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ASSOCIATIONS OF SKELETAL MUSCLE MASS, LOWER-EXTREMITY FUNCTIONING, AND COGNITIVE IMPAIRMENT IN COMMUNITY-DWELLING OLDER PEOPLE IN JAPAN

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Abstract: *Objective:* We examined whether skeletal muscle mass and lower extremity functioning are closely associated with multiple cognitive domains, including global cognition, memory, attention, executive functioning, and processing speed, in community-dwelling older Japanese adults. *Design:* A cross-sectional, population-based community study. *Setting:* This study was conducted among community-living older people enrolled in the Obu Study of Health Promotion for the Elderly. *Participants:* Participants comprised 5,104 adults (≥ 65 years, mean age: 71 years). *Measurements:* Data from 4273 participants were analyzed. Appendicular skeletal muscle mass was estimated from bioelectrical impedance analysis and expressed as appendicular skeletal muscle mass index (ASMI). Lower-extremity functioning was assessed by the Five-Times-Sit-to-Stand test (FTSS) and Timed Up and Go test (TUG). Cognitive functions were assessed by the Mini Mental State Examination, word list memory, Trail Making Test parts A and B, and Symbol Digit Substitution Task. Logistic regression analysis were performed to calculate odds ratios (ORs) of cognitive impairment in various domains among skeletal muscle mass, lower-extremity functioning levels adjusted for important demographic variables, and comorbidities. *Results:* Participants with lower ASMI and slower FTSS and TUG groups had lower cognitive functioning scores than did participants with higher ASMI and faster FTSS and TUG. The slowest quartiles (Q4) of FTSS and TUG were significantly associated with impaired global functioning (MMSE score < 24) compared to the fastest quartile (Q1) after multivariate adjustment (FTSS, OR = 1.46, 95% confidence interval (CI) = 1.12–1.90; TUG, OR = 1.65, 95% CI = 1.25–2.17). In other dimensions of cognitive functioning, FTSS and TUG were significantly associated with all cognitive impairment in the full adjustment model. *Conclusion:* Lower-extremity functioning, rather than skeletal muscle mass, is closely related to multiple cognitive domains. This study suggests that maintaining lower-extremity functioning, rather than skeletal muscle mass, may be required for detecting and preventing cognitive impairment.

Key words: Cognition, lower-extremity functioning, mobility, weakness, community-dwelling older people.

Introduction

Cognitive impairment is one of the most important health problems in an aging population because of the major risk factor for dependency and mortality (1-3). The prevention of cognitive impairment requires identifying potential risk factors earlier for successful aging.

Changes in body composition (including muscle mass and body fat), physical functioning (including mobility and strength), and cognitive functioning are common features of aging (4, 5) and are common under pathophysiological mechanisms (6-8). For instance, higher adiposity and high fat-free mass are related to slower cognitive decline (8). Changes in the rate of decline in physical functioning also precede future mild cognitive impairment (9). These studies suggest that body composition and physical functioning may be useful for the detection of cognitive impairment.

Skeletal muscle mass, which is estimated by bioimpedance analysis (BIA), and lower-extremity functioning, which is assessed by the Five-Times-Sit-to-Stand test (FTSS) and Timed Up and Go test (TUG), are associated with disability (10, 11). These measures are available in a limited space, can be assessed quickly, and reflect essential components of several physical factors that decline with aging.

Both low skeletal muscle mass and poor performance on measurements of lower-extremity functioning (e.g., FTSS, TUG) are associated with cognitive impairment (12, 13). However, in systematic reviews and meta-analyses, cognitive functioning has been shown to be related to sarcopenia, which is defined as age-related loss of muscle mass with reduced muscle strength and/or impaired physical performance (12, 13). Moreover, lower-extremity functioning has only been associated with global cognition functioning and/or executive functioning because few studies have used multiple examples of cognitive functioning with large samples (12, 13). Therefore, these associations using multiple domains of cognitive functioning should be considered to identify cognitive impairment related to low skeletal muscle mass and poor performance on the measurement of lower-extremity functioning.

