厚生労働科学研究費補助金

長寿科学総合研究事業

サルコペニアの予防を目的とした総合的研究
（H25-長寿-若手-009）

平成26年度　総括研究報告書

研究代表者　山田　実

平成27（2015）年　5月

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厚生労働科学研究費補助金（長寿科学総合研究事業）
総括研究報告書

サルコペニアの予防を目的とした総合的研究

研究代表者　山田　実　筑波大学・人間系　准教授

研究要旨

目的

本研究では、サルコペニア予防に有用な運動プログラムの開発を目標に、レジスタンストレーニングとウォーキング、さらにはその組み合わせによる効果の検証をクラスター無作為化比較対象試験によって検証した。

方法

21 地区 246 名を対象としたクラスター無作為化比較対象試験であった。21 地区を無作為に 3 地区に分類し、それぞれ①レジスタンストレーニング群、②ウォーキング群、③レジスタンス＋ウォーキング群として 3 ヶ月間の介入を実施した。レジスタンストレーニングは、週に 1 回の教室型とし、油圧式のトレーニングマシーンを用いて上肢、下肢、体幹の主要な筋群に対して 10 回×3 セット実施した。ウォーキング介入は日々のウォーキングであり、歩数計とカレンダーを配布して 2 週間毎にフィードバック（10%up の目標値の設定）を実施した。アウトカム指標としては、生体電気インピーダンス法による骨格筋量と各種運動機能（歩行速度、TUG、片脚立位、ファンクショナルリーチ）とした。サブ解析として、健常高齢者とフレイル高齢者の層別分析を実施した。フレイルは Fried らの定義に従い、体重減少、活力低下、活動度減少、歩行速度低下、握力低下の項目を採用し、ここでは 2 項目以上該当者をフレイルとした。

結果

3 群間の比較を二元配置分散分析によって検証したところ、骨格筋量（SMI）や移動能力、バランス能力で有意な主効果（時間）は認められるものの、有意な交互作用は得られなかった。しかしながら、SMI に関しては F=2.84、P=0.06 とその傾向は認められた。3 群間の SMI 変化率を比較すると、レジスタンス群 1.1%、ウォーキング群 0.7%、レジスタンス＋ウォーキング群 3.2%となっており、レジスタンス＋とウォーキングの併用で最も筋量増加に寄与する可能性が示唆された。この傾向は健常高齢者では弱まるものの、フレイル高齢者ではより顕著になる傾向にあった。

結語

レジスタンストレーニングとウォーキング、さらにはその組み合わせによる効果の検証をクラスター無作為化比較対象試験によって検証したところ、両者の組み合わせで最も介入効果が高まる傾向が得られた。この傾向は特にフレイル高齢者で顕著となる傾向にあった。

山田　実　筑波大学・人間系　准教授

A. 目的

サルコペニアの予防における介入研究は近年増加傾向にあり、2014年に報告されたレビュー論文でも運動を主体とした予防プログラムの有用性が示されている。しかしながら、様々な側面から検討が進んでいるとは言い難く、現時点ではあくまでレジスタンストレーニング主体の運動プログラムとなっている。

そこで本研究では、サルコペニア予防に有用な運動プログラムの開発を目標に、レジスタンストレーニングとウォーキング、さらにはその組み合わせによる効果の検証をクラスター無作為化比較対象試験によって検証した。

B. 研究方法

21地区246名を対象としたクラスター無作為化比較対象試験であった。21地区を無作為に3地区に分類し、それぞれ①レジスタンストレーニング群、②ウォーキング群、③レジスタンス＋ウォーキング群として3ヶ月間の介入を実施した（図1）。レジスタンストレーニングは、週に1回の教室型とし、油圧式のトレーニングマシーンを用いて上肢、下肢、体幹の主要な筋群に対して10回×3セット実施した（図2）。ウォーキング介入は日々のウォーキングであり、歩数計とカレンダーを配布して2週間毎にフィードバック（10%upの目標値の設定）を実施した（図2）。アウトカム指標としては、生体電気インピーダンス法による骨格筋量と各種運動機能（歩行速度、TUG、片脚立位、ファンクショナルリーチ）とした。サブ解析として、健常高齢者とフレイル高齢者の層別分析を実施した。フレイルはFriedらの定義に従い、体重減少、活力低下、活動度減少、歩行速度低下、握力低下の項目を採用し、ここでは2項目以上該当者をフレイルとした。

なお、本研究は京都大学医の倫理委員会の承認を受けて実施した。

C. 研究成果

246名はそれぞれ、レジスタンストレーニング群90名、ウォーキング群82名、併用群74名に分類され、それぞれ84名、78名、69名が分析対象となった（表1）。

3群間の比較を二元配置分散分析によって検証したところ、SMIや移動能力、バランス能力で有意な主効果（時間）は認められるものの、有意な交互作用は得られなかった（表2）。しかしながら、SMIに関してはF=2.84、P=0.06とその傾向は認められた（図3）。3群間のSMI変化率を比較すると、レジスタンス群1.1%、ウォーキング群0.7%、レジスタンス＋ウォーキング群3.2%となっており、レジスタンス＋とウォーキングの併用で最も筋量増加に寄与する可能性が示唆された。この傾向は健常高齢者では弱まるものの、フレイル高齢者ではより顕著になる傾向にあった（図4）。

D. 考察

本研究結果より、どのような運動を選択してもある程度は筋肉量が増加する傾向にあることが示唆された。また傾向としては、レジスタンストレーニングとウォーキングを組み合わせたグループで最も改善効果が高かった。このことは、例え低頻度な運動介入であっても介入非実施日に積極的なウォーキングを実施することで筋量増加効果が得られやすい可能性を示唆している。

