Furthermore, well-recognized health screening tools in the health sciences literature were used to better identify the participants' general health characteristics: MMSE, for cognitive function in older adults;[4] MNA, for a rapid nutritional assessment;[10] GDS, for psychological characteristics;[11] and LSA, related to seclusion and decline in ADL and physical function.[12] QOL was verified by the Short-Form 8 items (SF-8), which is an abbreviated version of SF-36 and consists of eight questions (domains) regarding general health, physical functioning, role-physical, bodily pain, vitality, social functioning, mental health and role-emotional. Such domains were also considered as physical and mental component summaries, as previously specified.[13] A higher score in the SF-8 indicates a better QOL score.

### *Statistical analysis*

The Kolmogorov–Smirnov test was used to verify the normality of the data. The data are presented as the median (interquartile range) or respective percentage. The $\chi^2$-test or Fisher's exact test were used to compare groups stratified by QOS with respect to sex, education, living situation, work, financial satisfaction, smoking, alcohol, number of consultations in 6 months, number of medications, morbidities, comorbidities and regular physical activity categories. Additionally, the $\chi^2$-test was used to compare the pedometer counts and LSA categorized according to values above or below the median (6562 steps/day and 86, respectively) due to their skewed characteristics, and the MMSE, MNA and GDS scores were categorized according to their respective cut-offs (i.e. 24, 12 and five, respectively). The Mann–Whitney *U*-test was used to compare age, BMI, self-reported sleep duration, and the SF-8 component summaries and domains. Logistic regression was carried out to analyze the potential associations for QOS in Japanese older adults. Sociodemographic, lifestyle and health condition variables were analyzed one by one as covariates in a partially adjusted model by sex and self-reported sleep duration. Finally, variables that reached $P < 0.1$ in the partially adjusted model (e.g. comorbidities, MMSE, GDS, LSA, SF8 physical and mental component summaries, general health, bodily pain, vitality, social functioning, and mental health) were inserted in a fully adjusted model, and analyzed as covariates considering QOS as a dependent variable. Statistical significance was set at $P < 0.05$. All analyses were carried out using the Statistical Package for the Social Science program version 20.0 (SPSS; IBM, Chicago, IL, USA).

## Results

A total of 145 subjects participated in the present study; they were then divided according to their QOS report into good sleep ($n = 115$) and poor sleep ($n = 30$) groups. In addition, the data in tables are also presented as the total sample. Their sociodemographic characteristics are shown in Table 1. No significant difference was found with respect to age; however, regarding sex, more males had a poor QOS ($P < 0.05$). Additionally, no significant differences were found for educational level, living situation, current work or financial satisfaction.

Regarding lifestyle and health conditions, the current number of smokers was less than 10% of the total participants, and less than 50% of the participants drank alcohol. There were no differences in the consultation frequency in 6 months, number of medications or morbidities (Table 2).

We found significant differences in the self-reported sleep duration ($P < 0.001$), BMI ($P < 0.05$), GDS ($P < 0.05$), SF-8 – physical component summary ($P < 0.01$), general health ($P < 0.001$), bodily pain ($P < 0.001$) and vitality ($P < 0.001$) between those individuals who evaluated their QOS as good and as poor. The poor QOS group had a shorter self-reported sleep duration, higher BMI and higher risk of depression than the good QOS group.

Furthermore, the good QOS group showed significantly higher scores in the different QOL summaries and domains: SF-8 – physical component ($P < 0.01$), general health ($P < 0.001$), bodily pain ($P < 0.001$) and vitality ($P < 0.001$). No significant differences were found regarding regular physical activity, pedometer counts or other variables (Table 3).

In the partially adjusted model (by sex and self-reported sleep duration), BMI and GDS failed to remain significantly different between groups. However, having a normal cognitive condition appeared to be a protective factor against poor QOS (odds ratio 0.24, 95% confidence interval [CI] 0.07–0.83). The SF-8 physical component summary, general health, bodily pain and vitality domains remained significant. Comorbidities ($P = 0.06$), LSA ($P = 0.05$), SF-8 mental component summary ($P = 0.06$) and mental health ($P = 0.05$) showed a tendency towards significance. Those individuals with higher QOL scores were less likely to assess their QOS as poor (Table 4).