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Consequently, we examined what parameters, including skeletal muscle mass and lower extremity functioning, were closely associated with multiple cognitive domains such as global cognition, memory, attention, executive functioning, and processing speed in a large sample of community-dwelling Japanese older adults. This investigation may lead to a faster detection of cognitive impairment in older adults.

Methods

Participants

This cross-sectional study analyzed data from the Obu Study of Health Promotion for the Elderly (OSHPE), a cohort study including community-dwelling older adults. The OSHPE study was part of the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes (NCGG-SGS), which aimed to establish a screening system and validate evidence-based interventions for preventing geriatric syndromes (14). Data collection methods have been detailed in a previous report (15). Among the participants who were enrolled in the OSHPE (N = 5,104), 831 were excluded from this study based on the following criteria: (i) Mini Mental State Examination (MMSE) score < 18; (ii) presence of Alzheimer's disease, Parkinson's disease, stroke, or depression; and (iii) missing assessment data required for this study (e.g., tablet version of Trail Making Test parts A and B (TMT-A and -B), less than completing 2 targets within 90 s). Consequently, 4273 participants were analyzed. This study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants were informed about study procedures and provided their written, informed consent.

Skeletal muscle mass, lower extremity functioning

Appendicular skeletal muscle mass (ASM) was estimated from BIA (MC-980A; Tanita, Tokyo, Japan). The measurement methods of ASM have been described in detail previously (16). Appendicular skeletal muscle index (ASMI) was calculated by dividing ASM (kg) by height squared (m^2).

Measurements of lower extremity functioning included the FTSS and TUG, which are used to assess lower-extremity strength and mobility, respectively. Well-trained assessors conducted these performance tests. In the FTSS, participants were asked to stand up and sit down five times as quickly as possible, using a chair without an armrest (17). Assessors recorded the time taken to perform five consecutive chair-stands (timed to 0.1 s) from a seated position on a 45-cm-tall chair, with arms folded across the chest. The time taken was used as the FTSS score. TUG involved the participant rising from a standard armchair, walking 3 meters at a normal and safe pace, turning around, walking back to the chair, and sitting down again (18). TUG was measured twice with a stopwatch, and the fastest time was included for analysis.

Cognitive functioning

Measures of multidimensional cognitive functioning including global cognitive functioning, memory, attention and executive functioning, and processing speed were assessed. Global cognitive functioning was assessed by the MMSE; a raw score less than 24 was defined as impaired global cognition. Memory, attention and executive functioning, and processing speed were assessed using the National Center for Geriatrics and Gerontology functional assessment tool (NCGG-FAT) (19).

Memory functioning was assessed using immediate recognition in a word-list memory task. The participants were instructed to memorize 10 words that were presented on a tablet PC. Each of the 10 target words was shown for 2 s. Thirty words, including 10 target words and 20 distracter words, were then presented, and participants were asked to choose the 10 target words immediately. We used the tablet version of TMT-A and -B to assess attention and executive functioning. In TMT-A, participants must touch the target numbers displayed randomly on the screen as rapidly as possible, in consecutive order. In TMT-B, participants are required to touch target numbers or letters alternately between consecutive numbers and letters. We recorded the number of successfully completed tasks within a maximum period of 90 s, and the score for each test was the number of successfully completed tasks divided by 90 s (20). Processing speed was assessed using tablet version of Symbol Digit Substitution Test (SDST). In the SDST, nine pairings of numbers and symbols were provided at the top of the screen. A target symbol was shown at the center of the screen. The participant then rapidly selected a number corresponding to a target symbol at the bottom of the screen. One point was given for each correctly chosen number in a 90-s period. The NCGG-FAT had high test-retest reliability and moderate to high validity (19). With respect to the operational definition of cognitive impairment in the present study, we defined significant impairment as the raw score being 1.5 SDs or more below average values of each neuropsychological test (memory, attention and executive functioning, and processing speed) in each age group (65–69 years, 70–74 years, 75–79 years, and ≥ 80 years).