また、このような結果は特にフレイル高齢者で顕著なる傾向があり、今後の介護予防を想定した場合に、有用な指導材料となりうると考えられた。

E. 結論

レジスタンストレーニングとウォーキング、さらにはその組み合わせによる効果の検証をクラスター無作為化比較対象試験によって検証したところ、両者の組み合わせで最も介入効果が高まる傾向が得られた。この傾向は特にフレイル高齢者で顕著となる傾向にあった。

F. 健康危険情報

特筆すべき情報はない。

G. 研究発表

1. Nishiguchi S, Yamada M, Arai H, Aoyama T, Tsuboyama T. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. J Am Med Dir Assoc. (In Press)
2. Adachi D, Nishiguchi S, Fukutani N, Kayama H, Tanigawa T, Yukutake T, Hotta T, Tashiro Y, Morino S, Yamada M, Aoyama T. Factors Associating with Shuttle Walking Test Results in Community-Dwelling Elderly People. Aging Clinical and Experimental Research (In press)

H. 知的財産権の出願・登録状況

なし

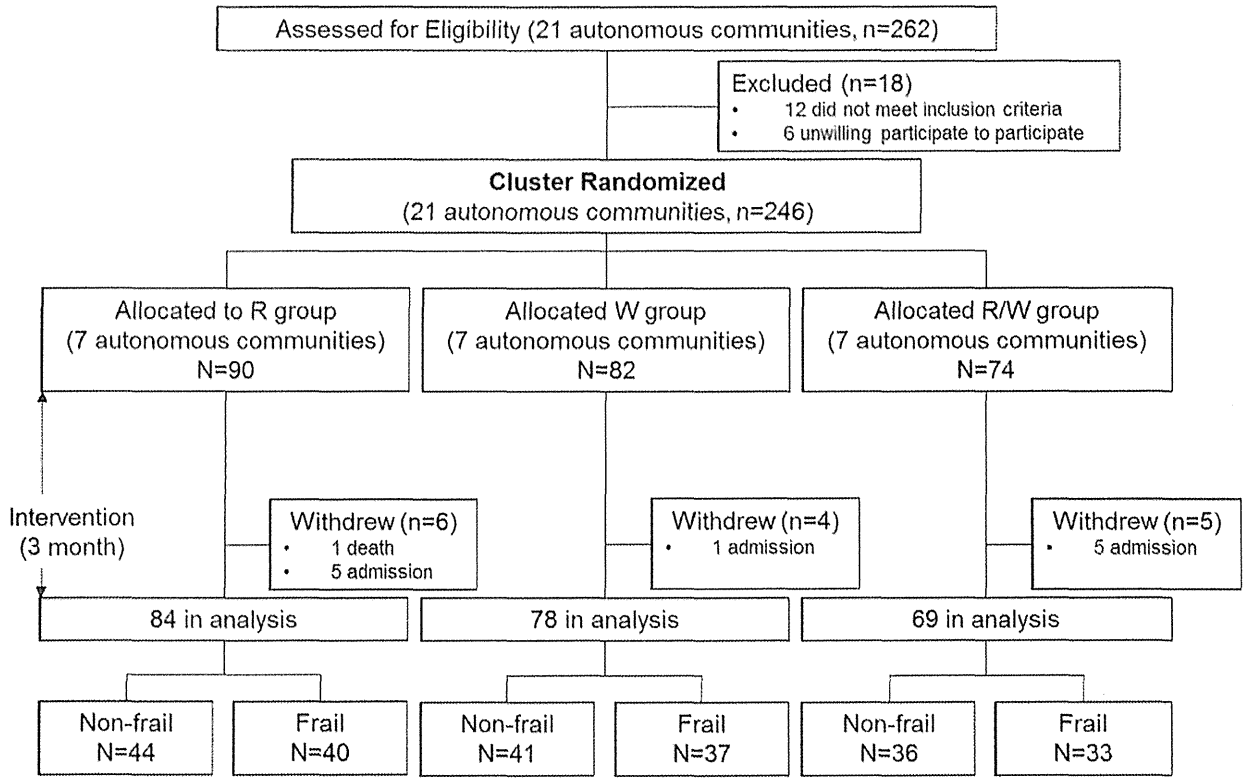

図 1　本研究のフロー

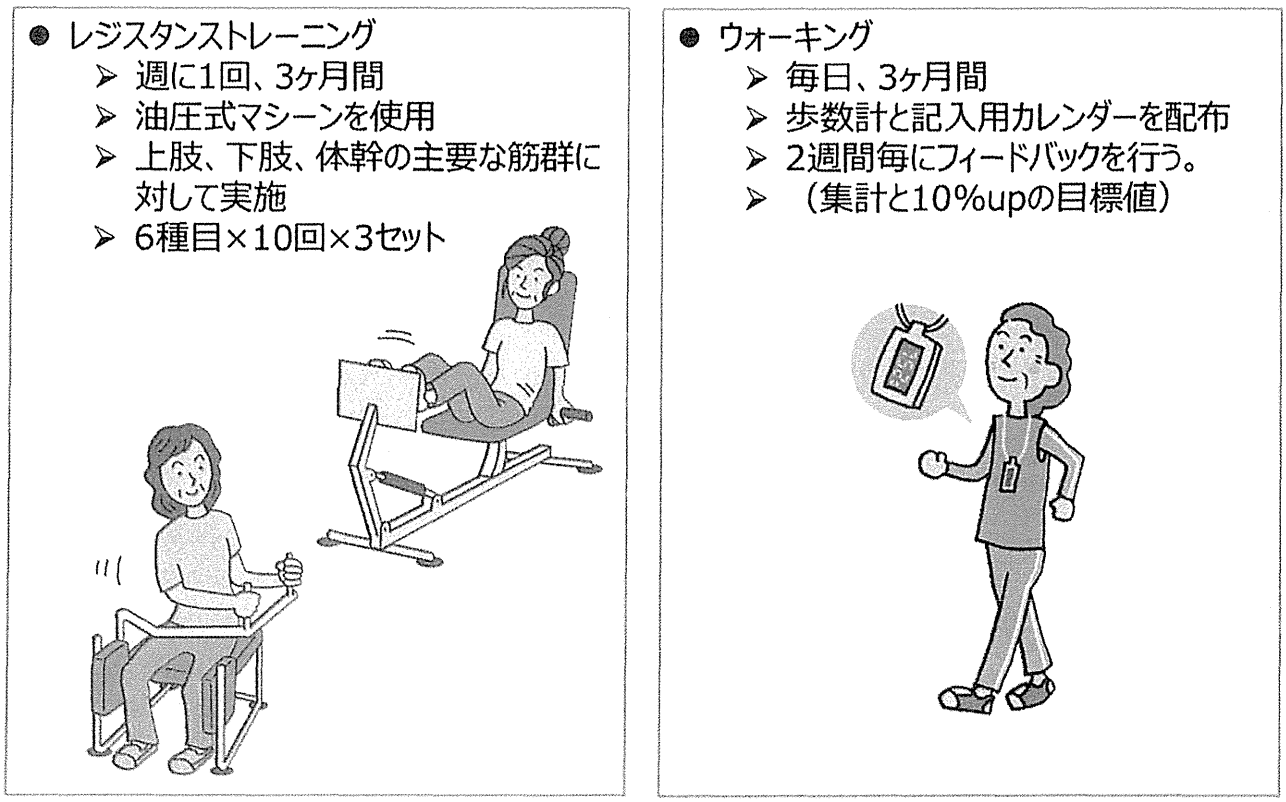

図 2　レジスタンストレーニングとウォーキングのイメージ

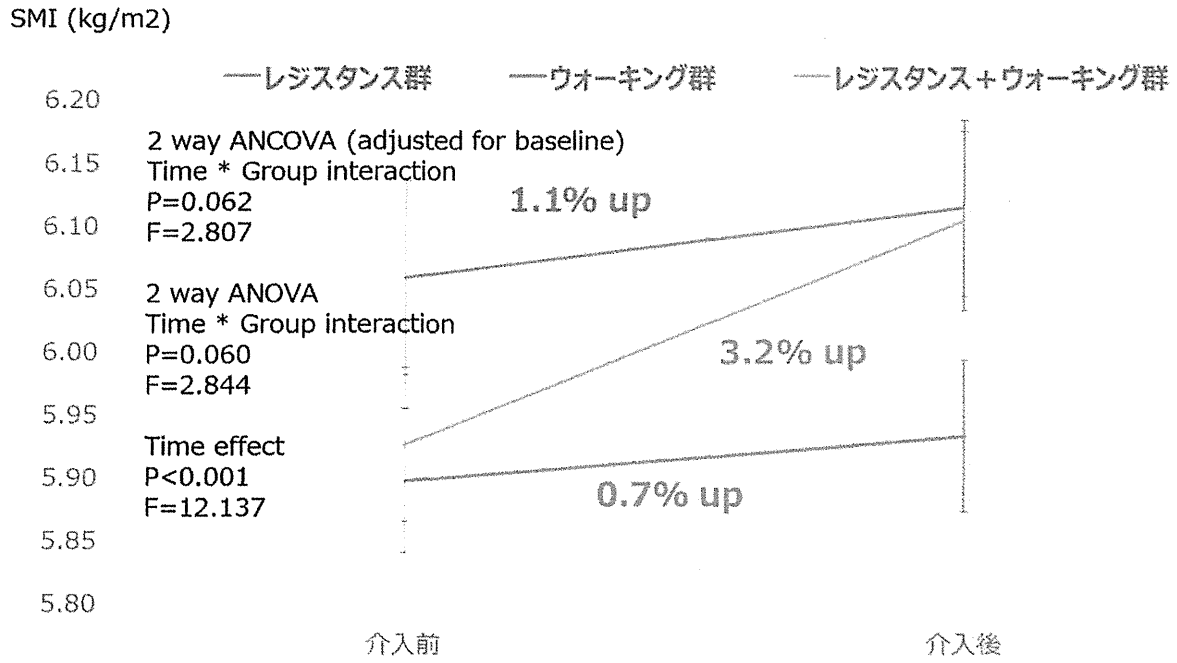

図 3 骨格筋量の介入前後比較

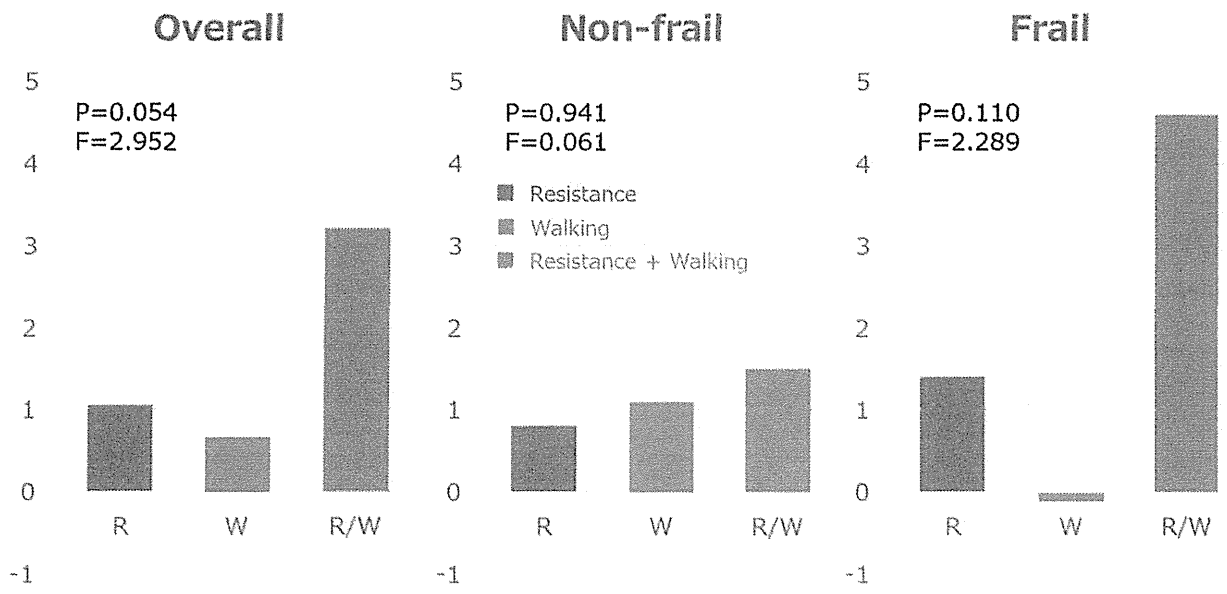

図 4 フレイル、非フレイル高齢者の効果の違い

表 1 対象者の属性

	Overall		Registanc		Walking		Resistance + Walking		F-value	P-value
	n=231		n=84		n=78		n=69			
Age	75.6	5.2	77.0	5.0	75.6	5.6	73.9	4.5	9.11	0.00
Height	151.0	8.6	152.6	8.0	150.9	5.0	149.1	11.7	3.67	0.03
Weight	52.7	8.8	53.5	10.1	51.9	7.9	52.5	7.9	1.62	0.20
BMI	23.2	4.5	22.9	3.4	22.8	3.5	24.1	6.2	5.35	0.01

