These cross-sectional and longitudinal analyses determined whether participants had experienced the onset of a decline in three IADLs, including using transportation, shopping, and managing finances. A discussion regarding the types of activity that are considered IADLs would be useful here. In older people, other activities, such as cooking, housekeeping, and handling medication, are necessary for the maintenance of independence. In addition, previous studies have divided IADLs into two categories based on differences between activities involving high or low cognitive demand [22,25]. Reppermund and colleagues suggested that the restriction of functional ability was more prominent in highly cognitively demanding activities in individuals with cognitive impairment, including that of a mild degree, relative to cognitively healthy individuals, and that relative to older women, older men seem to experience greater difficulty in the performance of IADLs that involve higher cognitive demand [25]. Furthermore, with regard to associations between cognitive function and IADL performance, processing speed was associated with the performance of IADLs involving both higher and lower cognitive demand, but memory was only associated with high-demand factors [25]. The questionnaire items used to assess IADL performance in the current study may have involved lower cognitive demand, but managing finances, in particular, seemed to require higher cognitive demand. Although it may be difficult to clarify differences in cognitive demand with respect to the IADLs assessed in the current study, our findings suggest that cognitive function, including memory and processing speed, may be an important factor in maintaining IADLs, such as using transportation, shopping, and managing finances in later life. Differences between men and women, with respect to factors associated with the onset of a decline in IADL performance, may have occurred because of differences in cognitive demand between activities.

Walking ability has been found to be a useful predictor for the onset of functional decline in older people [26]. We confirmed that walking speed was strongly associated with the ability to perform IADLs and was found to be an independent predictor for the onset of IADL decline. In the aged population, walking speed could be a valuable predictor of health status, including disability [27], falls [28], cognitive impairment [29], institutionalization [30], and survival [31]. The results of this study indicated that slower walking speed, even in independent older adults without IADL limitation, predicted subsequent activity limitation. This suggests that walking speed is worthy of being considered predictive of IADL limitation. Relative walking speed can be measured in any setting, without the need for specific skills or a particular environment. Therefore, walking speed could be considered a common variable with which to assess functional ability in older adults. In contrast, GDS score was not an independent predictor for subsequent IADL limitation in the longitudinal analyses. Some previous studies have suggested that depressive symptoms may be a predictor for an increase in disability [14,32]. The relationship between depressive symptoms and IADL limitation may be more complex [14]. This relationship is unlikely to be linear; more severe depressive symptoms (e.g., those of moderate or major depression), may have a greater impact on subsequent IADL limitation. These findings suggest that cognitive and physical health may be independent with respect to IADL in adults aged 75 years and over. The findings of this study may also assist in the better prevention system (e.g., decision support system and using exergaming) for early detection of the elderly risks like dementia and depression and improving physical fitness and life quality of elderly [33,34].

Strengths of the current study include the large sample size, the residential status and age of the participants (community-dwelling adults aged 75 or older), the duration of the study period (15 months),

and the longitudinal nature of the study design. However, we acknowledge that the use of self-reported IADL function as assessed by only three items is a major limitation in this study. The assessment of subsequent IADL limitation at follow up only included three self-reported aspects of daily activity, which were using transportation (bus or train), shopping, and managing finances. In addition, the follow-up period (15 months) was shorter than that used in previous research (e.g., 2–10 years). Other IADL areas, such as using a phone, preparing meals, housekeeping, and taking medicine, should be considered as well. We excluded older individuals with a self-reported history of Parkinson's disease, stroke, Alzheimer's disease, or depression and included participants were who living independently in the community and did not need any personal care or support; thus, people with mild neurological disorders or mild cognitive impairment were likely to be included. A more comprehensive assessment of IADL function will be needed in future research to clarify the longitudinal relationship between decline in IADL and cognitive functioning. Furthermore, because we did not repeat measures of cognitive function or walking speed, we could not assess bidirectional associations between cognitive and physical functioning and IADL limitation. Therefore, further work is required to explore interactive associations and the effects of changes in cognitive function and walking speed on subsequent IADL limitation.

5. Conclusions

The OSHPE findings demonstrated relationships between cognitive decline, impaired physical functioning, and IADL limitation. The results also indicated that walking speed, memory, and processing speed may predict subsequent IADL limitation in community-dwelling adults aged 75 years and older.

Acknowledgments

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Author Contributions

Hyuma Makizako, Hiroyuki Shimada, Takehiko Doi, Kota Tsutsumimoto, and Takao Suzuki were involved in planning the OSHPE study protocol. Hyuma Makizako drafted the manuscript. Hyuma Makizako, Hiroyuki Shimada, Takehiko Doi, Kota Tsutsumimoto, and Sho Nakakubo were involved in the baseline survey data collection. Sangyoon Lee, Ryo Hotta, Sho Nakakubo, Kazuhiro Harada, Sungchul Lee, Seongryu Bae, and Kenji Harada edited and approved the manuscript before being submitted. Takao Suzuki contributed to the study conception. All authors critically revised the manuscript for important intellectual content.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Study

Incidence and Predictors of Sarcopenia Onset in Community-Dwelling Elderly Japanese Women: 4-Year Follow-Up Study

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A B S T R A C T

Objectives: Several studies have explored the prevalence and risk factors of sarcopenia, but they have been based on cross-sectional data. The objective of this study was to determine the incidence and predictors of the onset of sarcopenia over 4 years in community-dwelling elderly women.
Design: Four-year longitudinal follow-up study.
Setting: Urban community in Tokyo, Japan.
Participants: A total of 538 nonsarcopenic women older than 75 years.
Measurements: Body composition was determined by bioelectrical impedance analysis. Functional fitness measurements, including grip strength, usual walking speed, timed up and go (TUG), and interview surveys were conducted at baseline and 4-year follow-up. Blood samples were obtained to analyze serum albumin and hemoglobin A1c, and kidney function was analyzed using serum creatinine and cystatin C. Sarcopenia was defined based on the criteria suggested by the European Working Group on Sarcopenia in Older People, and the development of all stages, that is, presarcopenia, sarcopenia, and severe sarcopenia as well as the components of sarcopenia skeletal muscle index (SMI), grip strength, and walking speed, were analyzed.
Results: The incidence of total sarcopenia was 39.6% (presarcopenia 23.8%, sarcopenia 11.2%, severe sarcopenia 4.6%). Older age was significantly predictive of the development of presarcopenia and severe sarcopenia. Body mass index (BMI) lower than 21.0 kg/m^2 was significantly predictive of the development of all stages of sarcopenia, as well as declines in SMI, grip strength, and walking speed. Slow TUG was a predictor of the development of presarcopenia and severe sarcopenia. Increased calf circumference showed protective effects from the development of all stages of sarcopenia. Greater albumin levels also showed lower risk of declines in SMI, walking speed, and development of presarcopenia. Cystatin C was positively associated with the development of severe sarcopenia (odds ratio 1.83, 95% confidence interval 1.08–3.12). Heart disease and hyperlipidemia history were associated with presarcopenia and sarcopenia, respectively.
Conclusion: Age, BMI, calf circumference, and TUG were consistent predictors of the various stages and components of sarcopenia. The data also suggest that cystatin C was associated with higher odds of incident severe sarcopenia, and further study into kidney function and onset of sarcopenia in large populations is needed.

Sarcopenia, the age-associated decline in muscle mass, is a prevalent condition associated with functional decline, falls, disability, morbidity, and mortality among the elderly population.[1,2] Several diagnostic criteria have been suggested since the term sarcopenia was coined by Rosenberg in 1989,[3] although a consensus is yet to be reached. The European Working Group on Sarcopenia

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in Older People (EWGSOP) published a set of criteria defining sarcopenia based on muscle mass, muscle strength, and physical performance. The EWGSOP also suggested conceptual stages, in which sarcopenia is characterized by low muscle mass and either low muscle strength or low physical performance. Severe sarcopenia includes declines in all 3 criteria (low muscle mass, strength, and physical performance).

Previous studies have reported age, low body mass index (BMI), underweight, and minimal physical activity as risk factors of sarcopenia, based on cross-sectional data.[4–6] Interestingly, although causality was not determined, declines in kidney function have cross-sectionally been associated with loss of lean muscle mass, mobility disability, reduced gait speed, and poor physical function.[7–9] There also have been previous findings suggesting that sarcopenia is common among community-dwelling adults with chronic kidney disease,[10] but minimal information is available on whether kidney function measured using cystatin C may be a predictor of sarcopenia. Longitudinal data are necessary to investigate the predictors associated with the onset of sarcopenia, and to confirm or add to the existing conclusions based on cross-sectional results. Furthermore, few studies, if any, have investigated the onset of sarcopenia longitudinally.

Understanding the predictors of sarcopenia onset would provide insight into possible preventive measures as well as identify individuals at risk. Therefore, the purpose of this study was to investigate the predictors of the onset of sarcopenia in community-dwelling elderly Japanese women.

Methods

Subjects

There were 19,900 people living in the Itabashi ward as of April 1, 2008, and 10,948 (55.0%) lived in the Southeastern area of the ward. To maintain a representation of this larger population, a letter inviting people older than 75 years to participate in a comprehensive geriatric health examination survey was sent to these 10,948 community-dwelling people. There were 1670 (15.3%) respondents willing to participate. Among them, 1289 (77.2%) elderly women participated in the survey conducted at the Tokyo Metropolitan Institute of Gerontology (TMIG). Of these women, 575 (44.6%) were present on-site at the time of the follow-up survey in 2012 (Figure 1). For the purposes of this study, the women who were defined as sarcopenic in 2008 were excluded. Of 1082 nonsarcopenic women in 2008, 554 women participated only in the postal interview survey for the follow-up in 2012, and because all body composition, muscle strength, and blood component data could not be obtained, these people were excluded from the analysis. Any missing data or dropouts between 2008 and 2012 were excluded from the analysis.