Other variables

Licensed nurses recorded demographic data, including age, sex, number of prescribed medications, and medical history in face-to-face interviews. Depressive symptoms were measured using the geriatric depression scale (GDS) score (21), and a cut-off score of ≥ 6 for the GDS was determined as having depressive symptoms.

Statistical analysis

To examine the associations among ASMI, FTSS, and TUG with cognitive functioning, we developed ordinal scales, because ASMI, FTSS, and TUG were not normally distributed. We divided the participants into four groups according to sex-specific quartiles based on levels of ASMI (Q1–Q4; Q1 the

highest skeletal muscle mass, Q4 the lowest skeletal muscle mass). In addition, participants were divided into four groups according to quartiles based on levels of FTSS and TUG (Q1–Q4; Q1 the fastest FTSS and TUG time, Q4 the slowest FTSS and TUG time). Comparisons among these groups of each ASMI, FTSS, and TUG were conducted using an analysis of variance for continuous data and a chi-square test for categorical data: p for trends were calculated across quartiles of ASMI, FTSS, and TUG.

Finally, we performed a multiple logistic regression analysis to investigate whether skeletal muscle mass and lower extremity functioning were associated with each cognitive function. The status of each cognitive function (MMSE, word list memory, TMT-A, TMT-B, SDST) was set as the dependent variable and the FTSS, TUG, or ASMI quartile was set as the independent variable, adjusted for potential confounding variables that have been associated with cognitive functioning in previous studies. For all regression analyses, minimally adjusted models were adjusted for age, sex, and education. Fully adjusted models were adjusted for age, sex, education, prescribed medications, hypertension, diabetes mellitus, dyslipidemia, and depressive symptoms. For the multiple logistic regression analysis, odds ratios (OR) and 95% confidential intervals (CI) were calculated. All data management and statistical computations were performed using the IBM SPSS Statistics 22.0 software package (IBM Japan, Tokyo) and JMP 13 (SAS Institute Japan, Tokyo, Japan). Statistical significance was set at $p < .05$ in all analyses.

Results

Table 1 summarizes participants' demographic data. Participants were classified into quartiles based on levels of ASMI in men (Q1 ≥ 8.23 kg/m^2; Q2 7.60–8.23 kg/m^2; Q3 7.08–7.60 kg/m^2; Q4 ≤ 7.08 kg/m^2) and in women (Q1 ≥ 6.60 kg/m^2; Q2 6.16–6.60 kg/m^2; Q3 5.75–6.16 kg/m^2; Q4 ≤ 5.75 kg/m^2), FTSS (Q1 ≤ 6.8 s; Q2 6.8–8.2 s; Q3 8.2–9.8 s; Q4 ≥ 9.8 s), and TUG (Q1 ≤ 7.1 s; Q2 7.1–8.0 s; Q3 8.0–9.1 s; Q4 ≥ 9.1 s). All characteristics of participants in Q4 by ASMI, FTSS, and TUG were significantly different from Q1 groups except for sex (ASMI and FTSS) and dyslipidemia (FTSS and TUG).

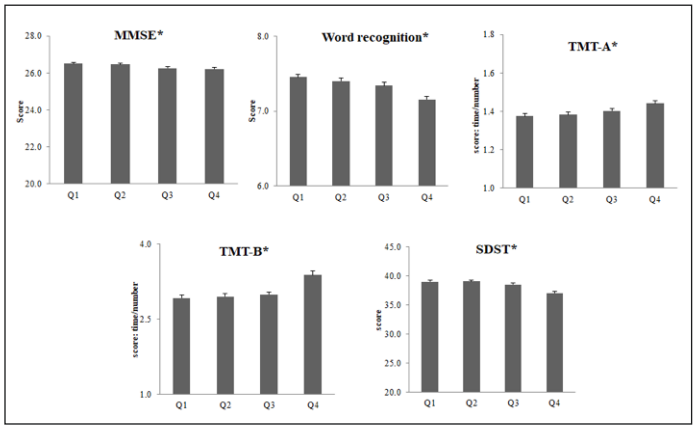
The group differences in cognitive performance are shown in Figures 1–3. Participants in Q4 groups of ASMI, FTSS, and TUG performed significantly worse than Q1 groups in MMSE and other neuropsychological tests ($p < .05$). The change rate from Q1 to Q4 groups in cognitive tests are from 1.1% to 15.6% (ASMI based group), from 4.0% to 43.7% (FTSS based group) and from 3.9% to 46.5% (TUG based group), respectively. This result suggests that lower-extremity functioning affect cognitive impairment rather than low skeletal muscle mass.

