



Association between Reduction of Muscle Mass and Faster Declines in Global Cognition among Older People : A 4-Year Prospective Cohort Study

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博 士 論 文

Association between Reduction of Muscle Mass and Faster Declines in Global

Cognition among Older People: A 4-Year Prospective Cohort Study

(地域在住高齢者における筋肉量の減少と全般的認知機能低下の関連：

4年間の前向きコホート研究)

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Association between Reduction of Muscle Mass and Faster Declines in Global Cognition among Older People: A 4-Year Prospective Cohort Study

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ABSTRACT

Objectives: A few studies reported that both decrease and increase in body mass index (BMI) were associated with the development of dementia in later life. However, it is unclear what changes in body composition are associated with cognitive decline. This study investigated the longitudinal influences of changes in body composition on cognitive function among community-dwelling adults.

Design, Setting and Participants: This longitudinal study included older adults aged ≥ 60 years without cognitive impairment who participated in National Institute for Longevity Sciences – Longitudinal Study of Aging.

Measurements: Cognitive function was assessed using the MMSE. Body composition was measured by a dual-energy X-ray absorptiometry system. Then, BMI, fat mass index (FMI), fat-free mass index (FFMI), and muscle mass index (MMI) were calculated. The changes in body composition over 6 years (second wave to fifth wave) were calculated, and three groups were created: decreased group, decrease of $>5\%$; stable group, change within 5% , and increased group, increase of $>5\%$. In statistical analysis, a linear mixed model was applied by sex to investigate the influences of body composition changes on cognitive function over 4 years (fifth wave to seventh wave).

Results: This study analyzed 515 participants (mean age, 67.05 years; 53.4% men). Men with decreased group in FFMI and MMI exhibited faster declines in MMSE scores than those with stable group (β [95% CI]: FFMI, -0.293 [-0.719 to -0.020]; MMI, -0.472 [-0.884 to -0.059]). In women, there was no significant association between body composition changes and cognitive functions.

Conclusions: Decrease in fat-free mass and muscle mass is associated with faster cognitive declines in men. These results suggest the importance of continuous monitoring of muscle mass to prevent cognitive decline in later life.

Introduction

Dementia is a rapidly growing global public health problem in an aged society (1). The number of people with dementia globally is expected to increase from 57.4 million in 2019 to 152.8 million in 2050 (2). As most cases of dementia are progressive and irreversible and the development of effective disease-modifying drugs is challenging, there is a growing need to reduce the risk of dementia (1).

Obesity, which is closely related to cardiovascular metabolic risk factors such as diabetes and hypertension, has been reported as a potentially modifiable risk factor for dementia in midlife (3). However, in later life, obesity or high body mass index (BMI) has been reported to have a protective effect (4), and lower BMI and weight loss were rather reported as risk factors for incident dementia (5,6). These inconsistent findings might be due to unintentional weight loss during the preclinical stage of dementia (7). Some studies investigating the trajectory of BMI until the development of dementia have found that weight loss begins to occur approximately 10 years before the onset of dementia (8,9). Moreover, a large cohort recent study has reported that 2-year BMI changes, i.e., >5% decrease and >10% increase in later life, were associated with the development of dementia, suggesting a U-shaped association between BMI changes and risk of dementia (10). Considering these findings, later life needs to focus on weight change that may precede the onset of dementia.

Although these data supported the importance of weight change, it is unclear which changes in body composition are associated with cognitive decline and dementia. Generally, with aging, body composition often changes in older adults: muscle mass decreases and fat mass increases (11). Among patients with early-stage Alzheimer's disease, total fat-free mass

was reduced compared to that in individuals with normal cognitive function, and this change was associated with cognitive function and white matter volume (12). This finding may indicate that reductions in fat-free mass or muscle mass especially may be involved with cognitive decline and dementia. However, previous studies have examined the influences of body composition that were assessed at a single time point (13,14), and no longitudinal study has examined the influences of changes in body composition that were measured at two time points on cognitive function in later life.