In Table 5, a fully adjusted model was analyzed in a stepwise logistic regression method. Considering this model, MMSE (odds ratio 0.13, 95% CI 0.03–0.55), bodily pain (odds ratio 0.91, 95% CI 0.84–1.00) and vitality (odds ratio 0.82, 95% CI 0.73–0.92) were then confirmed as protective factors for participants who evaluated their QOS as poor.

## Discussion

To our knowledge, only a few studies have investigated QOS in Japanese older adults, and none have directly analyzed the associations of QOS with a broad range of

**Table 1** Subjects' general characteristics (total sample and stratified by quality of sleep)

| Variables | Total ($n$ = 145) | Self-reported quality of sleep Good ($n$ = 115) | Poor ($n$ = 30) | $P$ |
|---|---|---|---|---|
| Age (years) | 73 (70–77) | 73 (70–77) | 74 (70.7–77) | 0.78 |
| Female (%) | 53.1 | 57.4 | 36.7 | 0.04 |
| Educational level (%) | | | | 0.59 |
| Elementary school | 2.1 | 1.7 | 3.3 | |
| Junior high school | 30.3 | 29.6 | 33.3 | |
| High school | 52.4 | 51.3 | 56.7 | |
| Technical school | 4.8 | 5.2 | 3.3 | |
| University | 10.3 | 12.2 | 3.3 | |
| Living situation (%) | | | | 0.57 |
| Alone | 9.0 | 9.6 | 6.7 | |
| Only spouse | 47.6 | 46.1 | 53.3 | |
| Spouse and child | 22.8 | 20.9 | 30.0 | |
| Only child | 7.6 | 8.7 | 3.3 | |
| Other | 13.1 | 14.8 | 6.7 | |
| Work (%) | | | | 0.96 |
| Does not work/retired | 43.7 | 44.6 | 40.0 | |
| Volunteer | 4.2 | 4.5 | 3.3 | |
| Regular work | 4.2 | 4.5 | 3.3 | |
| Farm work | 42.3 | 41.1 | 46.7 | |
| Other | 5.6 | 5.4 | 6.7 | |
| Financial satisfaction (%) | | | | 0.17 |
| Satisfied | 68.3 | 70.4 | 60.0 | |
| Normal | 17.9 | 14.8 | 30.0 | |
| Dissatisfied | 13.8 | 14.8 | 10.0 | |

Values are median (interquartile range) or percentages.

important health indicators as we did herein. The present study supported the hypothesis that QOS is associated with important health indicators, such as lifestyle characteristics, cognitive status, nutrition, depression, seclusion and QOL in Japanese community-dwelling older adults. In the present study, more males had a poor QOS, and no other significant differences were found for sociodemographic information between the groups. In addition, we found a small number of smokers and alcohol consumers, who accounted for less than half of our total participants (such differences were also not associated with QOS), and the participants presented similar characteristics regarding their health conditions.

A study carried out in Japan found that poor perceived QOS was associated with advancing age, and that more females complained of poor QOS than males; however, QOS in men decreased considerably at an older age.[14] We might be able to explain why males showed poorer QOS in the present study if we consider the intrinsic characteristics of these participants. Although the present study was not designed to specifically identify sex differences, we verified no statistical differences between males and females in all the health indicators and QOL variables (data not shown). However, when comparing only males according to their QOS, we found that those with poor QOS had shorter sleep duration, higher BMI and lower QOL (considering general health, bodily pain and vitality) than those with good sleep (data not shown). In the USA, a study verified an inverse linear association between sleep duration and higher BMI in adults,[15] and another study ascertained that short sleep duration was strongly associated with greater adiposity in older men and women.[16] In Japan, studies have found contrasting results regarding sleep and weight; one found an association of short sleep duration with reduced weight, whereas another found no association.[17,18] However, such studies did not specifically address QOS, focusing instead on sleep duration. Although the relationship between BMI and QOS is still not clear, we believe that it might have influenced our outcome.