表 2 介入前後の各パラメーターの比較

		Pre-intervention		Post-intervention		Time effect		Time * Group interaction	
		Mean	SD	Mean	SD	F-value	P-value	F-value	P-value
SMI	Resistance	6.06	0.89	6.11	0.86	**12.14**	**0.00**	**2.84**	**0.06**
	Walking	5.90	0.58	5.93	0.63				
	Resistance + Walking	5.93	0.51	6.10	0.68				
	Overall	5.96	0.69	6.05	0.74				
One leg stand	Resistance	13.6	13.9	15.6	15.4	**9.26**	**0.00**	0.37	0.69
	Walking	9.5	9.2	11.4	12.3				
	Resistance + Walking	17.3	17.1	20.7	19.8				
	Overall	13.9	14.4	16.2	16.6				
Functional reach	Resistance	31.7	6.6	32.5	6.4	0.25	0.61	2.04	0.13
	Walking	32.5	8.9	31.1	9.7				
	Resistance + Walking	33.9	4.1	33.9	5.0				
	Overall	32.5	6.6	32.6	7.0				
5m Comfortable Walking time	Resistance	4.9	1.1	5.0	1.1	1.34	0.25	**7.02**	**0.00**
	Walking	4.6	1.0	4.6	1.2				
	Resistance + Walking	4.7	1.1	4.5	0.9				
	Overall	4.8	1.1	4.7	1.1				
TUG	Resistance	9.5	2.6	9.2	2.0	**6.12**	**0.01**	0.16	0.85
	Walking	8.3	1.7	8.1	1.9				
	Resistance + Walking	8.6	1.9	8.4	1.9				
	Overall	8.8	2.2	8.6	1.9				

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
山田実	サルコペニアに対する介入の考え方	荒井秀典	別冊　医学のあゆみ	医歯薬出版		2015	101-106
山田実	フレイルで特に注目すべき身体機能	葛谷雅文・天海照祥	フレイル　超高齢社会における最重要課題と予防戦略	医歯薬出版		2014	121-126