Based on the EWGSOP definition,[11] presarcopenia was defined as reduced muscle mass (skeletal muscle index [SMI] mass/height^2 <6.42 kg/m^2),[12] sarcopenia was defined as reduced muscle mass (SMI mass/height^2 <6.42 kg/m^2)[12] and either reduced muscle strength (the cutoff for grip strength was adjusted for BMI; elderly women with BMI ≤23.0 had a grip strength cutoff of ≤17 kg; BMI between 23.1 and 26.0 cutoff was ≤17.3 kg; BMI between 26.1 and 29.0 cutoff was ≤18 kg; and BMI >29.0 cutoff was 21.0 kg)[13] or performance (usual walking speed <1.0 m/s),[14] and severe sarcopenia was defined as the presence of all 3 categories, that is, reduced muscle mass, strength, and performance.

The study protocol was approved by the Clinical Research Ethics Committee of TMIG. Procedures were fully explained to all participants, and written informed consent was obtained.

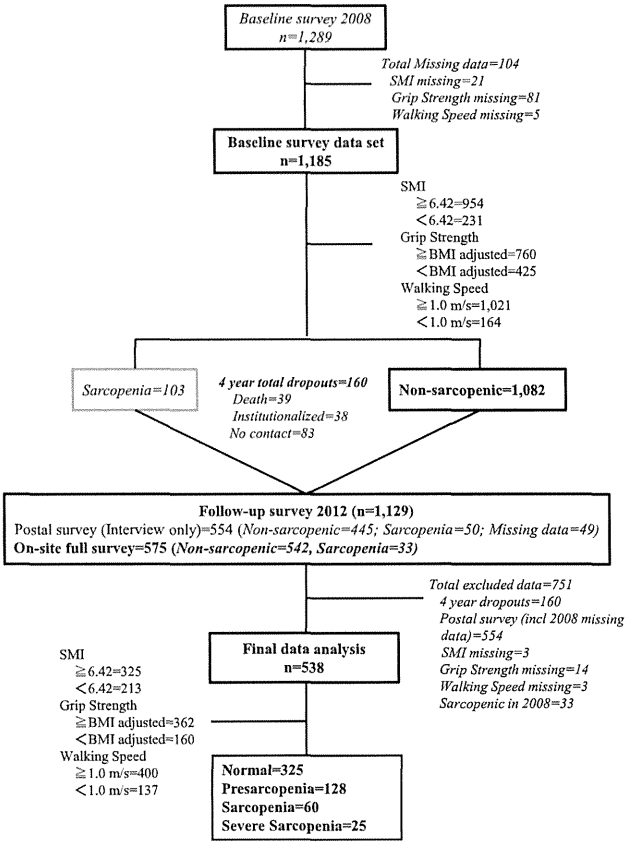

Fig. 1. Detailed flow chart of participants and dropouts over 4 years.

Diagnostic Measures for Sarcopenia

Muscle mass was measured by using a segmental multifrequency bioelectrical impedance analysis instrument that operated at frequencies of 5, 50, 250, and 550 kHz (Well-Scan 500; Elk Corp, Tokyo, Japan). Segmental muscle mass values of the legs and arms were summed to obtain appendicular skeletal muscle mass. Appendicular skeletal muscle mass (ASM) and SMI were determined by the following formula: ASM = left arm + right arm + left leg + right leg muscle, SMI = ASM/height (m) × height (m).[15] Grip strength was measured using a hand-held Smedley type dynamometer. Usual walking speed was measured on a flat, 11-m walking path, with markers at the 3-m and 8-m points. Participants were asked to walk the full 11 m, and a stopwatch was used to measure the time taken to walk 5 m between the markers. The faster of 2 trials was recorded.

Interview

Face-to-face interviews were conducted to assess pain, knee pain, falls, number of falls, fear of falling, injury and fractures, independent activities of daily living (IADL), self-rated health, and chronic conditions, such as history of heart disease, hyperlipidemia, osteoporosis, osteoarthritis (OA), and more. Participants were asked about any fall incidences in the previous 1 year, number of falls, and any injuries and fractures; a fall was defined as an event that resulted in a person coming to rest inadvertently on the ground or other lower level.[16] IADLs were measured using the Instrumental Self-Maintenance dimension of the TMIG index of competence.[17] For each of the 5 items (public transportation, shopping, food preparation, payment, handle finances), "yes" was scored as 1 and "no" as 0 (maximum

score: 5). Participants with a TMIG index Instrumental Self-Maintenance score of less than 4 were defined as having IADL disability.

Anthropometric and Physical Function Measures

Measurements of height and weight were converted to BMI. Bone mineral density (BMD) of the distal radius and ulna of the nondominant forearm was measured by dual-energy X-ray absorptiometry using a DTX-200 osteometer (Osteometer MediTech, Signal Hill, CA). Calf circumference was measured on the left leg in a seated position with the knee and ankle at right angles, feet resting on the floor. Measurements were made at the level of the widest circumference and subcutaneous tissue was not compressed. Knee extension strength was measured as the peak isometric force as the participants extended the knee with maximum power with their knee joint at 90°. A dynamometer was placed at the ankle joint to measure the force of extension. The greater measurement of 2 trials was recorded. For the timed up and go (TUG) test, time was measured in seconds as the time the participants stood up from a straight-backed chair placed against a wall, walked 3 m toward a cone as quickly and safely as possible, walked around the cone, and sat down on the chair again.[18] The faster of 2 trials was recorded. Assistive walking devices were allowed in measures of walking speed and TUG if the participant expressed concerns about walking without a device, or if the investigators suspected dangers of falling.

Blood Indicators

Blood samples were collected in a nonfasting state, in a seated position. Analyses were carried out centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). Cystatin C concentrations were measured with the sol particle homogeneous immunoassay method (Nescauto GC Cystatin C; Alfresa Pharma, Osaka, Japan).[19] The specific assays used for each measure and methods were as follows: serum albumin (bromcresol green), serum 25-hydroxyvitamin D (DiaSorin-RIA2), hemoglobin (latex agglutination), β 2-microglobulin (latex agglutination immunoassay), hematocrit (sheath flow direct current detection), and serum creatinine (enzymatic).

Covariates for Multivariate Analysis

Parameters such as muscle mass, grip strength, and walking speed used in the definition of sarcopenia were not included as covariates. In this study, covariates were classified under 3 domains in the multivariate analysis: anthropometric and fitness, blood components, and chronic conditions and lifestyle.

Anthropometric and fitness

Age, BMD, calf circumference, and TUG were analyzed as continuous variables and BMI was coded as 1 for less than 21.0 kg/m^2 and 0 for 21.0 kg/m^2 or higher.

Blood components

Albumin, 25-hydroxyvitamin D, beta 2-microglobulin, hemoglobin A1c, high-density lipoprotein (HDL) cholesterol, and cystatin C were analyzed as continuous variables.

Chronic conditions and lifestyle

The chronic conditions included in this analysis were pain, knee pain, falls, osteoporosis, heart disease, hyperlipidemia, and knee OA. Pain and knee pain were coded as 1 for yes and 0 for no, and falls was coded as 1 for yes, having fallen in the previous year and 0 for no falls. Osteoporosis, heart disease, hyperlipidemia, and knee OA were considered present for those who had been diagnosed by a physician and then coded as 1 and 0 for no symptoms.

Data Analysis

Data were presented as mean ± SD for continuous variables and percentages for categorical variables. A 1-way analysis of variance was used to compare variables collected in 2008, including anthropometric values, body composition, and functional fitness measures among the 4 groups: those who remained nonsarcopenic, and those who developed presarcopenia, sarcopenia, or severe sarcopenia in 2012. Chi-square tests were performed for comparisons in categorical variables among the 3 groups between baseline and 4-year follow-up.

Forward stepwise multiple logistic regressions were used to analyze the factors associated with the components included in the definition of sarcopenia and the onset of presarcopenia, sarcopenia, and severe sarcopenia. Model I included the anthropometric and fitness variables potentially associated with sarcopenia. Model II included the blood components on top of the anthropometric and fitness variables, and chronic conditions and lifestyle variables were added in Model III. Nonsignificant variables were forced into the models of the multiple logistic regression analyses to obtain the odds ratio (OR) and 95% confidence interval (CI). P values less than .05 were considered statistically significant. All analyses were performed using the SPSS software, Windows version 20.0 (SPSS Inc., Tokyo, Japan).

Results

Figure 1 shows the participant flow over 4 years. The total dropout rate was 58.3%. Over 4 years, 39 people died, 38 were institutionalized, and we were unable to reach 83 participants. Because body composition, strength, or blood component data could not be obtained in those who participated only in the postal interview survey (n = 554), the final analysis was performed on 538 of 575 people who participated in the full on-site survey (Figure 1). The data of all those who dropped out are outlined in the appendix (Appendix 1).