Furthermore, Gu *et al.* found that living arrangements (living with a spouse or family member compared with living alone) appeared to be associated with QOS; moreover, current alcohol drinkers had a 27% higher odds ratio of reporting good QOS compared with those who did not drink alcohol.[19] Those discrepancies with other

Table 2 Bivariate comparisons for the subjects' lifestyle and health conditions (total sample and stratified by quality of sleep)

| Variables | Total ($n$ = 145) | Self-reported quality of sleep Good ($n$ = 115) | Poor ($n$ = 30) | $P$ |
|---|---|---|---|---|
| Smoking (%) | 8.3 | 7.8 | 10.0 | 0.71 |
| Alcohol drinking (%) | 38.6 | 37.4 | 43.3 | 0.55 |
| No. consultations in 6 months (%) | | | | 0.72 |
| No | 15.3 | 15.8 | 13.3 | |
| Once or twice | 20.1 | 21.1 | 16.7 | |
| Three or four times | 14.6 | 15.8 | 10.0 | |
| Five or six times | 26.4 | 23.7 | 36.7 | |
| Seven or more | 23.6 | 23.7 | 23.3 | |
| No. medicines (%) | | | | 0.12 |
| No | 19.3 | 20.8 | 13.8 | |
| One | 19.3 | 18.9 | 20.7 | |
| Two | 21.5 | 18.9 | 31.0 | |
| Three | 11.1 | 14.2 | – | |
| Four or more | 28.9 | 27.4 | 34.5 | |
| Morbidities (%) | | | | |
| Lower back pain | 10.3 | 10.4 | 10.0 | 1.00 |
| Diabetes | 12.4 | 12.2 | 13.3 | 1.00 |
| Osteoporosis | 8.3 | 7.0 | 13.3 | 0.27 |
| Hypertension | 44.1 | 42.6 | 50.0 | 0.46 |
| Hyperlipidemia | 15.2 | 14.8 | 16.7 | 0.77 |
| Arthropathy | 4.8 | 6.1 | – | 0.34 |
| Respiratory problems | 2.8 | 2.6 | 3.3 | 1.00 |
| Comorbidities (%) | 23.4 | 22.6 | 26.7 | 0.64 |

Values are percentages.

studies might be a result of the homogenous characteristics of the participants that we studied, as no differences were found for many conditions.

The term QOS is widely used in the literature; however, its use involves different interpretations (e.g. some studies consider it as an insomnia occurrence, whereas others use a subjective rate approach). Therefore, we will discuss QOS in a general approach, considering sleep disturbances and duration as interference factors in QOS. When comparing the QOS groups, a difference was found in the self-reported sleep duration, with a longer sleep duration indicating a better QOS. Studies suggested that older adults who slept 7–9 h per day (similar to the values that we found – good QOS 7 [6.5–8]) were more likely to be healthy than those with shorter (≤6 h) or longer (≥10 h) sleep durations.[19] In addition, older adults with a shorter sleep duration had sleep complaints more frequently, especially night-time complaints and feeling unrested in the morning. In contrast, a longer sleep duration was associated with daytime sleepiness, independent of health status.[20] Furthermore, both longer and shorter sleep durations were associated with mortality in Japanese adults.[17]

Although BMI and depression became non-significant when the analyses were adjusted by sex and sleep duration, associations were found in an unadjusted comparison. Studies have identified the association of sleep and BMI, as discussed earlier; however, it is not a consensus.[15–18] Additionally, Kang *et al.* verified that patients with depression had a significantly higher frequency of poor sleep.[2]

In terms of cognitive conditions, having a normal cognitive status (≥24 on MMSE) appeared to be a protective factor for a better QOS (odds ratio 0.24, 95% CI 0.07–0.83), which is consistent with other studies. A 1-year longitudinal study found that the sleep disturbances score was significantly associated with incident general cognitive impairment in women, and more so with incident non-amnestic cognitive impairment. In men, the global sleep condition was significantly associated with incident general cognitive impairment.[4] Furthermore, cognitive decline was associated with sleep disturbance in non-demented community-dwelling older women in a 15-year follow-up study carried out by Yaffe *et al.*[5] Such interactions might be explained by the strength of the circadian/homeostatic interaction on modulating sleep and cognition, which are deteriorated in older healthy people.[21]

For the QOL assessment, the physical component summary, and the domains of general health, bodily

