusion criteria were older adults who were already ADL-dependent and were eligible to receive benefits from LTCI services. The subjects were followed prospectively for 2 years. During the follow-up period, 226 subjects died or moved; thus, we analyzed 8063 elderly adults. This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

2.2. Serum creatinine and albumin

The serum creatinine and albumin levels of the subjects were measured. The estimated glomerular filtration rate (eGFR) was calculated using a formula reported by Matsuo et al. (2009): eGFR (mL/min/1.73 m^2) = 194 × Scr$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female). This equation originated from the MDRD study group (Coresh, Astor, Greene, Eknoyan, & Levey, 2003) arranged for Japanese individuals, and it is recommended by the Japanese Society of Nephrology. The study cohort was divided into 4 groups according to serum albumin and eGFR quartiles.

2.3. Frailty checklist

The frailty checklist included simple yes/no questions concerning lifestyle (questions 1–5), motor abilities (questions 6–10), nutrition (questions 11–12), oral functions (questions 13–15), seclusion (questions 16–17), forgetfulness (questions 18–20), and emotions (questions 21–25) (Table 1). The total score on the frailty checklist is useful for predicting the risk of being newly certified as needing LTCI services (Coresh et al., 2003). Furthermore, physical exercise is an effective means of improving the total score on the frailty checklist (Imai et al., 2007).

2.4. Body mass index

The patients' height and weight were measured to calculate their body mass index (BMI).

2.5. Outcome measure

The outcome measure was new LTCI service need certification over a 2-year period. The selection process for classifying dependent older adults first involves a questionnaire that evaluates the person's current mental and physical condition (74 items), which is analyzed using a computerized algorithm. A long-term care approval board reaches a final decision based on the algorithm-aided analysis of the questionnaire, a doctor's recommendation, and a home visit report. Individuals who become certified as dependent older adults are subdivided into seven levels (support levels 1 and 2 and care levels 1–5), depending on their conditions. They are provided home and community-based or institutional services according to their care needs. Individuals who are not eligible for long-term care or support care may utilize preventive care services.

2.6. Statistical analysis

The baseline characteristics of the subjects who were certified or non-certified as needing LTCI services were compared. Differences in the demographic variables between the 2 groups were analyzed using Student's *t*-test or a chi-square test. In addition, differences in the demographic variables among the 4 groups stratified by eGFR quartile were examined using an analysis of variance (ANOVA) and a post hoc test. Kaplan-Meier survival curves were calculated for the group newly determined to need LTCI services and were stratified by eGFR quartile. Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of the relationships between

Table 1
The frailty checklist used in Japan.

Domain	Question	Items	Yes	No
Lifestyle	1	Do you ride the bus or train alone?	0	1
	2	Do you buy household goods for everyday use?	0	1
	3	Do you withdraw and deposit savings?	0	1
	4	Do you visit your friends' homes?	0	1
	5	Do you give advice to family and friends?	0	1
Motor abilities	6	Can you climb stairs without holding onto a handrail or the wall?	0	1
	7	Can get up from a chair without grabbing something?	0	1
	8	Are you able to keep walking for about 15 min?	0	1
	9	Have you fallen in the past year?	1	0
	10	Are you very worried about falling?	1	0
Nutrition	11	Have you ever lost more than 2–3 kg of weight in a 6-month period?	1	0
	12	BMI is less than 18.5.	1	0
Oral function	13	I cannot eat hard foods as well as 6 months ago.	1	0
	14	Have you ever choked on tea or soups?	1	0
	15	Are you concerned with being thirsty?	1	0
Seclusion	16	Do you leave your home at least once a week?	0	1
	17	Compared to last year, has the number of times you go out decreased?	1	0
Forgetfulness	18	Are you told that you are forgetful or you always tell me the same thing?	1	0
	19	Do you look up phone numbers and make phone calls yourself?	0	1
	20	Do you sometimes forget the date and month?	1	0
Emotions	21	(In the past 2 weeks) I do not feel fulfillment in my daily life.	1	0
	22	(In the past 2 weeks) The activities I used to enjoy are no longer enjoyable.	1	0
	23	(In the past 2 weeks) The activities I used to carry out with ease have become troublesome.	1	0
	24	(In the past 2 weeks) I do not think I am a useful person.	1	0
	25	(In the past 2 weeks) I feel tired for no reason.	1	0

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Table 2
Baseline characteristics of the study subjects in both groups.