In addition, biological sex-based differences exist in the amount and distribution of changes in body composition. Men have more fat-free and muscle mass than women, whereas women have more fat mass than men (15). Regarding fat distribution, men are more likely to accumulate abdominal adipose tissue than women, whereas women usually accumulate adipose tissue around the hips and thighs (15). A systematic review reported that changes in muscle and fat mass with aging, and the relationship between body composition and health outcomes, differ according to sex (16). Therefore, relationship between changes in body composition and cognitive function should be investigated in men and women separately.

The aim of this longitudinal study was to investigate the influences of changes in body composition on cognitive function among older community-dwelling adults.

Methods

Study design and populations

This longitudinal study used data from the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA), a community-based study involving community-

dwelling people (17). NILS-LSA participants were recruited from a population in Obu City and Higashiura Town in Aichi Prefecture, Japan using stratified random sampling according to age and sex. Participants were followed up every 2 years from the first wave (November 1997–April 2000) to the seventh wave (July 2010–July 2012). Mini-Mental State Examination (MMSE) data are available after the second wave (April 2000 to May 2002). From these data, to clarify the changes in cognitive function after changes in the body composition, the baseline period (second to fifth wave, 6 years) and follow-up period (fifth to seventh wave, 4 years) were defined (**Figure 1-A**).

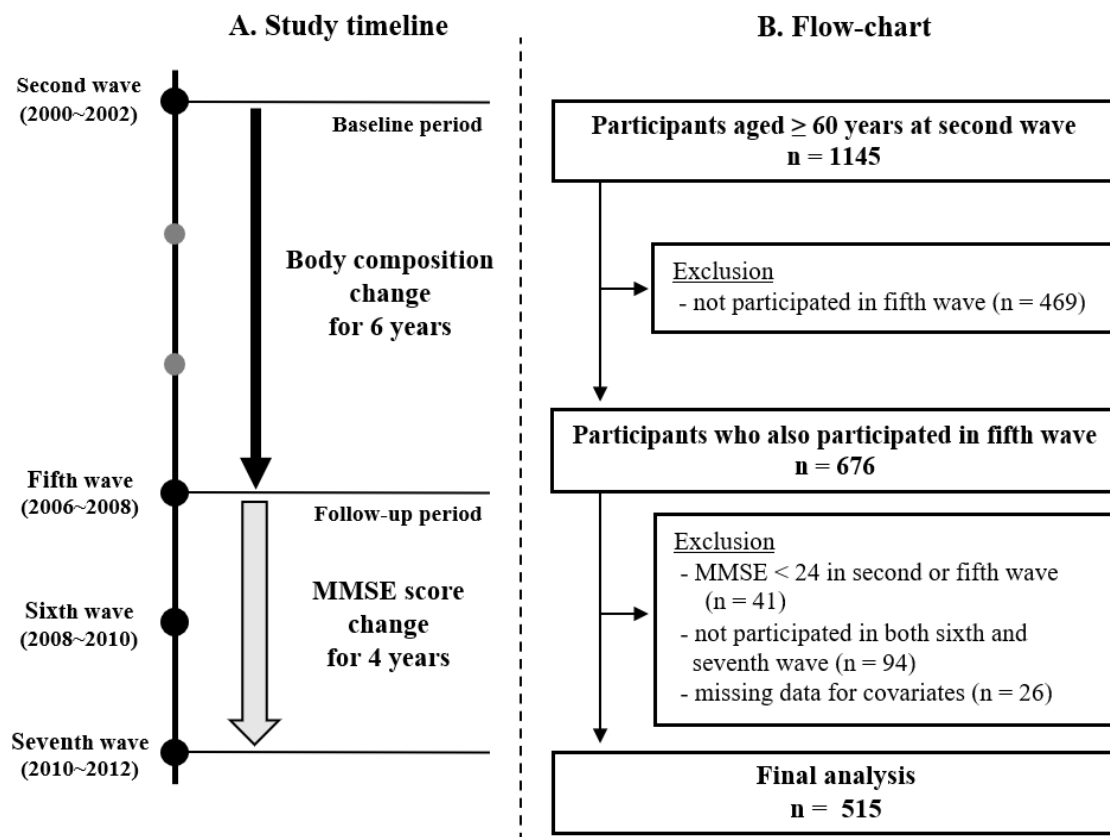


Figure 1. Flow chart and timeline of the study
Abbreviation: MMSE, Mini-Mental State Examination

For analyses, community-dwelling older adults aged ≥ 60 years at the second wave who participated in both the second and fifth waves were included. The exclusion criteria were MMSE scores < 24 in either the second and fifth waves, failure to participate once in the sixth and seventh waves, and missing data for covariates.