In comparing the 2008 baseline values of anthropometric, functional fitness, blood component, and chronic condition data among nonsarcopenic, presarcopenic, sarcopenic, and severe sarcopenic participants, the results showed that nonsarcopenic participants had significantly greater BMI, BMD, muscle mass, calf circumference, and were also significantly stronger than those who developed presarcopenia, sarcopenia, or severe sarcopenia (Table 1; all $P < .001$). Those with severe sarcopenia had the slowest walking speed and TUG ($P < .001$). For the blood components, the severe sarcopenia group had the lowest albumin levels ($P = .001$) and highest cystatin C levels ($P < .001$). Furthermore, a greater percentage of those who developed severe sarcopenia originally experienced knee pain ($P = .008$) and IADL disability ($P < .001$).

The analysis of the different components of the sarcopenia definition revealed that older age and BMI lower than 21.0 kg/m^2 were significantly predictive of declines across all 3 components of SMI, grip strength, and walking speed, whereas calf circumference showed significant protective effects in all components (Table 2). Greater albumin levels (OR 0.90, 95% CI 0.82–0.98) showed protective effects for decrease in SMI. History of heart disease (OR 2.05, 95% CI 1.19–3.55) and hyperlipidemia (OR 1.74, 95% CI 1.10–2.77) were significantly associated with a greater risk of SMI decline. Greater BMD (OR 0.40, 95% CI 0.17–0.91) and regular exercise habit (OR 0.30, 95% CI 0.12–0.72) had protective effects of grip strength decline. The predictors for walking speed decline included longer TUG (OR 1.28, 95% CI 1.12–1.48) and higher HDL cholesterol (OR 1.01, 95%

Table 1
Baseline Comparison Between Healthy Community-dwelling Elderly Women and Women Who Developed Sarcopenia

Variables	Nonsarcopenic (n = 325)	Onset of Presarcopenia (n = 128)	Onset of Sarcopenia (n = 60)	Onset of Severe Sarcopenia (n = 25)	*P* Value*	Post Hoc†
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age, y	78.0 ± 2.6	77.3 ± 2.0	78.5 ± 2.4	80.0 ± 2.1	<.001	SS>N, PS; S>PS
Height, cm	148.4 ± 5.1	150.1 ± 5.0	147.5 ± 5.8	145.7 ± 5.4	<.001	PS>N, S, SS
Body weight, kg	53.7 ± 7.2	46.8 ± 5.3	46.1 ± 6.8	46.8 ± 4.9	<.001	N>PS, S, SS
BMI, kg/m^2	24.4 ± 3.0	20.8 ± 2.2	21.5 ± 2.6	21.9 ± 1.7	<.001	N>PS, S, SS
BMD, g/cm^2	0.30 ± 0.06	0.28 ± 0.05	0.28 ± 0.05	0.26 ± 0.05	<.001	N>PS, S, SS
Muscle mass, kg	32.4 ± 3.1	30.1 ± 2.6	29.2 ± 3.2	28.7 ± 2.5	<.001	N>PS, S, SS
Appendicular muscle mass, kg	16.3 ± 1.7	14.9 ± 1.4	14.5 ± 1.6	14.3 ± 1.3	<.001	N>PS, S, SS
Calf circumference, cm	34.6 ± 2.5	32.1 ± 2.1	32.0 ± 2.6	31.8 ± 2.8	<.001	N>PS, S, SS
Grip strength, kg	19.5 ± 4.1	20.4 ± 3.0	18.1 ± 3.1	14.1 ± 3.4	<.001	N, PS, S>SS; PS>S
Knee extension strength, Nm	63.5 ± 16.8	62.0 ± 13.9	53.3 ± 10.0	45.1 ± 14.5	<.001	N>PS, S>SS
Usual walking speed, m/s	1.30 ± 0.24	1.43 ± 0.19	1.30 ± 0.18	0.98 ± 0.16	<.001	PS>N, S, SS; N, S>SS
Timed up and go, s	7.46 ± 2.6	6.50 ± 1.3	7.27 ± 1.9	9.96 ± 2.9	<.001	SS>N, S>PS
Creatinine, mg/dL	0.66 ± 0.16	0.62 ± 0.11	0.65 ± 0.11	0.69 ± 0.18	.018	N>PS
Albumin, g/dL	4.26 ± 0.21	4.35 ± 0.22	4.27 ± 0.22	4.21 ± 0.22	.001	PS>N, SS
25 Hydroxyvitamin D, ng/mL	21.88 ± 6.56	22.57 ± 5.99	21.88 ± 5.62	23.12 ± 7.41	.620	
β 2-microglobulin, mg/L	1.92 ± 0.53	1.18 ± 0.52	1.89 ± 0.37	2.11 ± 0.57	.047	
Cystatin C, mg/L	0.95 ± 0.21	0.87 ± 0.16	0.92 ± 0.15	1.02 ± 0.19	<.001	SS>PS; N>PS
Chronic conditions and lifestyle variables						
Falls, yes, %	16.0	15.6	16.7	20.0	.957	
Multi frequency of falls, yes, %	3.1	3.9	6.7	4.0	.604	
Pain, yes, %	63.1	52.3	63.3	72.0	.110	
Knee pain, yes, %	37.7	23.0	25.9	45.8	.008	
IADL, disability, %	1.5	0.8	3.3	16.0	<.001	
Regular exercise, yes, %	42.8	40.6	43.3	24.0	.322	
Knee osteoarthritis history, yes, %	27.2	16.4	30.0	280.0	.079	
Osteoporosis history, yes, %	23.7	32.8	35.0	24.0	.110	
Heart disease history, yes, %	16.9	23.4	25.0	24.0	.254	
Hyperlipidaemia history, yes, %	38.8	43.8	45.0	40.0	.692	

N, nonsarcopenic; PS, presarcopenia; S, sarcopenia; SS, severe sarcopenia.
*One-way analysis of variance for continuous variables and chi-square test for categorical variables.
†A post hoc analysis was performed using the Scheffe method.

CI 1.00–1.03), cystatin C levels (OR 1.34, 95% CI 1.03–1.74), and knee pain (OR 1.73, 95% CI 1.08–2.76). Greater BMD (OR 0.51, 95% CI 0.32–0.79) and albumin (OR 0.17, 95% CI 0.06–0.46) were protective against reduction in walking speed over 4 years.

The stepwise logistic regression analysis for presarcopenia revealed that older age, low BMI (<21.0 kg/m^2), and longer TUG were risk factors for the development of presarcopenia across all 3 models (Table 3). Greater calf circumference and albumin levels had

Table 2
Adjusted ORs and 95% CIs for the Predictors of Declines in Muscle Mass, Grip Strength and Walking Speed in 3 Models

Independent Variable	> Cutpoint* Reference	SMI	Grip Strength	Walking Speed
		n = 146 OR (95% CI)	n = 186 OR (95% CI)	n = 148 OR (95% CI)
Anthropometric and fitness				
Age, per 1 y	1	1.02 (0.93–1.13)†	1.32 (1.12–1.54)†	1.22 (1.12–1.32)†
BMI, <21.0 kg/m^2	1	1.86 (1.04–3.31)†	1.39 (1.13–1.72)†	1.25 (1.11–1.40)†
BMD, per 1 unit	1	1.43 (0.88–2.32)	0.40 (0.17–0.91)†	0.51 (0.32–0.79)†
Calf circumference, per 1 unit	1	0.83 (0.73–0.94)†	0.65 (0.52–0.83)†	0.81 (0.72–0.92)†
Timed up and go, per 1 unit	1	1.00 (0.89–1.13)	1.06 (0.88–1.27)	1.28 (1.12–1.48)†
Blood components				
Albumin, per 1 unit	1	0.90 (0.82–0.98)†	0.23 (0.03–1.65)	0.17 (0.06–0.46)†
25 Hydroxyvitamin D, per 1 unit	1	1.02 (0.98–1.05)	1.00 (0.94–1.06)	1.02 (0.98–1.05)
β 2-microglobulin, per 1 unit	1	2.75 (0.97–7.83)	0.71 (0.12–4.20)	1.00 (0.41–2.48)
Hemoglobin A1c, per 1 unit	1	0.80 (0.51–1.26)	0.76 (0.32–1.84)	1.39 (0.90–2.13)
HDL cholesterol	1	1.00 (0.98–1.02)	1.01 (0.98–1.05)	1.01 (1.00–1.03)†
Cystatin C, per 1 unit	1	0.08 (0.01–1.17)	1.06 (0.77–1.46)	1.34 (1.03–1.74)†
Chronic conditions and lifestyle				
Regular exercise habit, yes	1	0.80 (0.48–1.32)	0.30 (0.12–0.72)†	0.79 (0.50–1.26)
Pain, yes	1	0.85 (0.51–1.41)	0.90 (0.36–2.27)	0.76 (0.45–1.31)
Knee pain, yes	1	1.36 (0.72–2.61)	2.19 (0.89–5.45)	1.73 (1.08–2.76)†
Falls, yes	1	0.93 (0.50–1.72)	0.83 (0.36–1.95)	1.78 (0.82–3.86)
Osteoporosis, yes	1	1.66 (0.96–2.88)	1.75 (0.70–4.36)	1.14 (0.70–1.85)
Heart disease, yes	1	2.05 (1.19–3.55)†	1.32 (0.45–3.91)	1.30 (0.74–2.30)
Hyperlipidemia, yes	1	1.74 (1.10–2.77)†	0.96 (0.39–2.35)	1.00 (0.64–1.56)
Knee OA, yes	1	1.24 (0.72–2.15)	1.52 (0.53–4.39)	1.19 (0.67–2.10)

*Skeletal muscle mass index ≧6.42; grip strength greater than BMI adjusted values; usual walking speed ≧1.0 m/s.
†Statistically significant *P* values ($P < .05$) for forward stepwise multiple logistic regressions.