	Certified for LTCI requirement ($n = 536$)			Non-certified for LTCI requirement ($n = 7527$)			
	Mean	SD	Min–max	Mean	SD	Min–max	*P*-Value
Age (years)	80.8	7.4	66–100	76.7	6.5	65–102	<0.001
Gender (female)	332 (61.9%)	4405 (58.5%)	0.043				
BMI (kg/m^2)	22.4	3.5	13.8–35.8	22.8	3.2	12.7–39.8	0.073
Frailty checklist (points)	6.5	4.9	0–23	4.3	4.0	0–24	<0.001
Serum albumin (g/dl)	4.2	0.3	3.2–5.0	4.3	0.3	2.6–5.4	<0.001
eGFR (ml/min/1.73 m^2)	68.5	20.7	22.2–121.3	71.4	17.2	20.3–123.8	<0.001

eGFR quartile and the time to new LTCI service need certification in univariate and multivariate analyses. Multivariate analyses were performed for each covariate and were adjusted for gender, BMI, frailty checklist score, and serum albumin level, factors that are known to be associated with frailty (Levey et al., 2006; Tomata et al., 2011; Yamada, Arai, Sonoda, & Aoyama, 2012). Survival time was defined as the time between enrollment (the date of the baseline measurements) and either the new LTCI service need certification or the end of the follow-up period (March 31, 2011). The data were analyzed using PASW (Windows version 18.0, SPSS, Inc., Chicago, IL). A P value <0.05 was considered statistically significant for all the analyses.

3. Results

During the 2-year follow-up, 536 subjects (6.6%) became newly certified as needing LTCI services (Table 2). Those who were certified for LTCI need were significantly older (80.8 ± 7.4 vs. 76.7 ± 6.5, $P < 0.001$) and had higher frailty checklist scores (6.5 ± 4.9 vs. 4.3 ± 4.0, $P < 0.001$), lower serum albumin levels (4.2 ± 0.3 vs. 4.3 ± 0.3, $P < 0.001$), and lower eGFR values (68.5 ± 20.7 vs. 71.4 ± 17.2, $P < 0.001$) than those who were not certified. More women than men became certified in this cohort (female: 61.6% vs. 58.5%, $P = 0.043$). However, the BMIs were not different between the two groups ($P = 0.073$) (Table 2). We also examined whether eGFR was associated with BMI, frailty checklist score, or serum albumin level. We found that the subjects with eGFR < 60.0 ml/min/1.73 m^2 were significantly older and had lower BMIs, higher frailty checklist scores, and lower serum albumin levels ($P < 0.05$) (Table 3).

Next, we examined the relationship between each variable and new LTCI need certification. The subjects with BMIs <20.5 exhibited a significantly elevated risk of LTCI service need according to multivariate analyses using a BMI of 22.7–24.7 as the reference (adjusted hazard ratio: 1.41 [95% CI 1.11–1.78]) (Table 4). The mean BMI was 22.7 ± 3.3, with a range from 12.7 to 39.8; 1975 participants (24.5%) had BMIs <20.5. The subjects with frailty checklist scores >6 had a significantly elevated risk of LTCI service need according to multivariate analyses using frailty checklist scores <2 as the reference (adjusted hazard ratio: 2.24 [95% CI 1.73–2.90]) (Table 4). The mean frailty checklist score was 4.5 ± 4.1, with a range from 0 to 24; 2042 participants (25.3%) had frailty checklist scores >6. Participants with serum albumin levels <4.1 g/dl tended to exhibit an elevated risk of LTCI service need according to multivariate analyses using a serum albumin level >4.4 g/dl as the reference (adjusted hazard ratio: 1.25 [95% CI 0.97–1.62]). However, the univariate analysis indicated that subjects with serum albumin levels <4.1 g/dl had an elevated risk of LTCI service need (Table 4). The mean serum albumin level was 4.2 ± 0.3 g/dl, with a range from 2.6 to 5.4; 1722 participants (21.3%) had serum albumin levels <4.1 g/dl.

Fig. 1 shows the Kaplan-Meier survival curves according to new LTCI service need certification, with the subjects stratified into 4 groups according to eGFR quartile. Individuals with eGFR values <60.0 ml/min/1.73 m^2 had a significantly elevated risk of LTCI service need according to multivariate analyses using an eGFR value of 71.4–83.6 ml/min/1.73 m^2 as the reference (adjusted hazard ratio: 1.44 [95% CI 1.12–1.86]) (Table 4). The mean eGFR was 71.2 ± 17.4 ml/min/1.73 m^2, with a range from 20.3 to 123.8 ml/min/1.73 m^2; 1963 participants (24.3%) had eGFR values <60 ml/min/1.73 m^2.