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Human Research at the National Center for Geriatrics and Gerontology, Japan (No. 1525), and all participants provided written informed consent before study participation.

Measurements

Cognitive function

Cognitive function was assessed using the Japanese version of the MMSE (18,19), which was administered in the second, fifth, sixth, and seventh waves. The MMSE was used to assess global cognitive performance, including the domains of time and place orientation, registration, attention and calculation, recall, language, and visual construction, in approximately 10 to 15 minutes. The measurement in the NLS-LSA was implemented by a trained psychologist or a psychology graduate student. The score ranges from 0–30, with higher scores indicating better cognitive function.

Body composition changes between the second and fifth waves

After measuring height (m) and weight (kg) using a digital scale, BMI was calculated as weight divided by height squared. Body composition was measured using a Hologic QDR 4500A dual-energy X-ray absorptiometry (DXA) system (Hologic, Bedford, MA, USA). In

the DXA system, the body is irradiated using two different X-ray energy levels, and the intrinsic software calculates body composition on the basis of the differential attenuation rates. Fat mass was calculated using the software built into DXA. Fat-free mass was calculated by subtracting fat mass from total body mass, and muscle mass was calculated by subtracting bone mass from total fat-free body mass. The fat mass index (FMI), fat-free mass index (FFMI), and muscle mass index (MMI) were calculated by dividing the fat mass (kg), fat-free mass (kg), and muscle mass (kg) by height (m) squared, respectively. Body composition changes over 6 years were defined as the differences in the values between the second and fifth waves. Participants were categorized into three groups on the basis of the changes in body composition: decreased group, reduction of >5%; stable group, change within 5%; and increased group, increase of >5% (10,20).

Other variables in the fifth wave

Other variables including age, sex, height, weight, years of education, smoking status (current smoker or non-current smoker), and self-reported comorbidities (stroke, hypertension, dyslipidemia, diabetes mellitus, and cardiac disease) were assessed. Genomic DNA was extracted from peripheral blood lymphocytes using standard procedures. Apolipoprotein E (APOE) genotypes were determined by polymerase chain reaction amplification (17), and participants were categorized as APOE-ε4 carriers and non-carriers (APOE4+ and APOE4-).

Statistical analysis

To describe the characteristics of participants in the second and fifth waves, we calculated the mean $\pm$ SD for age, years of education, MMSE, BMI, FMI, FFMI, MMI, height, weight, and the number of people (%) for other variables. The characteristics of the second and fifth waves were compared using the paired *t*-test and McNemar's test. Furthermore, we performed a *t*-test and chi-square test to compare the characteristics in the second wave between the older adults included in the main analysis (analyzed samples) and those who did not participate in the fifth wave (drop-out samples) in men and women.

We calculated the number of people (%) in the three-body composition change groups (decreased, stable, and increased) for BMI, FMI, FFMI, and MMI. The amount of body composition change over 6 years was described in each group as the mean $\pm$ SD.

We used a linear mixed model to assess the association between changes in body composition and changes in cognitive function over four years. A linear mixed model allows for the consideration of random participant-specific intercepts and the variability of MMSE score changes. In this analysis, the dependent variable was the change in MMSE score during the follow-up period, and the independent variables were the body composition change groups (decreased group, stable group, and increased group), time, and the interaction of the body composition change groups and time. Time was expressed as waves from the fifth to the seventh wave. The following variables in the fifth wave were entered as confounding factors: age, the interaction of age and time, years of education, APOE4, interaction of APOE4 and time, each body composition measure (e.g., BMI in the fifth wave was entered if the independent variable was the BMI change), stroke, hypertension, dyslipidemia, diabetes mellitus, and cardiac disease. We calculated the fixed effects of the independent

variables with a random intercept and a random slope. All confounding factors were selected from factors reported to be involved in the development of dementia based on previous studies (3,21-23), and the APOE4 $\times$ time interaction was selected as a confounding factor given that APOE- ϵ 4 has been established as a risk factor for cognitive and functional decline (24).