**Table 3** Bivariate comparisons for the subjects' health indicators and quality of life

| Variables | Total ($n$ = 145) | Self-reported quality of sleep Good ($n$ = 115) | Poor ($n$ = 30) | $P$ |
|---|---|---|---|---|
| Self-reported sleep duration (h) | 7 [6–7.5] | 7 [6.5–8] | 6 [5–7] | <0.001 |
| BMI (kg/m$^2$) | 23.1 [21.2–25.3] | 23 [20.8–24.7] | 23.7 [22.2–26.4] | 0.04 |
| Regular physical activity (%) | 65.2 | 67 | 58.6 | 0.40 |
| Pedometer count† (%) | 50.3 | 49.6 | 53.3 | 0.71 |
| MMSE (% at mild cognitive impairment)‡ | 19.0 | 10.4 | 23.3 | 0.07 |
| MNA (% at risk of malnutrition)‡ | 24.8 | 27 | 16.7 | 0.24 |
| GDS (% at risk of depression)‡ | 29.7 | 25.2 | 46.7 | 0.02 |
| LSA† (%) | 56.6 | 53 | 70 | 0.09 |
| SF-8 Physical component summary | 47.5 [42.9–51.1] | 47.8 [43.5–51.8] | 44.3 [40.7–48.7] | 0.01 |
| SF-8 Mental component summary | 51.3 [47.6–55.2] | 51.7 [47.9–55.3] | 50.7 [46.2–53.2] | 0.14 |
| SF-8 General health | 50.7 [50.7–50.7] | 50.7 [50.7–50.7] | 50.7 [41.1–50.7] | <0.001 |
| SF-8 Physical functioning | 48.5 [41.9–53.6] | 48.5 [41.9–53.6] | 48.5 [41.9–53.6] | 0.41 |
| SF-8 Role-physical | 48.4 [42.5–53.9] | 48.4 [42.5–53.9] | 48.4 [42.5–53.9] | 0.56 |
| SF-8 Bodily pain | 46.1 [46.1–60.2] | 51.7 [46.1–60.2] | 46.1 [44.1–46.1] | <0.001 |
| SF-8 Vitality | 54.4 [45.2–54.4] | 54.4 [54.4–54.4] | 45.2 [45.2–54.4] | <0.001 |
| SF-8 Social functioning | 54.7 [45.2–54.7] | 54.7 [45.2–54.7] | 45.2 [38.4–54.7] | 0.26 |
| SF-8 Mental health | 50.2 [50.2–57.4] | 50.2 [50.2–57.4] | 50.2 [44.9–57.4] | 0.09 |
| SF-8 Role-emotional | 49.0 [49–54.3] | 54.3 [49–54.3] | 49.0 [47.9–54.3] | 0.46 |

Values are median (interquartile range) or percentages. †Percentage of those below the median (pedometer count – 6562 steps/day; Life-Space Assessment [LSA] – 86). ‡Cut-off score for Mini-Mental State Examination (MMSE): 24; Mini-Nutritional Assessment (MNA): 12; Geriatric Depression Scale (GDS): 5. BMI, body mass index; SF-8, Short-Form 8.

pain and vitality were significantly different in the partially adjusted model (by sex and sleep duration). Those individuals with higher scores in such QOL domains were less likely to have a poor QOS. Our results regarding general health were in accordance with another study that verified that older adults with poor self-rated health were less likely to have good QOS (odds ratio 0.54, 95% CI 0.50–0.59).[22] However, in the fully adjusted model, only bodily pain and vitality remained significant.

Regarding bodily pain, a study stated that chronic pain and sleep difficulties were common in the older population living in the community; the authors observed strong and consistent associations between more severe and disseminated chronic pain and heterogeneous sleep complaints.[22] In a review study, Smith *et al.* also concluded that consistent evidence suggested that pain negatively impacts sleep both in the short- and long-term, and some evidence suggested that the relationship between pain and sleep might be reciprocal.[23] The direct relationship between pain and sleep quality is not often explored in clinical studies. Patients with chronic pain appear to be often prescribed analgesics at night or sedative pain medications, with most of the analgesics used for chronic pain and many of the sedative hypnotics used to promote sleep; however, both have direct analgesic and soporific effects.[23] Thus, the consideration of medications for pain and QOS might raise important concerns regarding the confounding effects. Moreover, medications often lead to a series of adverse drug reactions that health promoters might want to avoid, especially as a result of overdoses and polypharmacy in older adults.[24]

Furthermore, we did not find any evidence regarding vitality and QOS in the literature, and most of the articles investigated sleep with respect to the duration aspect. Goldman *et al.* found that individuals who slept ≤6 h/night had a 4.3% higher fatigue score than those who slept 7 h/night. Individuals with complaints of awakening too early in the morning had a 5.5% higher fatigue score than those without these complaints.[25] Such associations remained significant even after multivariate adjustment for multiple medical conditions. In such studies, the concept of fatigue used also included the levels of energy, vitality and strength.