Table 3
Adjusted ORs and 95% CIs for the Predictors of Presarcopenia in 3 Models

Independent Variable	> Cutpoint* Reference	Model I	Model II	Model III
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Anthropometric and fitness				
Age, per 1 y	1	1.13 (1.01–1.26)†	1.10 (1.00–1.22)†	1.11 (1.00–1.23)†
BMI, <21.0 kg/m^2	1	2.31 (1.19–4.49)†	6.40 (3.59–11.44)†	7.22 (4.02–12.96)†
BMD, per 1 unit	1	0.99 (0.63–1.56)	1.34 (0.87–2.06)	1.13 (0.82–2.06)
Calf circumference, per 1 unit	1	0.61 (0.54–0.69)†	0.64 (0.56–0.74)†	0.62 (0.50–0.76)†
Timed up and go, per 1 unit	1	1.29 (1.09–1.52)†	1.27 (1.09–1.49)†	1.30 (1.10–1.52)†
Blood components				
Albumin, per 1 unit	1		0.84 (0.76–0.94)†	0.85 (0.76–0.94)†
25 Hydroxyvitamin D, per 1 unit	1		0.99 (0.95–1.03)	0.99 (0.96–1.04)
β 2-microglobulin, per 1 unit	1		1.51 (0.96–2.38)	1.53 (0.98–2.42)
Hemoglobin A1c, per 1 unit	1		1.16 (0.76–1.79)	1.09 (0.68–1.74)
HDL cholesterol	1		1.00 (0.99–1.02)	1.00 (0.99–1.02)
Cystatin C, per 1 unit	1		1.17 (1.00–1.36)†	1.14 (0.97–1.33)
Chronic conditions and lifestyle				
Regular exercise habit, yes	1			0.70 (0.42–1.14)
Pain, yes	1			0.96 (0.54–1.71)
Knee pain, yes	1			0.80 (0.40–1.60)
Falls, yes	1			1.16 (0.56–2.39)
Osteoporosis, yes	1			0.69 (0.40–1.18)
Heart disease, yes	1			1.97 (1.11–3.49)†
Hyperlipidemia, yes	1			1.48 (0.91–2.41)
Knee OA, yes	1			1.21 (0.62–2.35)

*Skeletal muscle mass index ≧6.42 and grip strength greater than BMI adjusted or skeletal muscle mass index ≧6.42 and usual walking speed ≧1.0 m/s.
†Statistically significant *P* values ($P < .05$) for forward stepwise multiple logistic regressions.

protective effects against the development of presarcopenia. Cystatin C was a predictor of presarcopenia development in Model II (OR 1.17, 95% CI 1.00–1.36), and history of heart disease (OR 1.97, 95% CI 1.11–3.49) was also a predictor of presarcopenia.

The analysis for sarcopenia predictors revealed that low BMI was a significant predictor of the development of sarcopenia, whereas greater calf circumference protected against sarcopenia development across all 3 models (Table 4). Hyperlipidemia (OR 1.94, 95% CI 1.02–3.69) was a significant predictor of sarcopenia.

Older age and longer TUG were significant predictors of severe sarcopenia development, and greater calf circumference showed a protective effect for the development of severe sarcopenia (Table 5). Low BMI was a predictor of severe sarcopenia only in Models II (OR 1.54, 95% CI 1.33–1.78) and III (OR 1.45, 95% CI 1.17–1.81). Higher BMD was a protective variable of severe sarcopenia only in Model III (OR 0.21, 95% CI 0.06–0.82). Furthermore, higher cystatin C levels (OR 1.83, 95% CI 1.08–3.12) was predictive of severe sarcopenia development.

Discussion

The results showed that low BMI was consistently predictive of presarcopenia, sarcopenia, and severe sarcopenia, as well as the components of the definition (ie, declines in SMI, grip strength, and

Table 4
Adjusted ORs and 95% CIs for the Predictors of Sarcopenia in 3 Models

Independent Variable	> Cutpoint* Reference	Model I	Model II	Model III
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Anthropometric and fitness				
Age, per 1 y	1	1.09 (0.96–1.22)	1.07 (0.95–1.21)	1.08 (0.94–1.23)
BMI, <21.0 kg/m^2	1	1.55 (1.35–1.79)†	1.54 (1.33–1.78)†	1.57 (1.35–1.83)†
BMD, per 1 unit	1	1.10 (0.61–1.99)	1.05 (0.57–1.94)	1.10 (0.55–2.19)
Calf circumference, per 1 unit	1	0.82 (0.69–0.98)†	0.81 (0.68–0.97)†	0.83 (0.69–0.98)†
Timed up and go, per 1 unit	1	1.03 (0.89–1.19)	1.03 (0.89–1.19)	1.02 (0.87–1.20)
Blood components				
Albumin, per 1 unit	1		1.04 (0.88–1.22)	1.06 (0.88–1.27)
25 Hydroxyvitamin D, per 1 unit	1		1.00 (0.96–1.05)	1.01 (0.96–1.06)
β 2-microglobulin, per 1 unit	1		1.16 (0.31–4.43)	1.08 (0.28–4.26)
Hemoglobin A1c, per 1 unit	1		0.96 (0.52–1.76)	0.85 (0.45–1.59)
HDL cholesterol	1		1.00 (0.98–1.02)	1.00 (0.98–1.03)
Cystatin C, per 1 unit	1		1.01 (0.71–1.44)	1.01 (0.71–1.45)
Chronic conditions and lifestyle				
Regular exercise habit, yes	1			1.08 (0.53–2.21)
Pain, yes	1			0.70 (0.31–1.55)
Knee pain, yes	1			1.56 (0.60–4.08)
Falls, yes	1			0.87 (0.37–2.06)
Osteoporosis, yes	1			1.52 (0.73–3.15)
Heart disease, yes	1			1.00 (0.71–3.52)
Hyperlipidemia, yes	1			1.94 (1.02–3.69)†
Knee OA, yes	1			2.11 (0.93–4.76)

*Skeletal muscle mass index ≧6.42 and grip strength greater than BMI adjusted or skeletal muscle mass index ≧6.42 and usual walking speed ≧1.0 m/s.
†Statistically significant *P* values ($P < .05$) for forward stepwise multiple logistic regressions.

Table 5
Adjusted ORs and 95% CIs for the Predictors of Severe Sarcopenia in 3 Models

Independent Variable	> Cutpoint* Reference	Model I	Model II	Model III
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Anthropometric and fitness				
Age, per 1 y	1	1.27 (1.06–1.52)†	1.27 (1.05–1.52)†	1.25 (1.02–1.52)†
BMI, <21.0 kg/m^2	1	1.36 (0.32–5.74)	1.54 (1.33–1.78)†	1.45 (1.17–1.81)†
BMD, per 1 unit	1	0.75 (0.30–1.89)	0.58 (0.22–1.54)	0.21 (0.06–0.82)†
Calf circumference, per 1 unit	1	0.62 (0.49–0.78)†	0.62 (0.48–0.78)†	0.69 (0.49–0.96)†
Timed up and go, per 1 unit	1	1.21 (1.07–1.37)†	1.21 (1.06–1.36)†	1.42 (1.16–1.74)†
Blood components				
Albumin, per 1 unit	1		0.86 (0.66–1.12)	0.85 (0.64–1.14)
25 Hydroxyvitamin D, per 1 unit	1		0.99 (0.95–1.05)	0.94 (0.88–1.01)
β 2-microglobulin, per 1 unit	1		0.53 (0.09–3.06)	0.25 (0.04–1.78)
Hemoglobin A1c, per 1 unit	1		0.45 (0.14–1.45)	0.55 (0.06–4.84)
HDL cholesterol	1		1.00 (0.97–1.04)	1.00 (0.96–1.04)
Cystatin C, per 1 unit	1		1.37 (0.86–2.18)	1.83 (1.08–3.12)†
Chronic conditions and lifestyle				
Regular exercise habit, yes	1			0.59 (0.18–1.92)
Pain, yes	1			0.46 (0.09–2.31)
Knee pain, yes	1			0.99 (0.22–4.35)
Falls, yes	1			1.05 (0.22–4.91)
Osteoporosis, yes	1			1.21 (0.33–4.41)
Heart disease, yes	1			0.91 (0.26–3.15)
Hyperlipidemia, yes	1			1.46 (0.43–4.94)
Knee OA, yes	1			1.52 (0.39–5.88)

*Skeletal muscle mass index ≧6.42 and grip strength greater than BMI adjusted values and usual walking speed ≧1.0 m/s.
†Statistically significant *P* values ($P < .05$) for forward stepwise multiple logistic regressions.

walking speed). Greater calf circumference consistently predicted lower risk of developing all stages of sarcopenia. Slow TUG was also a consistent predictor of presarcopenia and severe sarcopenia. Cystatin C was a significant predictor of severe sarcopenia alone. These results support previous cross-sectional research that has shown that factors such as age, BMI, physical activity,[4,6] and leg strength[20] are associated with sarcopenia. Although the current study confirmed these findings with longitudinal data, there were several interesting findings that have not previously been observed.