All analyses were performed separately for men and women because body composition varies by sex, the decrease in muscle mass was larger among older men than women (25), and previous research regarding the association between body composition and cognitive function also reported different results between men and women (21-23). The linear mixed model was created using the R package lme4 (<https://cran.r-project.org/web/packages/lme4/index.html>).

Results

Characteristics of participants in the second and fifth waves

Figure 1-B shows the selection of participants in this study. Of 1145 older adults aged ≥ 60 who participated in the second wave, 676 older adults also participated in the fifth wave. Older adults who met the following criteria were excluded: MMSE < 24 in either the second and fifth waves ($n = 41$), did not participate in both the sixth and seventh waves ($n = 94$), and missing data for covariates ($n = 26$). Finally, 515 participants were included in the analysis.

In the second wave, the participants had a mean age of 67.05 ± 5.21 years, and 275 of the participants were men. The median (interquartile range) duration of follow-up from the fifth wave was 3.95 (3.86–4.00) years. **Table 1** presents the characteristics of participants in

the second and fifth waves by sex. Among all participants, 44 (16.0%) men and 31 (12.9%) women were APOE-ε4 carriers. Height and weight decreased between the second and fifth waves, but BMI did not show a significant change. The prevalence of stroke, hypertension, and cardiac disease in men and that of stroke, hypertension, and diabetes mellitus in women increased between the second and fifth waves.

Table 2 shows the comparison results of the characteristics in the second wave between the analyzed samples and drop-out samples. In men, the drop-out samples were older, had lower years of education, MMSE score, height, and weight, and had a higher prevalence of stroke, diabetes mellitus, and cardiac disease than the analyzed samples. The same trend was observed among women: the drop-out samples were older, had lower years of education, MMSE score, and height, and had a higher prevalence of APOE4 carrier, hypertension, and diabetes mellitus than the analyzed samples.

Over the 6 years, the MMSE score changed by -0.34 ± 1.85 points for men and -0.51 ± 1.57 points for women. Despite slightly changes in BMI (men, 0.01 ± 1.32 ; women, 0.05 ± 1.32), FMI increased in both sexes (men, 0.28 ± 0.86 ; women, 0.13 ± 1.01), whereas decreases were recorded for FFMI (men, -0.14 ± 0.81 ; women, -0.23 ± 0.98) and MMI (men, -0.15 ± 0.91 ; women, -0.20 ± 0.99).

Table 1. Characteristics of participants in the second and fifth waves

	Men (n = 275)			Women (n = 240)		
	Second wave	Fifth wave	<i>P</i>	Second wave	Fifth wave	<i>P</i>
Age, years	66.76 ± 5.16	73.01 ± 5.13		67.39 ± 5.26	73.67 ± 5.24	
Years of education	11.90 ± 2.78	11.95 ± 2.73		10.65 ± 2.26	10.65 ± 2.34	
APOE4+	44 (16.0)			31 (12.9)		
MMSE score	28.28 ± 1.45	27.93 ± 1.52	<0.001	28.54 ± 1.39	28.03 ± 1.52	<0.001
BMI, kg/m ²	22.95 ± 2.57	22.96 ± 2.69	0.927	22.75 ± 2.93	22.80 ± 3.08	0.594
FMI, kg/m ²	5.08 ± 1.36	5.36 ± 1.53	<0.001	7.42 ± 1.93	7.55 ± 2.08	0.050
FFMI, kg/m ²	18.07 ± 1.57	17.93 ± 1.65	0.004	15.76 ± 1.51	15.53 ± 1.37	<0.001
MMI, kg/m ²	16.77 ± 1.50	16.62 ± 1.65	0.007	14.61 ± 1.47	14.40 ± 1.33	0.002
Height, cm	163.58 ± 5.15	162.93 ± 5.28	<0.001	150.54 ± 5.29	149.59 ± 5.63	<0.001
Weight, kg	61.47 ± 7.76	61.00 ± 8.00	0.033	51.58 ± 7.20	51.05 ± 7.64	0.007
Current smoker	78 (28.4)	47 (17.1)	<0.001	12 (5.0)	10 (4.2)	0.157
Self-reported comorbidities						
Stroke	14 (5.1)	27 (9.8)	<0.001	5 (2.1)	13 (5.4)	0.011
Hypertension	93 (33.8)	124 (45.1)	<0.001	83 (34.6)	115 (47.9)	<0.001
Dyslipidemia	45 (16.4)	51 (18.5)	0.304	61 (25.4)	74 (30.8)	0.069
Diabetes mellitus	32 (11.6)	33 (12.0)	0.067	11 (4.6)	20 (8.3)	0.003
Cardiac disease	40 (14.5)	61 (22.2)	0.001	28 (11.6)	36 (15.0)	0.178