4. Discussion

In this study, we found that approximately 25% of adults aged 65 years or over had eGFR values <60 ml/min/1.73 m^2, which indicates that CKD is common among older Japanese adults. The multivariate analyses demonstrated eGFR values <60.0 ml/min/1.73 m^2 were independently associated with new certifications for LTCI service need. Thus, our data indicate that CKD is a critical marker of frailty in older adults.

According to the multivariate analyses, lower BMIs (less than 20.5), and higher frailty checklist scores (more than 6) were associated with certification for LTCI service need. These results are consistent with those of previous studies (Levey et al., 2006; Tomata et al., 2011; Yamada et al., 2012), which revealed that the subjects with the lowest BMIs had an elevated risk of requiring care and that frailty checklist scores were strongly associated with new LTCI service need certifications (Levey et al., 2006). Thus, it is important to assess nutrition, cognitive function, mood, and ADL for care prevention, and the frailty checklist includes these items.

In terms of nutrition, however, our study failed to demonstrate that serum albumin levels were significantly associated with new LTCI service need certification after adjusting for other frailty-related factors, although the univariate analysis demonstrated that

Table 3
Demographic differences according to eGFR quartile.

	eGFR (ml/min/1.73 m^2)									
	Q1: <60.0		Q2: 60.0–71.3		Q3: 71.4–83.6		Q4: >83.6		*P*-value	Post hoc
Gender (female)	1122 (57.2%)		1153 (54.2%)		1066 (54.2%)		1429 (71.2%)		<0.001	Q2,3 < Q1 < Q4
BMI (kg/m^2)	23.1	3.3	22.7	3.2	22.9	3.1	22.4	3.4	<0.001	Q1 > Q4 > Q2,3
Frailty checklist (points)	5.2	4.6	4.0	3.9	3.2	3.6	3.9	3.8	<0.001	Q1 > Q2 > Q4 > Q3
Serum albumin (g/dl)	4.11	0.27	4.16	0.26	4.21	0.25	4.21	0.26	<0.001	Q1 < Q2 < Q3,4

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Table 4
Predictors of new LTCI service need certification during a 2-year follow-up period.

		Certified for LTCI requirement		Non-certified for LTCI requirement		Univariate analysis			Multivariate analysis		
						HR	95%CI	P-value	HR	95%CI	P-value
Gender	Female	332	7.0%	4405	93.0%	ref			ref		
	Male	204	6.1%	3122	93.9%	0.88	0.76–1.03	0.11	0.98	0.83–1.17	0.86
BMI	Q1: <20.5	179	9.1%	1796	90.9%	1.53	1.21–1.92	<0.01	1.41	1.11–1.79	<0.01
	Q2: 20.5–22.6	120	5.9%	1915	94.1%	1.00	0.78–1.29	1.00	1.01	0.78–1.30	0.92
	Q3: 22.7–24.7	121	6.0%	1892	94.0%	ref			ref	-	
	Q4: >24.7	140	6.9%	1900	93.1%	1.13	0.88–1.44	0.35	1.09	0.85–1.39	0.51
Frailty checklist	Q1: <2	91	4.1%	2106	95.9%	ref			ref		
	Q2: 2–3	105	5.5%	1802	94.5%	1.36	1.03–1.80	0.03	1.30	1.30–1.73	0.13
	Q3: 4–6	117	6.1%	1800	93.9%	1.51	1.15–1.99	<0.01	1.41	1.06–1.86	0.01
	Q4: >6	247	12.1%	1795	87.9%	3.04	2.38–3.87	<0.01	2.63	2.05–3.39	<0.01
Serum albumin	Q1: <4.1	167	9.7%	1555	90.3%	1.75	1.36–2.24	<0.01	1.36	1.05–1.75	0.02
	Q2: 4.1–4.2	150	6.7%	2076	93.3%	1.19	0.92–1.53	0.18	1.04	0.81–1.35	0.75
	Q3: 4.3–4.4	140	6.0%	2200	94.0%	1.09	0.84–1.40	0.52	1.01	0.78–1.31	0.93
	Q4: >4.4	101	5.6%	1694	94.4%	ref			ref		
eGFR	Q1: <60.0	191	9.7%	1772	90.3%	1.99	1.55–2.54	<0.01	1.63	1.26–2.09	<0.01
	Q2: 60.0–71.3	142	6.7%	1983	93.3%	1.37	1.06–1.77	0.02	1.25	0.96–1.62	0.10
	Q3: 71.4–83.6	97	4.9%	1871	95.1%	ref			ref		
	Q4: >83.6	128	6.4%	1879	93.6%	1.29	0.99–1.68	0.06	1.17	0.89–1.53	0.26