Although the good QOS group had more people engaged in regular physical activity (good QOS group: 67% *vs* poor QOS group: 58.6%), we did not find significant differences regarding the practice of regular physical activity or pedometer counts, which could be as a result of our cross-sectional design. We believe that physical exercise is an appropriate therapeutic intervention to promote sleep benefits. A review study mentioned several lines of evidence: (i) moderate intensity endurance training in older sedentary men and women with sleep complaints was found to subjectively improve sleep quality; (ii) the duration of exercise was a consistent moderator variable on the acute effects of exercise

**Table 4** Partially adjusted (by sex and sleep duration) multivariate logistic regression considering quality of sleep as a dependent variable, and sociodemographic, lifestyle and health condition variables as covariates

| Variables | OR (95% CI) | *P* |
|---|---|---|
| Age | 1.03 (0.93–1.14) | 0.50 |
| Smoking | 1.29 (0.23–6.98) | 0.76 |
| Alcohol drinking | 0.79 (0.29–2.17) | 0.66 |
| Comorbidities | 2.81 (0.93–8.48) | 0.06 |
| BMI | 1.10 (0.94–1.28) | 0.20 |
| Regular physical activity | 0.55 (0.20–1.47) | 0.23 |
| Pedometer count† | 0.68 (0.27–1.71) | 0.41 |
| MMSE‡ | 0.24 (0.07–0.83) | 0.02 |
| MNA‡ | 0.53 (0.17–1.69) | 0.29 |
| GDS‡ | 2.21 (0.86–5.65) | 0.09 |
| LSA† | 0.38 (0.14–1.02) | 0.05 |
| SF-8 Physical component summary | 0.92 (0.86–0.99) | 0.03 |
| SF-8 Mental component summary | 0.92 (0.84–1.00) | 0.06 |
| SF-8 General Health | 0.85 (0.78–0.94) | 0.001 |
| SF-8 Physical functioning | 0.98 (0.93–1.03) | 0.55 |
| SF-8 Role-physical | 0.96 (0.89–1.02) | 0.23 |
| SF-8 Bodily pain | 0.91 (0.85–0.97) | 0.01 |
| SF-8 Vitality | 0.81 (0.73–0.90) | <0.001 |
| SF-8 Social functioning | 0.95 (0.89–1.00) | 0.09 |
| SF-8 Mental health | 0.91 (0.83–1.00) | 0.05 |
| SF-8 Role-emotional | 0.95 (0.87–1.03) | 0.28 |

†Analyzed values were categorized as above or below the median. ‡Analyzed values were categorized according to respective cut-offs. Variables were analyzed one by one together with sex and sleep duration in a multivariate logistic regression model. CI, confidence interval; OR, odds ratio; SF-8, Short-Form 8.

**Table 5** Stepwise logistic regression considering quality of sleep as a dependent variable and comorbidities, Mini-Mental State Examination, Geriatric Depression Scale, Life-Space Assessment, Short-Form 8 Physical and Mental component summaries, Short-Form 8 General health, Short-Form 8 Bodily pain, Short-Form 8 Vitality, Short-Form 8 Social functioning and Short-Form 8 Mental health as covariates (with sex and self-reported sleep duration inserted as adjusted covariates)

| Variables | OR (95% CI) | *P* |
|---|---|---|
| MMSE | 0.13 (0.03–0.55) | 0.006 |
| SF-8 Bodily pain | 0.91 (0.84–1.00) | 0.05 |
| SF-8 Vitality | 0.82 (0.73–0.92) | 0.001 |

CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio; SF-8, Short-Form 8.

on sleep; and (iii) in middle-aged to elderly subjects, a reduced likelihood of having a disorder in maintaining sleep and of having a sleep complaint has been associated with regular weekly activity.[26] Alfano *et al.* also suggested that physical activity was consistently related to better physical functioning, and to reduced fatigue and bodily pain in cancer survivors.[27] Furthermore, physical activity appeared to be related to vitality in Japanese individuals.[13]

Several limitations may accompany the present study, and should be considered when interpreting the results: (i) the cross-sectional design; (ii) the predominance of participants in the good QOS group that might indicate some bias as a result of the selection of healthy volunteers; and (iii) the collected sleep information in the present study considered basic sleep patterns with a self-reported approach. More specific questions, such as those regarding a wide range of sleep problems experienced by older persons, should be included. In addition, the use of specific sleep medication was not verified, and such medications might play an important role in QOS.[14] Thus, we were unable to investigate potential confounding factors resulting from sleep medications, other drugs or even caffeine consumption, considering that they would affect sleep. However, such bias might not restrict our general conclusions. In summary, the present study provides evidence that QOS is particularly linked with cognitive status, bodily pain and vitality in Japanese community-dwelling older adults. However, further research that controls for our limitations is warranted.