Note: Data are presented as n (%) or mean ± standard deviation.

Abbreviations: APOE4+, apolipoprotein E-ε4 carrier; MMSE, Mini-Mental State Examination; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; MMI, muscle mass index

Table 2. Comparison of the characteristics in the second wave between the older adults included the main analysis (analyzed samples) and those who did not participate in the fifth wave (drop-out samples).

	Men			Women		
	Analyzed samples N = 275	Drop-out samples N = 238	<i>P value</i>	Analyzed samples N = 240	Drop-out samples N = 231	<i>P value</i>
Age, years	66.76 ± 5.16	72.00 ± 5.38	<0.001	67.39 ± 5.26	71.74 ± 5.46	<0.001
Years of education	11.90 ± 2.78	10.67 ± 2.69	<0.001	10.65 ± 2.26	9.63 ± 2.29	<0.001
missing	0	0		0	1	
APOE4+	44 (16.0%)	48 (20.3%)	0.211	31 (12.9%)	45 (19.7%)	0.048
missing	0	1		0	2	
MMSE score	28.28 ± 1.45	27.29 ± 2.16	<0.001	28.54 ± 1.39	27.27 ± 2.39	<0.001
missing	0	4		0	2	
BMI, kg/m ²	22.95 ± 2.57	22.68 ± 3.12	0.356	22.75 ± 2.93	23.35 ± 3.73	0.093
FMI, kg/m ²	5.08 ± 1.36	5.13 ± 1.56	0.669	7.42 ± 1.93	7.60 ± 2.26	0.502
missing	0	3		0	12	
FFMI, kg/m ²	18.07 ± 1.57	17.79 ± 1.82	0.119	15.76 ± 1.51	15.96 ± 1.61	0.183
missing	0	3		0	15	
MMI, kg/m ²	16.77 ± 1.50	16.50 ± 1.77	0.109	14.61 ± 1.47	14.82 ± 1.61	0.156
missing	0	3		0	15	
Height, cm	163.58 ± 5.15	160.70 ± 6.20	<0.001	150.54 ± 5.29	147.95 ± 5.54	<0.001
Weight, kg	61.47 ± 7.76	58.73 ± 9.62	<0.001	51.58 ± 7.20	51.21 ± 9.18	0.314
Current smoker	78 (28.4%)	78 (32.8%)	0.279	12 (5.0%)	4 (1.7%)	0.049
Self-reported comorbidities						
Stroke	14 (5.1%)	30 (12.7%)	0.002	5 (2.1%)	8 (3.5%)	0.369

missing	0	2		0	0	
Hypertension	93 (33.8%)	98 (41.5%)	0.073	83 (34.7%)	107 (46.3%)	0.010
missing	0	2		0	0	
Dyslipidemia	45 (16.4%)	27 (11.5%)	0.111	61 (25.5%)	73 (31.7%)	0.136
missing	0	3		0	1	
Diabetes mellitus	32 (11.6%)	43 (18.1%)	0.038	11 (4.6%)	23 (10.0%)	0.025
missing	0	1		0	0	
Cardiac disease	40 (14.7%)	57 (24.1%)	0.007	28 (12.0%)	39 (17.3%)	0.103
missing	0	1		0	0	

Note: Data are presented as n (%) or mean $\pm$ standard deviation. Missing indicates the number of missing values.