Table 1
Participants' demographic characteristics

Characteristics	Overall (N = 4273)
Age (years)	71.8 ± 5.4
Sex, women, n (%)	2200 (51.5)
Prescribed medications (number)	1.9 ± 2.0
Education (years)	11.4 ± 2.5
Hypertension, n (%)	1895 (44.3)
Diabetes mellitus, n (%)	558 (13.1)
Dyslipidemia, n (%)	1745 (40.8)
Depression (GDS ≥ 6), n (%)	586 (13.7)
ASMI (kg/m^2) (women/men)	6.20 ± 0.66/7.66 ± 0.88
FTSS (s)	8.6 ± 2.8
TUG (s)	8.3 ± 1.7
MMSE (score)	26.3 ± 2.5
Word recognition (score)	7.3 ± 1.3
TMT-A (score: time/number)	1.4 ± 0.4
TMT-B (score: time/number)	3.1 ± 2.1
SDST (score)	38.4 ± 8.2

GDS, geriatric depression scale; ASMI, Appendicular skeletal muscle index; FTSS, Five Sit-to-Stand Test; TUG, Timed Up & Go test; MMSE, Mini Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; SDST, Symbol Digit Substitution Task. Value are mean ± SD or numbers (proportion).

Figure 1
Cognitive performance by ASMI quartile



The graph shows cognitive performance by ASMI quartile. Values are mean ± SE. This graph shows that analysis of variance identifies the effects of quartile on ASMI (*p trend < .05). ASMI, Appendicular skeletal muscle index; MMSE, Mini Mental State Examination; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; SDST; Symbol Digit Substitution Task; Q, quartile.

Table 2 represents the results of logistic regression models testing the relationships between ASMI, FTSS, and TUG and cognitive functioning. The slowest quartile (Q4) of FTSS and TUG were significantly associated with impaired global functioning (MMSE score < 24) as compared to the fastest quartile (Q1) after multivariate adjustment. However, impaired global cognition was not related to low skeletal muscle mass.

Table 2

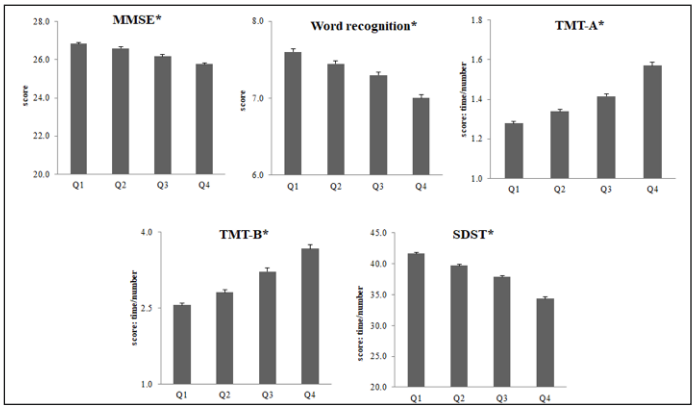
Logistic regression analysis between skeletal muscle mass and lower-extremity function and impairment in different dimensions of cognitive function