The multivariate analysis was adjusted for gender, BMI, frailty checklist score, and serum albumin level.

a significantly larger number of subjects in the first quartile were certified as needing LTCI. Furthermore, previous studies have indicated that lower serum albumin levels are associated with future functional decline in older adults (Kalyani et al., 2012; Kane, Shamliyan, Talley, & Pacala, 2012). We assume that this result was caused by our study lacking sufficient power to demonstrate a contribution of low serum albumin to new LTCI service need certifications and by the small number of subjects with malnutrition in this cohort. Nonetheless, CKD was found to be significantly associated with new LTCI service need certification. Therefore, it should be noted that CKD may independently predict new LTCI service need certification in older adults.

We found that the subjects with the highest eGFR values (4th quartile) tended to have a higher risk of new LTCI service need certification, lower BMIs, and higher checklist scores than those in the 3rd quartile, although this difference was not statistically significant. Because eGFR is calculated using serum creatinine levels, a higher eGFR may indicate lower muscle mass, especially in

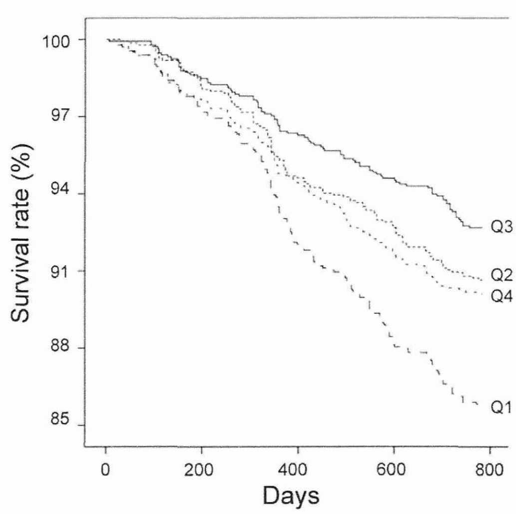

Fig. 1. Kaplan-Meier survival curves for new LTCI service need are shown for 4 groups according to eGFR quartile.

older adults. Therefore, it should be noted that older adults with elevated eGFR values may be frail. Further research is required to address the role of eGFR in frailty.

Malnutrition is known to be associated with frailty. Several studies have suggested that vitamin D deficiencies are common among patients with CKD (Reuben et al., 2002; Zuliani et al., 2001). Both vitamin D2 and D3 are first converted to 25-hydroxyvitamin D by hepatic vitamin D-25-hydroxylase and are then converted to the active form, 1,25-hydroxyvitamin D, by renal 1α-hydroxylase (Zuliani et al., 2001). Reduced activation of vitamin D has been associated with the development of hypertension, left ventricular hypertrophy, heart failure, and vascular calcification (Holick, 2007). In addition, vitamin D deficiency has been associated with sarcopenia, falls, fractures, and dementia (Bischoff-Ferrari, 2012; Chonchol, Kendrick, & Targher, 2011; Cozzolino & Ronco, 2011). Therefore, we hypothesized that CKD was a risk factor for new LTCI service need certification.

Two limitations of this study warrant mention. First, we did not collect information about the subjects' comorbidities. Therefore, the effects of comorbidities on the risk of new certifications for LTCI service need remain unclear. Second, the study participants may have had a greater motivation and interest in health issues than the non-participants. Therefore, it is possible that the non-participants had a higher prevalence of CKD and frailty.

In conclusion, this is the first study to demonstrate that CKD is independently associated with new certifications for LTCI service need. In addition, a relatively high percentage of the subjects had moderate to severe CKD (eGFR <60 ml/min/1.73 m^2). Intervention studies are needed to explore whether treating CKD may delay or prevent new certifications for LTCI service need among older adults.

Conflicts of interest

None of the authors have conflicts of interest or financial disclosures.

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