Abbreviations: APOE4+, apolipoprotein E- ϵ 4 carrier; MMSE, Mini-Mental State Examination; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; MMI, muscle mass index

Body composition changes

Table 3 presents the number of people (%) and the mean change in body composition over six years in each of the three groups (decreased, stable, and increased). BMI remained stable in approximately 70% of the participants, whereas increased FMI was noted in many participants (men, 53.5%; women, 38.3%). FFMI and MMI were stable in approximately 80% of the participants, but it was more common to observe a decrease in these indices in both men and women than an increase.

Table 3. The proportion of participants with body composition changes

N = 515	sex	Decreased group		Stable group		Increased group	
		Change over 6 years		Change over 6 years		Change over 6 years	
		Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)
BMI, kg/m ²	Men	-2.1 (1.1)	42 (15.3)	0.0 (0.6)	189 (68.7)	1.9 (0.7)	44 (16.0)
	Women	-1.9 (0.7)	39 (16.2)	0.1 (0.6)	165 (68.8)	2.0 (1.1)	36 (15.0)
FMI, kg/m ²	Men	-0.8 (0.6)	62 (22.5)	0.0 (0.1)	66 (24.0)	0.9 (0.6)	147 (53.5)
	Women	-1.0 (0.6)	66 (27.5)	0.0 (0.2)	82 (34.2)	1.1 (0.7)	92 (38.3)
FFMI, kg/m ²	Men	-1.1 (0.6)	47 (17.1)	0.0 (0.4)	219 (79.6)	2.2 (2.0)	9 (3.3)
	Women	-1.3 (1.8)	44 (18.3)	0.0 (0.4)	189 (78.8)	1.1 (0.3)	7 (2.9)
MMI, kg/m ²	Men	-1.4 (0.6)	37 (13.5)	-0.1 (0.6)	225 (81.8)	1.8 (1.6)	13 (4.7)
	Women	-1.5 (2.0)	26 (10.8)	-0.1 (0.6)	203 (84.6)	1.0 (0.6)	11 (4.6)

Abbreviations: SD, standard deviation; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; MMI, muscle mass index

Decline of cognitive function by body composition change

Table 4 presents the results of the multivariate linear mixed models. The linear mixed models suggested that the decline of the MMSE score was more rapid in men with decreased in FFMI than in men with stable FFMI ($\beta = -0.293$, 95% CI = -0.719 to -0.020). The estimated changes in the MMSE score over 4 years in group with decreased and stable FFMI were -1.12 (95% CI = -1.77 to -0.48) and -0.42 (95% CI = -0.70 to -0.14), respectively. The more rapid decline of the MMSE score was also observed in men with decreased in MMI compared to men with stable MMI ($\beta = -0.472$, 95% CI = -0.884 to -0.059). The estimated changes in the MMSE score over 4 years in group with decreased and stable MMI were -1.09 (95% CI = -1.75 to -0.44) and -0.45 (95% CI = -0.73 to -0.17), respectively. There was no significant association between BMI and FMI changes regarding the changes in cognitive function among men.

In women, there was no significant association between any body composition change and cognitive function.

Table 4. Influences of body composition changes on cognitive function

	Men			Women		
	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>
BMI change $\times$ time						
Decreased group	−0.132	−0.538 to 0.274	0.525	−0.204	−0.663 to 0.254	0.382
Stable group	ref.			ref.		
Increased group	−0.116	−0.514 to 0.282	0.282	0.012	−0.442 to 0.466	0.959
FMI change $\times$ time						
Decreased group	0.109	−0.309 to 0.527	0.608	0.001	−0.411 to 0.414	0.995
Stable group	ref.			ref.		
Increased group	0.087	−0.285 to 0.438	0.629	0.185	−0.187 to 0.557	0.329
FFMI change $\times$ time						
Decreased group	−0.293	−0.719 to −0.020	0.035	−0.218	−0.651 to 0.215	0.325
Stable group	ref.			ref.		
Increased group	−0.225	−1.160 to 0.708	0.636	−0.254	−1.190 to 0.679	0.594
MMI change $\times$ time						
Decreased group	−0.472	−0.884 to −0.059	0.025	0.024	−0.530 to 0.578	0.931
Stable group	ref.			ref.		
Increased group	−0.193	−0.868 to 0.480	0.575	0.088	−0.655 to 0.830	0.817

Adjusted for age, age $\times$ time, years of education, APOE4, APOE4 $\times$ time, each body composition (e.g., BMI in the fifth wave was entered if the independent variable was BMI change), stroke, hypertension, dyslipidemia, diabetes mellitus, and cardiac disease in the fifth wave.