山田実	サルコペニアと転倒	島田裕之	サルコペニアと運動	医歯薬出版		2014	30-36

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Adachi D, Nishiguchi S, Fukutani N, Kayama H, Tanigawa T, Yukutake T, Hotta T, Tashiro Y, Morino S, Yamada M, Aoyama T.	Factors Associating with Shuttle Walking Test Results in Community-Dwelling Elderly People	Aging Clinical and Experimental Research			In Press
Nishiguchi S, Yamada M, Tanigawa T, Sekiyama K, Kawagoe T, Suzuki M, Yoshikawa S, Abe N, Otsuka Y, Nakai R, Aoyama T, Tsuboyama T	A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial.	J Am Geriatr Soc			In Press
Adachi D, Yamada M, Nishiguchi S, Fukutani N, Hotta T, Tashiro Y, Morino S, Shirooka H, Nozaki Y, Hirata H, Yamaguchi M, Aoyama T.	Age-related decline in chest wall mobility: A cross-sectional study among community-dwelling elderly women belonging to different age groups	The journal of the American Osteopathic Association			In Press
Yukutake T, Yamada M, Fukutani N, Nishiguchi S, Kayama H, Tanigawa T, Adachi D, Hotta T, Morino S, Tashiro Y, Aoyama T, Arai H.	Arterial stiffness can predict cognitive decline in the Japanese community-dwelling elderly: A one year follow-up study.	Journal of Atherosclerosis and Thrombosis			In Press