A primary finding of this study was that a higher level of cystatin C was associated with a greater risk of severe sarcopenia onset. Sarcopenia has been reported to be common among community-dwelling older adults with chronic kidney disease,[10] and there have been studies showing significant relationships between cystatin C and physical function measures, mobility in particular, among the elderly; and sarcopenia has been seen in patients with end-stage renal disease.[21,22] Interestingly, the results of our study revealed that cystatin C was a predictor of severe sarcopenia but not sarcopenia. As these results suggest, sarcopenia is a complex systemic condition. One previous study suggested that a heightened inflammatory state could explain the association between chronic kidney disease and the development of functional impairment,[23] as higher levels of inflammatory markers were associated with declines in physical function and muscle mass as well as strength.[24,25] Although causality could not be determined in this study, there is a significant association between kidney dysfunction and severe sarcopenia. Cystatin C has been associated in previous research with declines in muscle mass, strength, and walking ability, separately. The results of the current study suggest that cystatin C may be a common mediating factor involved in muscle mass, strength, and walking ability, as associations were observed between cystatin C and the combination of all 3 factors. Perhaps the improvement of cystatin C could positively affect sarcopenia status. In a clinical setting, clinical practitioners who observe high cystatin C levels may also want to look closely for severe sarcopenia, and suggest ways to improve physical function as well as improvements in kidney function. Further research is needed to determine not only the mechanism of this relationship, but also interventions that may improve the quality of life of elderly people with kidney dysfunction and sarcopenia.

The relationship between BMD and physical performance is still unclear. There is conflicting and inconsistent evidence from various research studies, with some supporting the hypothesis that physical performance has no association with BMD, and other studies showing positive associations of BMD and lower extremity measures fitness.[26] A previous report suggested that hip BMD was a risk factor for sarcopenia in elderly men.[4] Similarly, in our study we found that higher BMD had protective effects against severe sarcopenia as well as grip strength and walking speed. This association was, however, seen only in severe sarcopenia and not sarcopenia alone. One recent study suggested that the treatment of sarcopenia may be increasingly important for the prevention of fractures.[27] Based on our findings and those of previous studies, perhaps clinical practitioners should suggest treatment options to improve sarcopenia as well as BMD or osteoporosis.

BMI may be a predictor of skeletal muscle mass for women.[20] Recently, one study indicated that nursing home residents who had a BMI higher than 21.0 kg/m^2 had lower risk of being sarcopenic, relative to those with BMI less than 21.0 kg/m^2.[6] Our data also showed that a BMI below 21.0 kg/m^2 significantly increased the risk of developing sarcopenia and severe sarcopenia.

Although research has suggested that calf circumference could be used to assess muscle mass,[28,29] one report indicated that calf circumference could not be used to predict sarcopenia, but may provide valuable information on muscle-related disability and physical function.[28] Recently, calf circumference has been positively related to lower frailty index and higher functional performance.[29] The authors suggested that calf circumference is a valuable tool for clinicians, and seems relevant for the screening of sarcopenia. Needless to say, the literature regarding calf circumference and sarcopenia is inconsistent. Participants in our study who had greater calf circumference had a significantly lower risk of developing all stages of sarcopenia over 4 years. Such results support the positive findings that calf circumference is indeed a simple, valuable measurement for predicting the risk of developing sarcopenia.

TUG was developed to predict falls in older people, and is also a commonly used assessment for physical function and balance.[30] Recently, TUG was found to be significantly associated with relative muscle mass and knee extension torque, and suggested that should

be accounted for when defining sarcopenia.[31] In the current study, TUG was a significant predictor of the onset of both sarcopenia and severe sarcopenia, suggesting that declines in balance may play a role in the development of sarcopenia.

The results revealed that age, BMI, and calf circumference were predictive of declines in all components of sarcopenia (ie, SMI, grip strength, and walking speed). HDL, cystatin C, and knee pain were all positively associated with the risk for decline in walking speed. Heart disease and hyperlipidemia were predictors of SMI decline, and regular exercise habit was protective against grip strength decline. These novel findings illustrate the predictors of the components of sarcopenia. The predictors were different for each component, and thus should be analyzed separately, as each is a complex condition itself.

The analyses also showed protective effects of higher albumin levels for declines in SMI and walking speed, as well as the development of presarcopenia. Previous studies suggested that low serum albumin is associated with weaker muscle strength in older people,[32] and even further that the increased risk of disability with low serum albumin concentrations may reflect an association with sarcopenia.[33] Therefore, because low albumin is associated with low nutritional status, muscle strength and/or mass may decline due to degradation of protein synthesis caused by malnutrition.[32]

There are several limitations that should be taken into account. First, investigation into the mechanism of the relationships observed was beyond the scope of this study. Although interesting associations were found, we could not determine causality or the mechanisms behind such relationships. Second, this study focused only on the incidence and predictors of sarcopenia in elderly women, and not in men. Therefore the conclusions made cannot be generalized to the population as a whole. However, sarcopenia is a greater public health problem in women than men because women live longer and have higher rates of disability.[34] Further population-based studies are necessary to identify the predictors of sarcopenia.

Based on the results of this study, the predictors of severe sarcopenia included age, BMI, BMD, calf circumference, TUG, and cystatin C. The novelty of the study lies in the relationship between cystatin C and severe sarcopenia. Kidney dysfunction before the development of sarcopenia may indicate a fivefold increase in the odds of sarcopenia onset, based on our longitudinal data. Further research is needed to confirm these results in larger populations.

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Appendix 1

Comparison of Selected Baseline Variables Between Participants of the On-site Survey (Followed) and Dropouts

Variables	Followed (n = 575)	Postal Survey (n = 554)	Institutionalized (n = 38)	Died (n = 39)	No contact (n = 83)	*P* Value*	Post Hoc†
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	78.01 ± 2.5	78.7 ± 2.7	78.4 ± 3.0	79.7 ± 2.8	79.2 ± 2.6	<.001	F<Pst, D, N
Height (cm)	148.4 ± 5.3	147.6 ± 5.6	148.0 ± 6.8	147.2 ± 6.0	146.8 ± 5.5	.027	
Body weight (kg)	50.2 ± 7.9	49.7 ± 7.9	48.6 ± 9.0	49.5 ± 8.1	48.4 ± 8.2	.272	
BMI (kg/m^2)	22.8 ± 3.3	22.8 ± 3.2	22.2 ± 3.9	22.8 ± 3.2	22.5 ± 3.7	.782	
BMD (g/cm^2)	0.29 ± 0.1	0.29 ± 0.06	0.27 ± 0.06	0.28 ± 0.06	0.28 ± 0.06	.104	
Muscle mass (kg)	31.0 ± 3.5	30.6 ± 3.7	30.0 ± 3.8	31.1 ± 4.4	30.2 ± 3.7	.148	
Appendicular muscle mass (kg)	15.5 ± 1.9	15.3 ± 2.0	14.9 ± 1.9	15.6 ± 2.5	15.2 ± 2.1	.189	
Calf circumference (cm)	33.4 ± 2.9	33.0 ± 2.9	32.6 ± 3.3	33.4 ± 3.8	32.6 ± 3.1	.071	
Grip strength (kg)	18.9 ± 4.1	18.0 ± 4.0	18.0 ± 4.0	17.0 ± 3.8	17.4 ± 3.9	<.001	F>Pst, N
Knee extension strength (Nm)	59.9 ± 16.5	56.8 ± 14.6	52.7 ± 14.1	53.4 ± 14.9	52.7 ± 14.6	<.001	F>Pst, N
Usual walking speed (m/s)	1.3 ± 0.2	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	<.001	F>Pst, I, D, N
Timed up & go (s)	7.4 ± 2.8	8.3 ± 3.6	9.3 ± 5.2	9.5 ± 6.3	9.3 ± 4.0	<.001	F<Pst, I, D, N
Creatinine (mg/dL)	0.65 ± 0.15	0.67 ± 0.18	0.63 ± 0.12	0.72 ± 0.23	0.67 ± 0.17	.020	
Albumin (g/dL)	4.28 ± 0.2	4.27 ± 0.24	4.27 ± 0.23	4.22 ± 0.30	4.27 ± 0.26	.692	
25 Hydroxyvitamin D (ng/ml)	22.16 ± 6.4	21.64 ± 6.34	20.21 ± 6.89	23.11 ± 11.91	21.55 ± 7.68	.236	
β 2-microglobulin (mg/L)	1.91 ± 0.5	2.02 ± 0.63	2.05 ± 0.70	2.36 ± 0.98	2.10 ± 0.66	<.001	D>Pst>F
Cystatin C (mg/L)	0.93 ± 0.2	0.97 ± 0.23	0.96 ± 0.25	1.11 ± 0.36	0.99 ± 0.27	<.001	D>Pst>F
Chronic conditions and lifestyle variables							
Falls (yes, %)	16.2	19.2	18.4	23.1	31.3	.020	
Multiple falls (yes, %)	3.7	4.2	7.9	5.1	13.3	.003	
Pain (yes, %)	60.7	66.7	71.1	64.1	62.7	.252	
Knee pain (yes, %)	32.2	33.4	43.2	26.5	31.2	.607	
IADL (disability, %)	3.0	6.0	10.5	7.7	8.4	.023	
Regular exercise (yes, %)	40.7	25.1	23.7	28.2	20.5	<.001	
Knee osteoarthritis history (yes, %)	23.9	22.4	13.2	20.5	26.5	.532	
Osteoporosis history (yes, %)	28.2	34.3	34.2	30.8	32.5	.274	
Heart disease history (yes, %)	19.3	20.2	13.2	35.9	21.7	.110	
Hyperlipidemia history (yes, %)	39.8	38.3	28.9	33.3	37.8	.670	

BMI, body mass index; BMD, bone mineral density; IADL, instrumental activities of daily living; F, followed; Pst, postal survey; I, institutionalized, D, died, N, no contact.