CI, confidence interval; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; MMI, muscle mass index; ref., reference; APOE4, apolipoprotein E- ϵ 4.

Discussion

This study investigated the influences of body composition changes on cognitive function in community-dwelling adults aged ≥ 60 years. The results suggested that men with a $>5\%$ decrease in FFMI and MMI over six years had a more rapid decline in MMSE scores than those with a change within 5%. However, this relationship was not observed among women.

A narrative review investigated the association between muscle mass and cognitive function (26), but most of these studies reported no significant association. Cross-sectional and longitudinal studies investigating the association between sarcopenia and cognitive function also have suggested that muscle strength and physical function, rather than muscle mass, were associated with cognitive function (13,14). However, these studies assessed muscle mass at a single timepoint without considering the effects of changes over time. To date, only one study has examined the association between body composition changes and cognitive function, and it is a case-control study that included 181 women aged ≥ 75 years (27). The study has reported no significant association between changes in FMI and MMI over 7 years and the development of cognitive impairment, but the evidence is limited because the study population was small and included only women. Therefore, the current study is the first that reported new findings that decreases in FFMI and MMI are associated with faster cognitive decline among older men.

Additionally, BMI decreases of $>5\%$, which was previously reported to be associated with the development of dementia in a study (10), were not associated with cognitive decline in this study. Although the onset of dementia and cognitive decline have different meanings,

one possible reason for this inconsistency might be the difference in the annual rates of BMI changes by different baseline periods (previous study, 5% in two years; current study, 5% in six years). The annual decrease rate of BMI in this study was smaller than in the previous study; therefore, more rapid decreases in BMI may be involved in cognitive decline. Considering that even a modest change, such as a decrease of >5% over 6 years, was associated with cognitive decline, decreases in FFMI and MMI could represent more sensitive predictors of cognitive decline than BMI among older community-dwelling adults. This finding emphasizes the importance of continuous body composition monitoring and control, especially for fat-free mass and muscle mass, to reduce the risk of cognitive decline in later life.

It has been reported that muscle mass usually declines in later life, and particularly older men often experience decreases in muscle mass (11,25). Prior research investigating the natural history of skeletal muscle index (SMI) among participants in NELS-LSA estimated that men aged ≥ 60 had approximately 0.090 to 0.198 kg/m² decrease in SMI decline over the 6-year (25). In this study, men with >5% decreases in MMI had 1.4 ± 0.6 kg/m² decrease in MMI over 6 years (Table 2). A simple comparison is difficult because the studies used different indices of muscle mass, but a >5% decrease in MMI cannot be explained by age-related changes alone. Therefore, the results of this study suggest that MMI decline, which exceeds age-related changes, accelerates the decline of cognitive function. In addition, the estimated changes in the MMSE score over 4 years in decreased group were -1.09 . Considering that the one-year MMSE change in community-dwelling older adults of the same age is approximately -0.1 points (28,29), the changes in MMSE observed in decreased group

of MMI may have implications beyond age-related cognitive decline.

Although the mechanisms of the association between decreases in muscle mass and cognitive decline were not clarified, basic science and epidemiological studies suggested the involvement of inflammatory markers and myokines. Among inflammatory markers, higher interleukin-6 (IL-6) and CRP levels are associated with decreased muscle mass (30-32) and increased risks of dementia and cognitive decline (33,34). The Health ABC study reported that older adults with higher IL-6 and CRP levels had a 24% higher risk of cognitive decline after 2 years of follow-up and similar results at 8 years (35). Further, the function to secrete muscle-derived factors may have decreased as a result of the loss of muscle mass. A review about muscle-brain crosstalk suggested that muscle-derived factors enable direct crosstalk between muscle and brain function (36). Muscle-derived myokines such as irisin penetrate the blood-brain barrier and increase the production of brain-derived neurotrophic factor (BDNF) in the hippocampus (36-38). A recent study has demonstrated that treadmill exercise increase plasma cathepsin B levels in humans and that cathepsin B enhanced the expression of BDNF and doublecortin in hippocampal progenitor cells in mouse (39).