Nishiguchi S, Yamada M, Fukutani N, Adachi D, Tashiro Y, Hotta T, Morino S, Aoyama T, Tsuboyama T.	Spot the Difference for Cognitive Decline: a quick memory and attention test for screening cognitive decline.	Journal of Clinical Gerontology and Geriatrics			In Press
Nishiguchi S, Yamada M, Arai H, Aoyama T, Tsuboyama T.	Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults.	J Am Med Dir Assoc.			In Press
Tanigawa T, Hirashima M, Fukutani N, Nishiguchi S, Kayama H, Yukutake T, Yamada M, Aoyama T.	Shoe-fit is correlated with exercise tolerance in community-dwelling elderly people.	Footwear Scienence			In Press
Sewo Sampaio, Yamada M, Arai H.	A comparison of frailty among Japanese, Brazilian Japanese descendants and Brazilian community-dwelling older women.	Geriatr Gerontol Int			In Press
Fukutani N, Yamada M, Nishiguchi S, Yukutake T, Kayama H, Tanigawa T, Adachi D, Hotta T, Morino S, Tashiro Y, Aoyama T, Tsuboyama T.	The physiological characteristics of community-dwelling elderly Japanese with airflow limitation: A cross-sectional study.	Aging Clin Exp Res	27(1)	69-74	2015
Woo J, Arai H, Ngc T P, Sayer AA, Wonga M, Syddall H, Yamada M, Zenge P, Wue S, Zhange TM.	Ethnic and geographic variations in muscle mass, muscle strength and physical performance measures.	European Geriatric Medicine	5	155-164	2014
Priscila Yukari Sewo Sampaio, Ricardo Auréliо Carvalho Sampaio, Yamada M, Arai H.	Comparison of frailty between users and non-users of a day care center using the Kihon Checklist in Brazil.	Journal of Clinical Gerontology and Geriatrics	5(3)	82-85	2014
Yamada M, Moriguchi Y, Mitani T, Aoyama T, Arai H.	Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40-79 years of age.	Geriatr Gerontol Int	14 Suppl 1	8-14	2014
Nishiguchi S, Yamada M, Kajiwara Y, Sonoda T, Yoshimura K, Kayama H, Tanigawa T, Yukutake T, Aoyama T.	Effect of physical activity at midlife on skeletal muscle mass in old age in community-dwelling older women: a cross-sectional study.	Journal of Clinical Gerontology and Geriatrics	5(1)	18-22	2014

Tanigawa T, Takechi H, Arai H, Yamada M, Nishiguchi S, Aoyama T.	Effect of physical activity on memory function in older 1 adults with mild Alzheimer's disease and mild cognitive impairment.	Geriatr Gerontol Int	14(4)	758-62	2014
Priscila Yukari Sewo Sampaio, Ricardo Auréliо Carvalho Sampaio, Yamada M, Ogita M, Arai H.	Validation and Translation of the Kihon Checklist (frailty index) into Brazilian Portuguese.	Geriatr Gerontol Int	14(3)	561-9	2014
Sampaio RA, Sewo Sampaio PY, Yamada M, Tsuboyama T, Arai H.	Self-reported quality of sleep is associated with bodily pain, vitality and cognitive impairment in Japanese older adults.	Geriatr Gerontol Int	14(3)	628-35	2014
Yukutake T, Yamada M, Fukutani N, Nishiguchi S, Kayama H, Tanigawa T, Adachi D, Hotta T, Morino S, Tashiro Y, Arai H, Aoyama T.	Arterial stiffness determined by cardio-ankle vascular index (CAVI) is associated with mild cognitive decline poor cognitive function in community-dwelling elderly.	Journal of Atherosclerosis and Thrombosis.	21(1)	49-55	2014
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journal homepage: www.jamda.com

Original Study

Differential Association of Frailty With Cognitive Decline and Sarcopenia in Community-Dwelling Older Adults

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Keywords:
Frailty
cognitive decline
sarcopenia
community-dwelling older adults

A B S T R A C T

Objectives: Frailty in older adults is a serious problem because of various adverse health outcomes in many countries with aging populations, such as Japan. The purpose of this study was to determine whether frailty and pre-frailty are associated with cognitive decline and sarcopenia in community-dwelling older adults.
Design: This is a cross-sectional study.
Setting: Japan.
Participants: The participants were 273 Japanese community-dwelling older women aged 65 years and older.
Measurements: We used the frailty criteria developed by the Cardiovascular Health Study to define physical frailty. We divided the cohort into nonfrail, prefrail, and frail according to frailty scores. Cognitive decline and memory decline were defined by using the Mini-Mental State Examination and Scenery Picture Memory Test, respectively. Sarcopenia was defined according to the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia.
Results: In the multivariate logistic regression analysis by using non-frail participants as the reference, pre-frail elderly individuals were significantly more likely to have sarcopenia than non-frail elderly individuals [odds ratio (OR): 2.77, 95% confidence interval (CI): 1.05–9.26], but not cognitive decline or memory decline. Frail elderly individuals were significantly more likely to have cognitive decline (OR: 5.76, 95% CI: 1.20–27.6), memory decline (OR: 5.53, 95% CI: 1.64–18.7) and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0) than non-frail elderly individuals.
Conclusions: Sarcopenia was associated with pre-frailty and frailty, whereas cognitive decline was associated only with frailty.