*One-way analysis of variance for continuous variables and chi-square test for categorical variables.

†A post hoc analysis was performed using the Scheffe method.

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Original Study

Physical Frailty Predicts Incident Depressive Symptoms in Elderly People: Prospective Findings From the Obu Study of Health Promotion for the Elderly

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Keywords:
Geriatric Depression Scale
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cognitive function
physical performance

A B S T R A C T

Objective: The purpose of this study was to determine whether frailty is an important and independent predictor of incident depressive symptoms in elderly people without depressive symptoms at baseline.
Design: Fifteen-month prospective study.
Setting: General community in Japan.
Participants: A total of 3025 community-dwelling elderly people aged 65 years or over without depressive symptoms at baseline.
Measurements: The self-rated 15-item Geriatric Depression Scale was used to assess symptoms of depression with a score of 6 or more at baseline and 15-month follow-up. Participants underwent a structural interview designed to obtain demographic factors and frailty status, and completed cognitive testing with the Mini-Mental State Examination and physical performance testing with the Short Physical Performance Battery as potential predictors.
Results: At a 15-month follow-up survey, 226 participants (7.5%) reported the development of depressive symptoms. We found that frailty and poor self-rated general health (adjusted odds ratio 1.86, 95% confidence interval 1.30–2.66, $P < .01$) were independent predictors of incident depressive symptoms. The odds ratio for depressive symptoms in participants with frailty compared with robust participants was 1.86 (95% confidence interval 1.05–3.28, $P = .03$) after adjusting for demographic factors, self-rated general health, behavior, living arrangements, Mini-Mental State Examination, Short Physical Performance Battery, and Geriatric Depression Scale scores at baseline.
Conclusions: Our findings suggested that frailty and poor self-rated general health were independent predictors of depressive symptoms in community-dwelling elderly people.

Depressive symptoms in later life are common psychological problems that affect the outcome of many medical illnesses including functional disability, and depression and cognitive impairment often co-occur.[1] Identifying modifiable indicators of incident depressive symptoms could help reduce and prevent physical and mental health problems in elderly adults.

Physical frailty is a common clinical syndrome in elderly adults that carries an increased risk of poor health outcomes. The most well-known biological syndrome model of frailty is characterized by weight loss, exhaustion, inactivity, slowness, and weakness (a person meeting 3 or more out of these 5 criteria is considered frail).[2] Physical inactivity is common in individuals with depression and physical frailty.

The authors declare no conflicts of interest.

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The prevalence of such physical frailty in depressed elderly people is higher than in nondepressed individuals.[3] Previous large cohort studies have examined longitudinal associations between physical frailty and depressive symptoms in elderly people. The Women's Health Initiative Observational Study found that depressive symptoms were significantly associated with incident frailty[4]; however, in the Women's Health and Aging Study I, this association was not significant.[5]

Although depressive symptoms seem to increase the risk of incident frailty, the Singapore Longitudinal Aging Study-I (SLAS-I) was the only study to suggest that physical frailty, assessed using 5 characterized components, was a significant predictor of incident depressive symptoms in elderly people.[6] However, the SLAS-I included both middle-aged and elderly people (participants were aged ≥55) and omitted some important covariates (eg, physical performance[7] and self-rated health[8,9]) that potentially affect longitudinal relationships between physical frailty and depressive symptoms.

To extend previous findings, we examine whether frailty is an important and independent predictor of incident depressive symptoms in elderly people without depressive symptoms. Our longitudinal study included adults aged 65 and over, was short-term (15 months) relative to previous studies (eg, 2–4 years), and sought to identify more substantial risk factors for incident depressive symptoms. We included as covariates potential moderators, including self-rated health, behavior, living environment, cognitive function, and physical performance.

Methods

Participants

This prospective cohort study involved 3025 community-dwelling elder adults enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). Individuals selected for participation in the OSHPE were chosen from the 15,974 older people (≥65 years) living in Obu, a residential suburb of Nagoya, Japan. A letter of invitation was sent to them to participate in the OSHPE. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, Obu residency, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (care level ≥3/5), disability in basic activities of daily living, and inability to undergo performance-based assessments.[10] Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a baseline OSHPE assessment including a face-to-face interview and measures of physical and cognitive function. A follow-up postal survey was conducted approximately 15 months following baseline assessment (November 2012–May 2013) with an offer of assistance with completion.

In this longitudinal study, we included participants who completed baseline assessments of physical performance and global cognition and follow-up assessments of depressive symptoms. We excluded participants with a history of Parkinson's disease, stroke, depression, Alzheimer's disease, Mini-Mental State Examination (MMSE)[11] scores of <18, or depressive symptoms at baseline. Informed consents were obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

Measures

Depressive symptoms

Depressive symptoms were measured at baseline and follow-up using the 15-item Geriatric Depression Scale (GDS).[12] The cut-off score of ≥6 has a sensitivity of 82% and a specificity of 75% with a structured clinical interview for depression.[13]

Demographic factors, health behaviors, and living environment

Licensed nurses recorded demographic data, including age, sex, and medical history in face-to-face interviews. Self-rated general health, fear of falling, current alcohol intake, smoking status, and living arrangements (ie, cohabiting or living with family) were assessed in the baseline survey.

Self-rated general health was measured using the question 'How would you rate your general health?' and a 4-point scale ranging from 'bad,' to 'very good.' We categorized participants into 2 groups based on their responses: 'bad' ('bad' + 'fairly bad') and 'good' ('fairly good' + 'very good').[14]

Fear of falling was assessed using a fourth-ordered choice and the closed-ended question, 'Are you afraid of falling?' Responses of 'very much' or 'somewhat' indicated fear of falling and responses of 'a little' or 'not at all' indicated no fear of falling.[15]

Participants answered questions about educational history (years), frequency of alcohol intake (daily, 5–6 days, 2–4 days, or ≤1 day per week, or never), smoking status (current, former, or never), and living arrangements [cohabitant or living with family (number)]. We classified educational history into 3 groups (≤9, 10–12, or ≥13), and alcohol use [frequent (≥5 days/week), occasional (≤4 days/week), or none], smoking (yes/no), and living alone (alone/not alone) into 2 groups.

Physical performance test and global cognitive function

We measured physical performance using the Short Physical Performance Battery (SPPB), which includes static balance, walking, and repeated chair rise tests.[16] Scores ranged from 0 (inability to perform the task) to 4 (optimum performance). Summary SPPB scores range from 0 to 12; higher scores indicated higher physical performance. The SPPB has excellent test-retest reliability.[17]

Global cognitive function was assessed using the MMSE,[11] with a cut-off point of 27/26 for intact/very mild impairment and 24/23 for very mild/mild impairment (cut-offs adopted from previous research).[18,19]

Frailty phenotype

The frailty phenotype was characterized by limitations in ≥3 of the following 5 domains[10]: (1) mobility, (2) strength, (3) endurance, (4) physical activity, and (5) weight loss. Mobility was measured in seconds using a stopwatch. Participants were asked to walk 6.4 m (divided into two 2.0-m end zones, and a 2.4-m middle zone) at their usual pace. We measured the time taken (in seconds) to pass middle zone to calculate gait speed (m/s). Use of a cane or walker was permitted provided participants could not practice the gait test. A cut-off point (<1.0 m/s) determined slow speed.[10,20] Grip strength was measured in kilograms using a Smedley-type handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan) in the dominant hand while standing. A sex-specific cut-off point (male: <26 kg, female: <17 kg) determined low grip strength (weakness).[20] A self-report measure of exhaustion, which included questions from the GDS such as 'Do you feel full of energy?' was used to assess endurance. A response of 'no' indicated exhaustion.[21] We evaluated the role of physical activity by asking (1) 'Do you engage in moderate levels of physical exercise or sports aimed at health?' and (2) 'Do you engage in low levels of physical exercise aimed at health?' Responses of 'no' to both questions indicated low physical activity. Nutritional status was established according to self-reports of weight loss in response to the following question: 'In the past 2 years, have you lost more than 5% of your body weight irrespective of intent to lose weight?' Participants who answered 'yes' were then classified as weight loss.[21]

Participants demonstrating none of these components were considered to be robust, and those demonstrating 1 or 2 components were considered to be of intermediate phenotype.

Statistical Analysis

We performed all analyses using SPSS v 19.0 (SPSS Inc, Chicago, IL). The overall alpha was set at less than 0.05. Student t tests and χ^2 tests were used to compare baseline measures between participants with depressive symptoms (GDS ≥6) and without (GDS <6) during a 15-month follow-up period. Associations between depressive symptoms and other factors were examined using multiple logistic regression models. In the multiple logistic regression analyses, the final model included age, sex, education, self-rated general health, fear of falling, smoking status, alcohol use, living arrangements, global cognition, physical performance, frailty status, and GDS scores at baseline. Odds ratios (ORs) and 95% confidence intervals (CIs) for the incidence of depressive symptoms were calculated.

Results

Characteristics of Participants

Of the 5104 participants enrolled in the OSHPE who underwent baseline assessment, 4432 (86.8%) responded to the 15-month follow-up postal survey.

Of these responders, 618 were excluded because of a history of Parkinson's disease, stroke, depression, Alzheimer's disease, or cognitive problem (MMSE <18) at baseline, or missing values on baseline measures of physical performance or global cognition. Another 495 had clinical depressive symptoms at baseline, and 294 had missing values on GDS at baseline or follow up. Data from 3025 elderly adults were included in the final analyses. Table 1 summarizes participant characteristics. Participants' mean age was 71.4 ± 5.1 years, and 50.3% were women. Baseline mean MMSE, SPPB, and GDS scores were 26.6 ± 2.5, 11.7 ± 0.8, and 1.9 ± 1.5, respectively. At 15-month follow-up, 226 participants (7.5%) had a GDS score of ≥6 and were considered to have developed depressive symptoms.