This study has showed that an association between muscle mass reduction and rapid cognitive decline was observed in men but not in women. Previous research also observed sex differences in the relationship between body composition and cognitive function (21-23). We also previously reported sex differences and demonstrated that female APOE- ϵ 4 carriers with mild cognitive impairment have lower weight and fat mass but not fat-free mass; these relationships were not observed among men (40). Sex hormone levels may be involved in the differences in the effects of muscle loss in men and women (41). Decreases in the levels of

testosterone, the major sex hormone in men, are associated with declining muscle mass (42,43), and this change is an independent predictor of dementia and cognitive decline (44,45). By contrast, estrogen, the major sex hormone in women, has often been reported to be significantly associated with cognitive function (46). However, no consistent results have shown that estrogen has a beneficial effect on muscle mass in older women (47). Therefore, differences in the role of sex hormones in men and women may have contributed to the gender differences in the relationship between muscle mass and cognitive decline. Future studies need to accumulate more evidence that accounts for sex hormones in men and women to further understand sex differences in the relationship between changes in body composition and cognitive decline.

In this study, an increase of >5% in FFMI and MMI was not associated with changes in cognitive function, but an increase in muscle mass was generally associated with an increase in physical activity (48), which is known to have beneficial effects on cognition. The association between increased muscle mass and cognition was still unclear because there were only a few participants with an increase of >5% in muscle mass in this study. Further larger cohort studies are needed to investigate the effects of changes in muscle mass.

This study had some methodological strengths and important contributions to both research and practice. First, as this study was a longitudinal study investigated the influences of body composition changes on cognitive decline, this finding leads to a better understanding of the causality between decline in muscle mass and cognitive decline. In addition, although this longitudinal study could not completely preclude reverse causation, older adults with cognitive dysfunction (MMSE score < 24) in the baseline period (second and fifth waves)

were excluded to minimize the effect of reverse causation. Second, this study directly examined the association between changes in body composition at two time points and cognitive decline. This allowed us to avoid reverse causation due to weight loss prior to the onset of dementia. Finally, body composition was accurately measured by DXA, and adjustment was performed for APOE- ϵ 4, a genetic risk factor for cognitive decline, in this analysis.

The present study had some limitations. First, the findings of this study were based on data from a certain area in Japan, and a nationwide survey is needed to clarify the influences of body composition changes on cognitive function. However, because participants of NILS-LSA were randomly selected from community-dwelling people in the most typical lifestyle areas in Japan (16), our findings may be generalizable to populations aged ≥ 60 years without cognitive impairment. Second, given that DXA measures muscle mass by subtracting fat-free mass from bone mass, soft tissue weight (water, fibrotic tissue, and connective tissue) are included (49). The results of the present study should be interpreted considering the fact that FFMI and MMI do not fully reflect body muscle mass. Third, we could not determine whether there were differential effects on several cognitive domains and whether the observed cognitive decline was attributable to neurodegenerative diseases such as Alzheimer's disease. Fourth, the follow-up period for cognitive function was relatively short. Longer-term follow-up is needed in future studies. Fifth, among the older adults aged ≥ 60 who participated in the second wave, 40% of older adults did not participate in the fifth wave. Compared with the analyzed samples in this study, those who did not participate in the fifth wave may have dropped out because of older age, cognitive decline, or comorbidities. Thus,

the results of the present study should be interpreted with caution so as not to underestimate the relationship between changes in body composition and cognitive function.

In conclusion, MMSE scores declined more rapidly among older men with >5% decreases in FFMI and MMI than among older men with a change in FFMI and MMI within 5%. These findings suggest the importance of continuous monitoring and control for muscle mass to reduce the risk of cognitive decline in later life. Future studies should confirm the influences of body composition changes on cognitive function, including factors such as inflammatory markers, myokines, and sex hormones, with longer-term follow-up.

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Conflict of interest

All authors report no conflicts of interest.

Ethical statement

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Human Research at the National Center for Geriatrics and Gerontology, Japan (No. 1525). All participants provided written informed consent before study participation.

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