Frailty in older adults is a serious concern in countries with aging populations, such as Japan. In general, frailty is defined as a vulnerable state that places older adults at high risk for adverse health outcomes, such as falls, hospitalization, and mortality.[1,2] Using the frailty criteria developed by the Cardiovascular Health Study, the overall prevalence of frailty in community-dwelling adults aged 65 or older in the United States has been found to range from 7% to 12% and was greater in women than in men.[1] In Japanese, the prevalence of frailty in community-dwelling adults aged 65 or older was 11.3%, and it increased with aging.[3] Frail older adults are considered to have a substantially increased risk of disability, dependency, and need for long-term care insurance. Therefore, prevention and early detection of frailty is important for addressing age-related health care issues.

The causes of frailty are not clearly defined, but it has been suggested that age-related physical changes are the main causes of frailty.[4] Sarcopenia, defined as progressive loss of skeletal muscle mass, strength, and physical function, is regarded as a key component of physical frailty.[5,6] The Interventions on Frailty Working Group assessed various methods for screening, recruiting, evaluating, and

The authors declare no conflicts of interest.

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1525-8610/

retaining frail elderly individuals in clinical trials.[7] They reported that most researchers focused on the following domains when identifying physical frailty: mobility, such as lower-extremity performance and gait abnormalities; muscle weakness; poor exercise tolerance; unstable balance; and factors related to body composition, such as weight loss, malnutrition, and muscle loss.[7] Age-dependent loss of skeletal muscle mass is a multifactorial process; contributing factors include physical inactivity, malnutrition, oxidative stress, changes in endocrine function, and increases in inflammatory cytokines.[5] Thus, the domains of frailty overlap with the factors related to sarcopenia, and both frailty and sarcopenia mutually result in adverse health outcomes.[5,6]

Of note, some definitions of frailty include cognitive function and dementia.[4,8] Several cross-sectional studies have reported an association between physical frailty and cognitive function.[1,7,9,10] In addition, longitudinal studies have revealed that a higher level of physical frailty is associated with increased risk of incident Alzheimer's disease (AD)[11] and mild cognitive impairment.[12] It has been indicated that frailty is associated with AD pathology[13] and its biological mechanisms.[14] However, not all dementia patients become frail; therefore, the association between frailty and cognitive impairment warrants further study.

Frailty is associated with sarcopenia and cognitive decline. Furthermore, frailty has been considered to include other aspects, such as psychosocial issues and comorbidities.[15] However, it is unclear whether the associations between frailty and cognitive decline as well as between frailty and sarcopenia are different according to the level of frailty. Therefore, the purpose of this study was to determine whether frailty and prefrailty are associated with cognitive decline and sarcopenia in community-dwelling older adults.

Methods

Participants

Participants for this study were recruited through the local press; 273 Japanese women aged 65 years and older (mean age 73.0 ± 5.4 years) responded. We included community-dwelling older adults who were independent in activities of daily living. Participants were interviewed and excluded if they met any of the following criteria: severe cardiac, pulmonary, or musculoskeletal disorders; severe neurologic disorders, such as Parkinson disease and stroke; and participation in Japan's long-term care service. The following data were collected from each participant: age, height, weight, and number of medications being consumed.

Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

Assessment of Frailty

We measured physical frailty domains determined in a previous study.[3] As in that study, we considered the frailty phenotype to be characterized by limitations in the following 5 domains by using frailty criteria developed by the Cardiovascular Health Study[1]: slowness, weakness, exhaustion, low activity, and shrinking. To measure slowness, each participant's 10-m normal walking speed (m/s) was calculated, and a slow walk was defined as <1.0 m/s. To measure weakness, low grip strength was established according to a sex-specific cutoff of the average grip strength in each arm (women: <17 kg). Exhaustion was assessed via self-report by using the Geriatric Depression Scale[16] (ie, exhaustion was defined as a negative ["no"] answer to the question "do you feel full of energy?)" We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (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?" If a participant answered "no" to both of these questions, then we considered their physical activity to be low. Shrinking 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?" If a participant answered "yes" to this question, then we considered them to have shrunk. We calculated the number of affected domains and classified participants as follows: prefrailty = 1 or 2, frailty ≥3.[1]

Measurement of Cognitive Function

Participants' cognitive function was measured by using 2 neuropsychological tests: the Mini-Mental State Examination (MMSE)[17] and the Scenery Picture Memory Test (SPMT).[18]

Global cognitive function was assessed by using the MMSE, a standard test in cognitive aging research to assess mental status. The MMSE tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. It has 11 questions and a possible maximum score of 30. We divided the participants into a normal or a cognitive decline group based on a cut-off of 23/24 as the MMSE score.[19]

The SPMT is a simple memory test that assesses visual memory combined with verbal responses. This test uses a line drawing of a living room in a house with 23 objects commonly observed in daily life on an A4 piece of paper. The examinee is instructed to look at the picture for 1 minute and remember the items. After this encoding period, participants are distracted by completing a brief digits forward test. Participants are then asked to recall the objects in the picture without a time limitation. The recall usually takes approximately 2 minutes. The number of items recalled is the score for the SPMT. We divided the participants into a normal or memory decline group based on a cut-off of 9/10 as the SPMT score.[18]

Definition of Sarcopenia

We defined sarcopenia by using the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia, which assesses the presence of both low muscle function (low physical performance or low muscle strength) and low muscle mass.[20] A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co, Ltd, Seoul, Korea) was used to perform bioelectrical impedance analysis.[21] This system uses electrical current at multiple frequencies (5, 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water. Participants stood on 2 metallic electrodes and held metallic grip electrodes. Using segmental body composition, appendicular skeletal muscle mass was determined and used for further analysis. Skeletal muscle mass index (SMI) was calculated by dividing muscle mass by height squared in meters (kg/m^2). This index has been used in several epidemiological studies.[22,23] If a participant had both low muscle function (slow walking speed, ≤0.8 m/s; low grip strength for women, ≤18 kg) and low SMI (low muscle mass for women, ≤5.7 kg/m^2), then they were defined as having sarcopenia.[20]