Baseline Measures and Onset of Depressive Symptoms

Table 1 summarizes the demographics and baseline measures for participants with and without depressive symptoms. Participants with incident depressive symptoms were significantly older, predominantly female, and demonstrated greater fear of falling, worse self-rated general health and physical performance, and higher baseline GDS scores relative to participants without depressive symptoms. In the 5 components that determined frailty status, participants with depressive symptoms exhibited significantly greater proportions of slowness, weakness, exhaustion, and low activity at baseline relative to participants without depressive symptoms.

Associations Between Incident Depressive Symptoms at 15-Month Follow-Up and Variables at Baseline

After adjusting for age (fitted in 5-year age bands) and sex, poor self-rated general health and fear of falling were significantly associated with incident depressive symptoms (Table 2). Poor global cognition and physical performance were significantly associated with incident depressive symptoms after adjusting for age and sex (Table 3); however, these associations were not significant in the final model (Table 4). The final model, which included age, sex, education, self-rated general health, fear of falling, smoking status, alcohol use, living arrangements, global cognition (MMSE), physical performance (SPPB), frailty status, and GDS scores at baseline, showed that poor self-rated general health was an independent predictor of depressive symptoms (OR 1.86, 95% CI 1.30–2.66, $P < .01$) but that fear of falling was not (OR 1.27, 95% CI 0.93–1.73, $P = .13$). Further, no associations between incident depressive symptoms and age, sex, education, current smoker, alcohol use, and living alone were found in the final model (Table 4). In contrast, frailty was an independent predictor of incident depressive symptoms and the OR for depressive symptoms in participants who demonstrated frailty relative to robust participants was 1.86 (95% CI 1.05–3.28, $P = .03$) in the final model (Table 4).

Table 1
Comparison of Demographic Factors, Health Behaviors, Measures of Physical and Cognitive Performance Tests, Frailty Components, and GDS Scores Between the Stable Nondepressive and the Incident Depressive Symptoms Groups at Baseline

Variables at Baseline	All Participants (n = 3025)	Stable Nondepressive Symptoms* (n = 2799)	Incident Depressive Symptoms* (n = 226)	*P*
Age, mean ± SD (years)	71.4 (5.1)	71.3 (5.0)	72.4 (6.0)	.003
Female, n (%)	1522 (50.3)	1392 (49.7)	130 (57.5)	.024
Education,† mean ± SD (years)	11.6 (2.5)	11.6 (2.5)	11.4 (2.4)	.233
Medical history, n (%)				
Hypertension	1329 (43.9)	1223 (43.7)	106 (46.9)	.350
Heart disease	460 (15.2)	417 (14.9)	43 (19.0)	.096
Diabetes mellitus	392 (13.0)	358 (12.8)	34 (15.0)	.332
Osteoporosis†	285 (9.4)	251 (9.0)	34 (15.0)	.003
Knee osteoarthritis	393 (13.0)	353 (12.6)	40 (17.7)	.029
Cancer†	284 (9.4)	265 (9.5)	19 (8.4)	.598
Self-rated general health, n (%)				
Very good	645 (21.3)	622 (22.2)	23 (10.2)	<.001
Fairly good	2078 (68.7)	1931 (69.0)	147 (65.0)	
Fairly bad	277 (9.2)	227 (8.1)	50 (22.1)	
Bad	25 (0.8)	19 (0.7)	6 (2.7)	
Fear of falling, n (%)				
Very afraid	203 (6.7)	166 (5.9)	37 (16.4)	<.001
Somewhat afraid	1002 (33.1)	914 (32.7)	88 (38.9)	
A little	552 (18.2)	522 (18.6)	30 (13.3)	
Not at all	1268 (41.9)	1197 (42.8)	71 (31.4)	
Smoking, n (%)				
Current	291 (9.6)	267 (9.5)	24 (10.6)	
Former	946 (31.3)	883 (31.5)	63 (27.9)	
Never	1788 (59.1)	1649 (58.9)	139 (61.5)	.499
Alcohol, n (%)				
Daily	703 (23.2)	653 (23.3)	50 (22.1)	.295
5–6 days/week	172 (5.7)	164 (5.9)	8 (3.5)	
2–4 days/week	261 (8.6)	243 (8.7)	18 (8.0)	
1 day or less/week	303 (10.0)	285 (10.2)	18 (8.0)	
Never	1586 (52.4)	1454 (51.9)	132 (58.4)	
Living, n (%)				
Alone	260 (8.6)	234 (8.4)	26 (11.5)	.062
With 1 person	1490 (49.3)	1394 (49.8)	96 (42.5)	
With 2 or more	1275 (42.1)	1171 (41.8)	104 (46.0)	
Global cognition				
MMSE, mean ± SD (score)	26.6 (2.5)	26.6 (2.5)	26.3 (2.7)	.055
Physical performance				
SPPB, mean ± SD (score)	11.7 (0.8)	11.7 (0.7)	11.5 (1.1)	<.001
Baseline GDS, mean ± SD (score)	1.9 (1.5)	1.8 (1.5)	3.2 (1.5)	<.001
Frailty components, n (%)				
Slowness	346 (11.4)	302 (10.8)	44 (19.5)	<.001
Weakness	310 (10.2)	276 (9.9)	34 (15.0)	.013
Exhaustion	1090 (36.0)	952 (34.0)	138 (61.1)	<.001
Low activity	748 (24.7)	669 (23.9)	79 (35.0)	<.001
Shrinking	325 (10.7)	293 (10.5)	32 (14.2)	.085

*Incident depressive symptoms were established according to a cut-off score of GDS (≥6) at 15-month follow-up survey.
†Missing values on education (n = 8) and medical history (osteoporosis, n = 1; cancer, n = 1).

Table 2
Associations Between Incident Depressive Symptoms at 15-Month Follow-Up and Demographic Factors, Health Behaviors, and Living Arrangements at Baseline (n = 3025)

Baseline Characteristics	Total Participants	Incident Rate (GDS ≥6), n (%)	OR (95% CI) Adjusted for Age and Sex*
Age			
65–69	1309	88 (6.7)	1
70–74	986	60 (6.1)	0.912 (0.649–1.280)
75–79	470	46 (9.8)	1.524 (1.049–2.215)†
80 or more	260	32 (12.3)	2.000 (1.301–3.073)‡
Sex			
Male	1503	96 (6.4)	1
Female	1522	130 (8.5)	1.392 (1.057–1.833)†
Education§			
9 or less	936	72 (7.7)	1
10–12	1353	101 (7.5)	0.924 (0.632–1.352)
13 or more	728	52 (7.1)	0.978 (0.687–1.392)
General health			
Very good/fairly good	2723	170 (6.2)	1
Fairly bad/bad	302	56 (18.5)	3.267 (2.346–4.551)‡
Fear of falling			
A little/not at all	1820	101 (5.5)	1
Very afraid/somewhat afraid	1205	125 (10.4)	1.801 (1.349–2.405)‡
Current smoker			
Yes	291	24 (8.2)	1
No	2734	202 (7.4)	0.709 (0.446–1.129)
Alcohol			
Frequent (5 days or more/week)	875	58 (6.6)	1
Occasional (4 days or less/week)	564	36 (6.4)	0.962 (0.671–1.379)
Not at all	1586	132 (8.3)	0.847 (0.573–1.253)
Living			
Alone	260	26 (10.0)	1
Not alone	2765	200 (7.2)	0.859 (0.551–1.342)

*Age adjusted OR age was fitted in 5-year age bands: 65–69; 70–74; 75–79; 80 or more.
†$P < .05$.
‡$P < .01$.
§Missing values on education (n = 8).

Discussion

In this longitudinal cohort study of community-dwelling elderly adults without depressive symptoms at baseline, 7.5% individuals reported depressive symptoms at 15-month follow up. Physical frailty and poor self-rated health were independent predictors of incident depressive symptoms after adjusting for demographic factors, health behaviors, living arrangements, global cognition, physical performance, and GDS score at baseline.

Table 3
Associations Between Incident Depressive Symptoms at 15-Month Follow-Up and General Cognition, Physical Performance, and Frailty Status at Baseline (n = 3025)

Baseline Assessments	Total Participants	Incident Rate (GDS ≥6), n (%)	OR (95% CI) Adjusted for Age and Sex*
Global cognition (MMSE score)			
27–30	1695	117 (6.9)	1
24–26	951	69 (7.3)	1.024 (0.750–1.399)
18–23	379	40 (10.6)	1.533 (1.036–2.267)†
Physical performance (SPPB score)			
12 (full)	2488	164 (6.6)	1
10–11	444	45 (10.1)	1.435 (1.000–2.060)†
9 or below	93	17 (18.3)	2.453 (1.359–4.429)‡
Frailty[a]			
Robust	1170	40 (3.4)	1
Intermediate	1661	150 (9.0)	2.719 (1.899–3.893)‡
Frail	194	36 (18.6)	5.637 (3.400–9.346)‡

A Frailty phenotype was defined by number of 5 domains (mobility, strength, endurance, physical activity, and weight loss): Robust = 0; Intermediate = 1-2; Frail ≥3.
*Age adjusted OR age was fitted in 5-year age bands: 65–69; 70–74; 75–79; 80 or more.
†$P < .05$.
‡$P < .01$.