		Quartile						
		1	2		3		4	
	Overall prevalence, n (%)		Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
MMSE	630 (14.7)							
ASMI								
Minimally adjusted*		1.00 (reference)	0.85 (0.66–1.10)	.212	1.13 (0.88–1.44)	.342	0.81 (0.63–1.05)	.106
Fully adjusted†		1.00 (reference)	0.84 (0.65–1.08)	.176	1.10 (0.86–1.41)	.454	0.78 (0.60–1.01)	.062
FSST								
Minimally adjusted*		1.00 (reference)	0.91 (0.69–1.21)	.519	1.32 (1.01–1.71)	.040	1.47 (1.13–1.91)	.004
Fully adjusted†		1.00 (reference)	0.91 (0.69–1.20)	.501	1.31 (1.01–1.70)	.045	1.46 (1.12–1.90)	.005
TUG								
Minimally adjusted*		1.00 (reference)	1.31 (0.99–1.72)	.058	1.53 (1.17–2.00)	.002	1.64 (1.25–2.16)	< .001
Fully adjusted†		1.00 (reference)	1.30 (0.99–1.72)	.061	1.52 (1.16–2.00)	.002	1.65 (1.25–2.17)	< .001
Word recognition	284 (6.6)							
ASMI								
Minimally adjusted*		1.00 (reference)	1.20 (0.86–1.68)	.287	0.87(0.61–1.25)	.457	1.09 (0.77–1.55)	.618
Fully adjusted†		1.00 (reference)	1.19 (0.85–1.67)	.310	0.87 (0.60–1.25)	.448	1.07 (0.75–1.53)	.721
FSST								
Minimally adjusted*		1.00 (reference)	1.06 (0.73–1.52)	.768	1.14 (0.79–1.63)	.485	1.56 (1.09–2.23)	.014
Fully adjusted†		1.00 (reference)	1.03 (0.71–1.49)	.867	1.10 (0.76–1.58)	.615	1.47 (1.02–2.11)	.037
TUG								
Minimally adjusted*		1.00 (reference)	1.22 (0.84–1.77)	.307	1.28 (0.88–1.87)	.198	2.13 (1.48–3.06)	< .001
Fully adjusted†		1.00 (reference)	1.19 (0.82–1.74)	.368	1.25 (0.85–1.82)	.255	2.04 (1.41–2.95)	< .001
TMT-A	261 (6.1)							
ASMI								
Minimally adjusted*		1.00 (reference)	1.09 (0.76–1.56)	.655	1.02 (0.71–1.47)	.904	1.12 (0.77–1.61)	.557
Fully adjusted†		1.00 (reference)	1.11 (0.77–1.59)	.580	1.08 (0.75–1.57)	.680	1.18 (0.81–1.71)	.394
FSST								
Minimally adjusted*		1.00 (reference)	1.43 (0.92–2.22)	.109	2.10 (1.39–3.19)	< .001	2.82 (1.87–4.25)	< .001
Fully adjusted†		1.00 (reference)	1.41 (0.91–2.19)	.128	2.05 (1.35–3.11)	< .001	2.67 (1.77–4.04)	< .001
TUG								
Minimally adjusted*		1.00 (reference)	1.09 (0.73–1.62)	.682	1.37 (0.93–2.01)	.115	2.06 (1.41–3.00)	< .001
Fully adjusted†		1.00 (reference)	1.05 (0.70–1.57)	.818	1.32 (0.90–1.95)	.159	1.90 (1.29–2.80)	.001
TMT-B	205 (4.8)							
ASMI								
Minimally adjusted*		1.00 (reference)	0.89 (0.60–1.33)	.581	0.67 (0.44–1.02)	.059	0.89 (0.60–1.31)	.545
Fully adjusted†		1.00 (reference)	0.88 (0.59–1.30)	.511	0.65 (0.43–1.00)	.049	0.84 (0.56–1.26)	.411
FSST								
Minimally adjusted*		1.00 (reference)	1.52 (0.93–2.47)	.094	2.06 (1.30–3.28)	.002	2.03 (1.27–3.25)	.003
Fully adjusted†		1.00 (reference)	1.50 (0.92–2.45)	.103	2.01 (1.26–3.21)	.003	1.94 (1.20–3.11)	.006
TUG								
Minimally adjusted*		1.00 (reference)	1.34 (0.84–2.13)	.214	1.39 (0.87–2.20)	.168	2.23 (1.43–3.48)	< .001
Fully adjusted†		1.00 (reference)	1.32 (0.83–2.11)	.239	1.37 (0.86–2.17)	.189	2.16 (1.38–3.40)	< .001
SDST	277 (6.5)							
ASMI								
Minimally adjusted*		1.00 (reference)	0.99 (0.70–1.41)	.964	1.00 (0.70–1.41)	.979	0.93 (0.65–1.33)	.693
Fully adjusted†		1.00 (reference)	0.99 (0.70–1.40)	.944	1.01 (0.71–1.43)	.969	0.91 (0.63–1.32)	.623
FSST								
Minimally adjusted*		1.00 (reference)	1.98 (1.28–3.06)	.002	1.96 (1.27–3.04)	.003	3.64 (2.40–5.52)	< .001
Fully adjusted†		1.00 (reference)	1.93 (1.24–2.98)	.003	1.90 (1.22–2.94)	.004	3.40 (2.23–5.19)	< .001
TUG								
Minimally adjusted*		1.00 (reference)	1.15 (0.75–1.76)	.519	1.74 (1.16–2.59)	.007	3.36 (2.29–4.94)	< .001
Fully adjusted†		1.00 (reference)	1.11 (0.73–1.71)	.624	1.68 (1.13–2.51)	.011	3.18 (2.14–4.70)	< .001