Statistical Analysis

Prior to the analysis, we classified participants into the following 3 groups according to their frailty score: nonfrailty, prefrailty, and frailty. Differences in the demographic variables, MMSE, SPMT, and

Table 1
Demographic Differences According to Frailty Scores

	Total (n = 273)	Frailty Level			*P* for Trend	Post-hoc
		Nonfrailty (n = 89)	Prefrailty (n = 155)	Frailty (n = 57)		
Age (y)	73.0 ± 5.4	73.1 ± 4.6	72.3 ± 5.6	76.6 ± 5.1	<.001†	a, b
BMI (kg/m^2)	22.5 ± 3.2	22.2 ± 3.0	22.7 ± 3.3	21.9 ± 3.8	.291	—
Medications	2.32 ± 2.24	2.18 ± 2.35	2.23 ± 2.10	3.27 ± 2.55	.072	—
Walking speed (m/s)	1.40 ± 0.20	1.43 ± 0.18	1.41 ± 0.20	1.21 ± 0.20	<.001†	a, b
Grip strength (kg)	22.4 ± 4.0	23.4 ± 3.4	22.6 ± 3.8	18.3 ± 4.1	<.001†	a, b
Cognitive decline (n)	18 (6.56%)	4 (4.49%)	9 (5.81%)	5 (8.77%)	.047*	
Memory decline (n)	20 (7.33%)	6 (6.74%)	4 (2.58%)	10 (17.5%)	<.001†	
Sarcopenia (n)	22 (8.06%)	2 (2.25%)	9 (5.81%)	11 (19.3%)	<.001†	

AWGS, Asian Working Group for Sarcopenia; BMI, body mass index.
Nonfrailty was defined as frailty score of 0, prefrailty was score 1 or 2, frailty was score 3 or greater.
Cognitive decline was defined as the cut-off of MMSE score (23/24).
Memory decline was defined as the cut-off of SPMT score (9/10).
Sarcopenia was defined by using the AWGS-recommended diagnostic algorithm.
a, significant difference between frailty and nonfrailty ($P < .01$).
b, significant difference between score frailty and prefrailty ($P < .01$).
*$P < .05$.
†$P < .01$.

SMI among the 3 groups were examined by using the analysis of variance. When a significant effect was found, differences were determined with the Tukey-Kramer post-hoc test. Differences in the prevalence of cognitive decline, memory decline, and sarcopenia among the 3 groups were evaluated by using the χ^2 test. In addition, multivariate logistic regression analyses, adjusted for age, body mass index, and medications, were performed to determine whether physical frailty was associated with cognitive decline, memory decline, or sarcopenia. For this analysis, cognitive decline, memory decline, and sarcopenia were dependent variables, whereas the 3 frailty groups (dummy coded with non-frailty group as the reference group) were independent variables. Subsequent multivariate logistic regression analyses were performed to determine the independent association between each level of frailty and the risk of cognitive decline or sarcopenia. In these subsequent analyses (adjusted for age and medications), the frailty groups were the dependent variables, and cognitive decline and sarcopenia were independent variables. Odds ratios (ORs) with 95% confidence intervals (CI) were presented. Statistical analyses were carried out by using SPSS Statistics for Windows, version 20.0 (SPSS Inc, Chicago, IL), with a significance threshold of 0.05.

Results

Demographic data for participants stratified by frailty group are shown in Table 1. There were 89 participants (32.6%) in the nonfrailty group, 155 participants (56.8%) in the prefrailty group, and 29 participants (10.6%) in the frailty group. Analysis of variance showed that there were significant differences in age, walking speed, and grip strength among the 3 groups (Table 1). In the χ^2 test, there were