Table 4
Results of the Final Model Assessing Associations Between Incident Depressive Symptoms at 15-Month Follow-Up and Baseline, Measurements (n = 3025)

Baseline Variables	OR (95% CI) Adjusted for Factors in Final Model*
Age	
65–69	1
70–74	0.891 (0.623–1.273)
75–79	1.228 (0.820–1.839)
80 or more	1.211 (0.712–2.062)
Sex	
Male	1
Female	1.318 (0.927–1.875)
Education[a]	
9 or less	1
10–12	0.755 (0.504–1.131)
13 or more	0.936 (0.648–1.352)
General health	
Very good/fairly good	1
Fairly bad/bad	1.856 (1.295–2.660)‡
Fear of falling	
A little/not at all	1
Very afraid/somewhat afraid	1.271 (0.932–1.732)
Current smoker	
Yes	1
No	0.766 (0.470–1.247)
Alcohol	
Frequent (5 days or more/week)	1
Occasional (4 days or less/week)	1.125 (0.771–1.641)
Not at all	1.023 (0.680–1.538)
Living	
Alone	1
Not alone	0.833 (0.519–1.337)
Global cognition (MMSE score)	
27–30	1
24–26	0.953 (0.688–1.322)
18–23	1.298 (0.850–1.983)
Physical performance (SPPB score)	
12 (full)	1
10–11	1.100 (0.751–1.614)
9 or below	1.456 (0.766–2.768)
Frailty[a]	
Robust	1
Intermediate	1.382 (0.931–2.052)
Frail	1.856 (1.049–3.283)†

*Final model includes the following variables: age; sex; education; self-rated general health; fear of falling; smoking status; alcohol; living; MMSE; SPPB; frailty status and GDS score at baseline.
†$P < .05$.
‡$P < .01$.

Previous findings from longitudinal studies indicate that factors similar to components of physical frailty, such as mobility problems,[22] physical inactivity,[23] and fatigue[24] appear to increase the risk for developing depressive symptoms in elderly adults. Findings from the present longitudinal data indicate an important role for physical frailty as a predictor of depressive symptoms and extend previous findings. To our knowledge, physical frailty, defined using a clinical biological syndrome model including weight loss, exhaustion, inactivity, slowness, and weakness, as a predictor of the onset of depressive symptoms among community-dwelling elderly adults has only been reported in one study, the SLAS-I.[6]

The SLAS-I involved a relatively younger aged Chinese population (mean age 65.9 years, n = 1827) and demonstrated prospective associations between physical frailty at baseline and depressive symptoms at follow-up.[6] In the SLAS-I longitudinal analysis of data from participants without depressive symptoms at baseline, frail individuals were more likely than nonfrail individuals to show new depressive symptoms at 2- and 4-year follow-up and the adjusted OR

for frailty was 3.75. Even though our participants were older (mean age 71.4 years), and the follow-up period was shorter (15 months) than in the SLAS-I, using specific phenotypic criteria to define physical frailty, our results indicated that in participants without depressive symptoms at baseline, frail individuals were approximately twice as likely to develop depressive symptoms as robust individuals after controlling for potential confounds.

In addition, the present results must be interpreted carefully as the endurance component of the frailty phenotype was measured using an actual item from the 15-item GDS scale. Other previous studies have also measured the endurance component of the frailty phenotype using the sub-items of a depression scale, such as the GDS scale[21] or Center for Epidemiological Studies Depression scale.[2] Therefore, we consider the endurance component of the frailty phenotype to overlap with the component of the depression assessments. Therefore, this issue can be seen as one of our study's limitations, as there were no significant differences in the incident rate regarding frail people with (32/164, 19.5%) or without (4/30, 13.3%) exhaustion.

Positive or negative life events may be associated with changes in mood, anxiety, and depression. Thus, the onset of depressive symptoms may be influenced by life events during long-term follow up, whereas short-term follow up allows us to control this influence and examine the baseline status of symptom onset. Our findings from a relatively short-term follow-up period suggest that nondepressed elderly adults with physical frailty at baseline are at greater risk of the onset of depressive symptoms in the near future. However, we recognize that negative life events occurring during the follow-up period may affect the onset of depressive symptoms; this should be considered in future research.

The frailty phenotype has been found to be an independent predictor of risk of adverse outcomes including falls, hip fracture, disability, hospitalization, and death.[2,21] Although frail elderly adults are more likely to remain so, these components of frailty are modifiable and could improve through interventions or behavior change. Previous observational longitudinal studies have indicated that approximately 10% to 20% of frail or pre-frail individuals transitioned into states of lesser frailty during the follow-up period.[25,26] In addition, the efficacy of exercise-based interventions for improving markers of physical frailty in community-dwelling elderly people was reported.[27] Thus, improvement in frailty may lead to prevention of depression in elderly people.

We also found that poor self-rated health was an independent predictor of incident depressive symptoms. Prior longitudinal studies have indicated the reverse as bidirectional associations between self-rated health and depression in community-dwelling elderly adults were found.[8,9] The results of this study support this longitudinal relationship, and promotion of general health in elderly adults may be critical to preventing the onset of depressive symptoms. Conversely, MMSE and SPPB scores at baseline were not significantly associated with depressive symptoms in our sample. Depressive symptoms appear to be an important predictor of cognitive and physical decline.[28,29] Therefore, the possibility of the reverse and temporal associations should be investigated in future research.

Although we included statistical controls such as demographic factors, health behavior, living arrangements, global cognition, physical performance, and GDS score at baseline, there may be other potential confounders. Psychosocial characteristics, particularly having few or no close social contacts, should be included as potential confounders.[30] In addition, because we did not repeat measures of physical frailty, we could not mention bidirectional associations between frailty and depressive symptoms. Therefore, further work is needed to determine bidirectional and temporal associations and the effects of improvements in frailty on depression prevention.

Conclusions

Our findings indicated that in community-dwelling elderly adults without depression symptoms, physical frailty, and poor self-rated health are independent predictors of new incident depressive symptoms after adjusting for demographic factors, health behavior, living arrangements, global cognition, physical performance, and GDS score at baseline.

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Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed

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ABSTRACT

The decrease in serum insulin-like growth factor-1 (IGF-I) with aging is related to the neurobiological processes in Alzheimer's disease. IGF-1 mediates effects of physical exercise on the brain, and cognition has a common pathophysiology with physical function, particularly with gait. The aim of this study was to examine whether mild cognitive impairment (MCI) and slow gait are associated with the serum IGF-1 level. A population survey was conducted in 3355 participants (mean age, 71.4 years). Cognitive functions (attention, executive function, processing speed, visuospatial skill, and memory), gait speed, and demographic variables were measured. All cognitive functions and gait speed were associated with the IGF-1 level ($p < 0.001$). The association of IGF-1 with slow gait was weakened by adjustment for covariates, but MCI and the combination of MCI and slow gait were independently related to the IGF-1 level in multivariate analysis ($p < 0.05$). Our findings support the association of a low IGF-1 level with reduced cognitive function and gait speed, particularly with a combination of MCI and slow gait.

1. Introduction

Insulin-like growth factor-1 (IGF-1) is an important mediator of growth hormone effects in body growth and tissue remodeling (Nishijima et al., 2010) and contributes to the promotion of neuronal plasticity and skeletal muscle (Clegg et al., 2013; Florini et al., 1991; van Dam et al., 2000). IGF-1 also has protective effects on the neurobiological processes that are compromised by aging and Alzheimer's disease (AD), including those with potent neurotrophic and neuroprotective actions (Baker et al., 2012; de la Monte and Wands, 2005; Deak and Sonntag, 2012; Sonntag et al., 2005). A decrease in IGF-1 may be related to the pathology of AD because IGF-1 increases clearance of amyloid beta (Aβ) in the brain and upregulates Aβ carriers and transport of Aβ-carrier protein complexes (Carro et al., 2002, 2006). In humans, low levels of serum IGF-1 are a risk for AD and dementia (Watanabe et al., 2005; Westwood et al., 2014).

Mild cognitive impairment (MCI) is a prodromal status in the course of AD. Subjects with MCI have characteristics between healthy subjects and AD, including pathology, biomarkers, brain function, and cognitive function (Petersen, 2004, 2011). The common features of MCI, particularly in cases showing progression to AD, are higher levels of Aβ42 and tau, brain atrophy, and reduced cognitive function (Petersen, 2011). Subcutaneous injections of growth hormone–releasing hormone enhances the IGF-1 level and improves cognitive function in MCI subjects (Baker et al., 2012), but it is unclear whether lower levels of serum IGF-1 are a characteristic of MCI.

Cognitive impairment has a strong link with physical frailty, especially with slow gait linked with worsening of cognitive function. Slow gait has been associated with the cognitive decline (Mielke et al., 2013) and with accumulation of brain pathology related to AD at autopsy (Buchman et al., 2013), whereas longitudinal studies indicate that slow gait precedes MCI and dementia (Buracchio et al., 2010; Solfrizzi et al., 2013). Importantly, a combined status of slow gait and cognitive impairment increases the risk for dementia compared with each status alone (Waite et al., 2005). The mechanism of the association between physical and cognitive impairment was not examined, but IGF-1 may mediate this association.

The mechanism underlying the benefit of exercise on cognition is also thought to involve IGF-1 (Liu-Ambrose et al., 2012). Exercise-dependent stimulation of angiogenesis and neurogenesis seems to

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