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## Disclosure statement

None of the authors have a conflict of interest or financial disclosures.

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1** Bivariate comparisons according to quality of sleep for the males' health indicators and quality of life.
**Table S2** Bivariate comparisons according to quality of sleep for the females' health indicators and quality of life.
**Table S3** Bivariate comparisons according to sex for the participants' health indicators and quality of life.
**Table S4** Bivariate comparisons according to quality of sleep by sex for the participants' health indicators and quality of life.

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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

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**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; ••: ••–••.**

**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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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 $\chi^2$-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 ($r = 0.493$, $P = 0.032$).

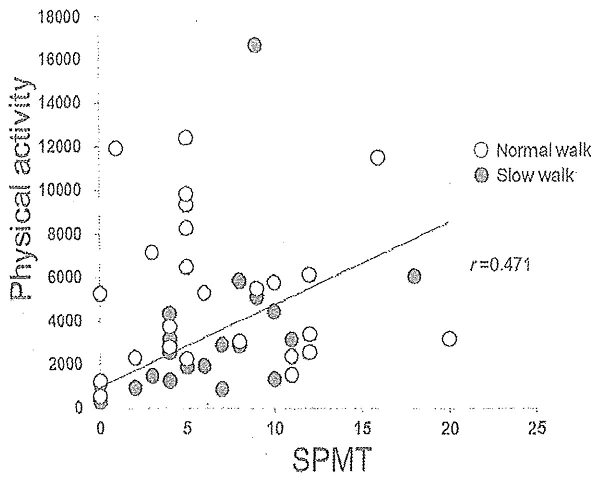


**Figure 1** Relationship between physical activity and the Scenery Picture Memory Test (SPMT) in the normal walking and slow walking groups. In the slow walking group, physical activity was correlated significantly with SPMT ($r = 0.471$, $P = 0.031$).

Stepwise multiple linear regression analysis showed that no item was significantly associated with SPMT in the normal walking group, whereas only physical activity (β = 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

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

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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

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***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 ($\leq 26$, $>26$), 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.

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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:

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

$\rho$: blood density, Ps: systolic blood pressure, Pd; diastolic blood pressure, $\Delta$P: 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 $\chi^2$ 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, $p=0.02$).

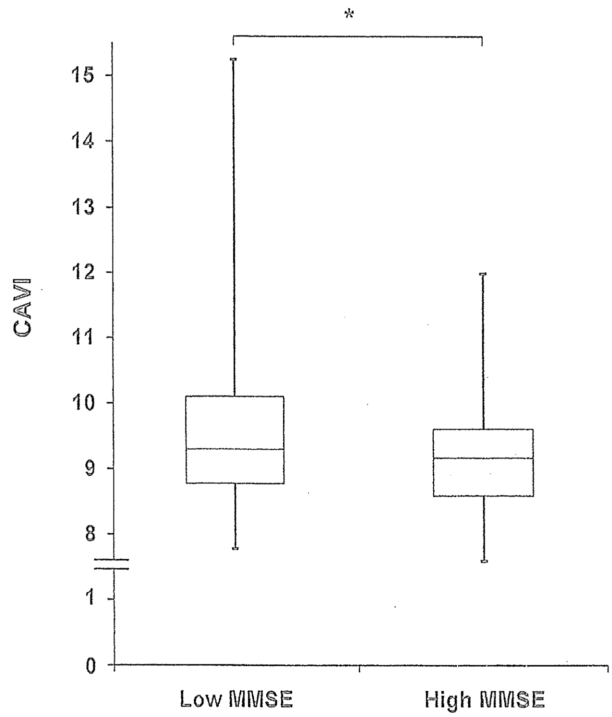


**Fig. 1.** Differences in the mean CAVI values between the high and low MMSE groups.

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

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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

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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 |