* Adjusted for age, sex, and education; †Adjusted for age, sex, prescribed medications, education, hypertension, diabetes mellitus, dyslipidemia, and depression; ASMI, Appendicular skeletal muscle index; FTSS, Five-Times-Sit-to-Stand test; TUG, Timed Up and Go test; MMSE, Mini Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; SDST, Symbol Digit Substitution Task.

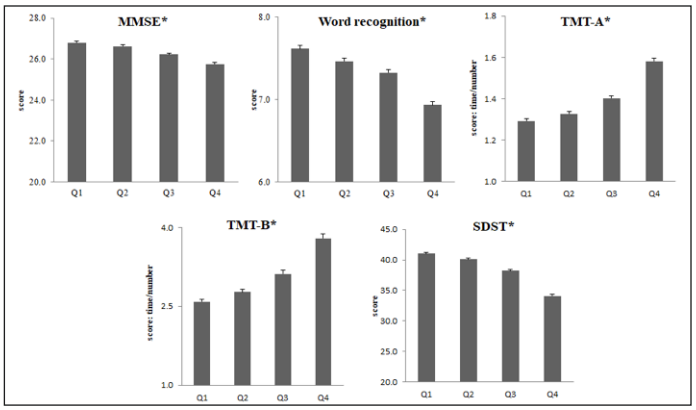
For other dimensions of cognitive functioning, ASMI was significantly associated only with TMT-B in full adjust model, not other cognitive functions. The results for the minimally adjusted model showed significantly lower performance of all cognitive functions in the lowest performance of FTSS and TUG divided in Q4 compared with those in Q1. These associations remained significant after adjustment for prescribed medications, education, hypertension, diabetes mellitus, dyslipidemia, and depression.

Figure 2
Cognitive performance by FTSS quartile



The graph shows cognitive performance by FTSS quartile. Values are mean ± SE. This graph shows that analysis of variance identifies the effects of quartile on FTSS (*p trend < .05). FTSS, Five-Times-Sit-to-Stand test; MMSE, Mini Mental State Examination; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; SDST; Symbol Digit Substitution Task; Q, quartile.

Figure 3
Cognitive performance by TUG quartile



The graph shows cognitive performance by TUG quartile. Values are mean ± SE. This graph shows that analysis of variance identifies the effects of quartile on TUG (*p trend < .05). TUG, Timed Up and Go test; MMSE, Mini Mental State Examination; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; SDST; Symbol Digit Substitution Task; Q, quartile.

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Discussion

This study revealed that lower-extremity functioning, rather than skeletal muscle mass, was significantly associated with cognitive impairment in multiple dimensions and global cognitive functioning in more than 4000 community-dwelling Japanese older adults. This result suggests that the maintenance of lower-extremity functioning may contribute to detecting and preventing cognitive impairment.

Consistently, Demnitz et al. (12) reported that lower-extremity functioning was related to global cognition. In contrast, regarding skeletal muscle mass, the MMSE scores gradually decreased from Q1 to Q4; however, no association was observed in the multiple logistic regression analysis. This result was not consistent with previous studies. Wirth et al. (22) found an association between skeletal muscle mass and cognitive functioning at later stages of global cognitive impairment. Participants with severe cognitive impairments (MMSE < 18) and Alzheimer's disease were excluded from this study, which may explain the association between skeletal muscle mass and cognitive functioning. Taken together, the results of this study suggest that lower-extremity functioning was associated with global cognitive impairment rather than muscle volume.

A novel finding from our study is that lower-extremity functioning was closely related to multiple cognitive impairments. In addition to the results from a systematic review and meta-analyses (12), the current study shows that lower-extremity functioning was associated with memory and attention functioning and processing speed. The TUG test is a valid test of functional mobility and showed moderate correlation with gait speed (r = -0.61) (18). The network of brain that control walking involves regions responsible for attentional, executive and visuospatial functioning (23). In addition, previous studies have suggested that gait speed is related to cognitive functioning in a comprehensive range of domains including memory, attention and executive functioning, processing speed, and visuospatial recognition (24, 25). Our current results have supported these previous studies and have suggested that TUG, which contains gait components, might be associated with not only specific cognitive functions but also a comprehensive range of cognitive functioning such as memory, attention and executive functioning, and processing speed.

FTSS is a valid measure of lower extremity strength. Although in a recent review a consensus was not reached on the association between weaknesses such as handgrip and multiple cognitive impairments (26), a previous study reported that weakness was associated with developing mild cognitive impairment (27). Muscle strength is also motor functioning, and reflects changes in the aging process; moreover, FTSS performance, which was used as a strength parameter in this study, is influenced by several factors, such as balance and multiple sensorimotor factors (28). Therefore, lower extremity strength, which is assessed by FTSS, might be related to multiple cognitive functions.

Additionally, lower-extremity functioning was associated with multiple cognitive impairments rather than skeletal muscle mass. A prior study examining the relationship between

muscle strength and skeletal muscle mass in aging reported that muscle strength decline is much more rapid than loss of skeletal muscle mass (29), suggesting that lower-extremity functioning, rather than skeletal muscle mass, might be affected by aging. Moreover, because both motor functioning, such as lower-extremity functioning, and cognitive functioning rely on the central nervous system, a compromised central nervous system may lead to deficits in both functions (26). Therefore, lower-extremity functioning might be useful in the detection of multiple cognitive impairments, rather than skeletal muscle mass.

The strengths of our study include its evaluation of the various domains of physical and cognitive functioning with a large sample size, which was much larger than that of a past study (30). Additionally, prior studies examining the associations between cognitive functioning and skeletal muscle mass and lower-extremity functioning used limited neurocognitive functioning (12, 13). The results of this study may contribute to the detection and prevention of cognitive impairment. On the other hand, our study has several limitations. First, we measured ASM by BIA. Although BIA is reported to be a highly reliable and accurate method of assessing skeletal muscle mass (31), more precise methods such as dual-energy X-ray absorptiometry should be used to estimate skeletal muscle mass. Second, due to the cross-sectional design, the causal association between skeletal muscle mass, lower extremity functioning, and cognitive impairment remains to be determined by future longitudinal studies.

Conclusion

In summary, this study found that lower-extremity functioning, rather than skeletal muscle mass, was significantly associated with cognitive impairment in multiple dimensions of global cognitive functioning, even after adjusting for sociodemographic and clinical factors. These results suggest that maintaining lower-extremity functioning can contribute to detecting and preventing cognitive impairments. Future studies are needed to clarify these associations including longitudinal studies and biological mechanisms.

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Conflicts of interest: None.

Author contributions: Ishii performed the analyses and drafted the manuscript. Shimada and Makizako conceived and designed the study. Shimada, Makizako, Doi and Tsutsumimoto revised the manuscript. Doi and Tsutsumimoto prepared the data.

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Ethical standards: Ethical standards for epidemiological study were adhered to according to guidelines from the Ministry of Health, Labour and Welfare, Japan.

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