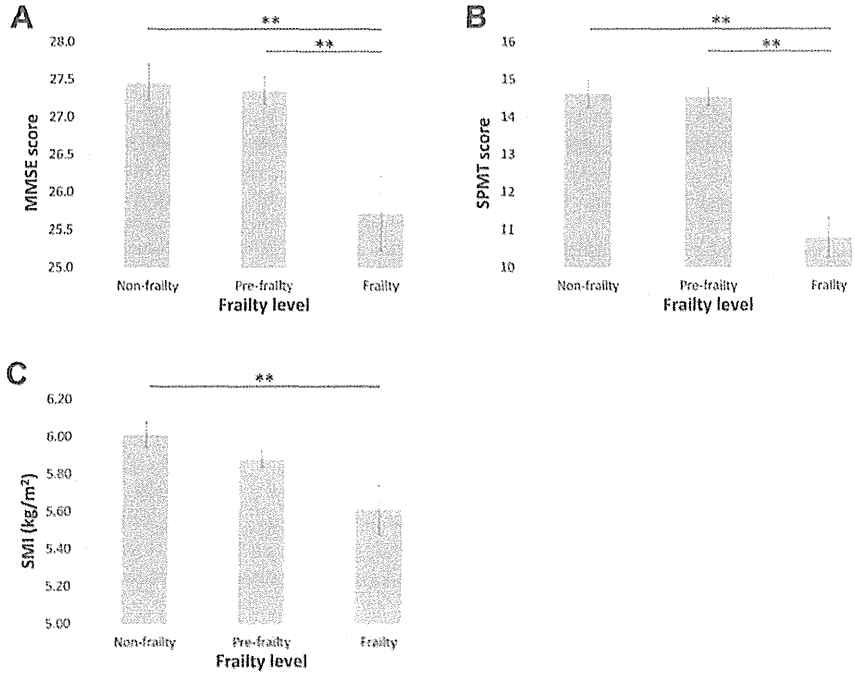

Fig. 1. Comparison of the MMSE, SPMT, and SMI between the groups according to the level of frailty. (A) There were significant differences in the MMSE scores between the 3 groups ($F = 6.78$, $P = .001$). (B) There were significant differences in the SPMT scores between the 3 groups ($F = 18.5$, $P < .001$). (C) There were significant differences in the SMI between the 3 groups ($F = 5.17$, $P = .006$). *$P < .05$, **$P < .01$.

Table 2
Relationship Between the Level of Frailty and Cognitive Decline, Memory Decline, and Sarcopenia

Frailty Level	Cognitive Decline		Memory Decline		Sarcopenia	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Nonfrailty	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Prefrailty	1.79 (0.47–6.84)	.394	0.37 (0.10–1.36)	.134	2.77 (1.05–9.26)	.044*
Frailty	5.76 (1.20–27.6)	.029*	5.53 (1.64–18.7)	.006†	19.1 (3.73–98.0)	<.001†

The analyses for cognitive decline and memory decline were adjusted for age, BMI, and medications.
The analysis for sarcopenia was adjusted for age and medications.
*$P < .05$.
†$P < .01$.

significant differences in the prevalence of cognitive decline, memory decline, and sarcopenia (Table 1). In addition, the frailty group had significantly lower MMSE ($F = 6.78$, $P = .001$, Figure 1, a) and SPMT ($F = 18.5$, $P < .001$, Figure 1, b) than the nonfrailty and prefrailty groups, and lower SMI ($F = 5.17$, $P = .006$, Figure 1, c) than the nonfrailty group.

Eighteen participants (6.6%) had cognitive decline, 20 participants (7.3%) had memory decline, and 23 participants (8.4%) had sarcopenia. In the multivariate logistic regression analysis after adjustment for age, body mass index, and medications, by using nonfrailty group as the reference, the prefrailty group was significantly more likely to have sarcopenia (OR: 2.77, 95% CI: 1.05–9.26, $P = .044$) but not cognitive decline or memory decline (Table 2). The frailty group was significantly more likely to have cognitive decline (OR: 5.76, 95% CI: 1.20–27.6, $P = .029$), memory decline (OR: 5.53, 95% CI: 1.64–18.7, $P = .006$), and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0, $P < .001$) (Table 2).

In the logistic regression analysis in which the frailty groups were the dependent variables and cognitive decline and sarcopenia were independent variables, cognitive decline was independently only associated with a frailty score of ≥3 (OR: 3.73, 95% CI: 1.23–11.4, $P = .020$), whereas sarcopenia was independently associated with both prefrailty (score ≥1; OR: 5.33, 95% CI: 1.22–23.3, $P = .026$) and frailty (score ≥3; OR: 13.1, 95% CI: 4.98–34.2, $P < .001$). These associations remained significant after adjustment for age and medications (Table 3).

Discussion

The results of this study showed that frailty (defined as frailty score ≥3) was associated with cognitive decline, memory decline, and sarcopenia, and that prefrailty (frailty score = 1 or 2) was associated with only sarcopenia. It is a new and interesting finding that there were differences in the association between physical frailty and cognitive decline, memory decline, and sarcopenia according to level of frailty.

In this study, we showed that frailty, but not prefrailty, was associated with cognitive decline and memory decline. Our results also showed that frailty and prefrailty were associated with sarcopenia, in contrast to cognitive and memory decline. In Japanese, multicenter, population-based studies, the prevalence of dementia was not high among those aged 65–74 years (less than 10%), but was higher among those aged 75 years and older.[24] The prevalence of sarcopenia exhibited the same tendency, with the prevalence rising among those aged 75 years and older.[25,26] Thus, older adults (particularly those 75 and older) are prone to both cognitive impairment and sarcopenia. However, low physical performance, low physical strength, and the decrease of muscle mass, which overlap with both sarcopenia and frailty, can be found from middle age.[27–29] Thus, as shown in the results of this study, it is possible that sarcopenia is associated with frailty at an earlier stage than is cognitive impairment, and that sarcopenia is affected more by frailty than is cognitive impairment.

A recent study investigated the association of physical frailty and pre-frailty with dementia and cognitive impairment.[30] In that study, physically frail older adults were over 4 times more likely to have AD, and 8 times more likely to have cognitive impairment than robust older adults were. Prefrail older adults showed an increased risk for dementia in the aforementioned study, but some estimates were not statistically significant in the fully adjusted models.[30] The results of that study were consistent with our study. Previous studies indicated that frailty is associated with AD pathology[13] and biological mechanisms,[14] such as diffuse neuritic plaques, oxidative stress, and inflammation. It is also possible that frailty and AD share common lifestyle risk factors, such as physical inactivity and smoking, that lead to their pathophysiology, which contributes simultaneously to physical frailty and AD.[13] On the other hand, it has been indicated that comorbidities caused by cognitive impairment were also associated with frailty in patients with AD or mild cognitive impairment.[31] Thus, it is likely that these associations interact with one another, leaving the causal association between physical frailty and cognitive decline unclear. Further studies are required to understand these associations.

Definitions of frailty and sarcopenia overlap, and sarcopenia is considered one of the core symptoms of physical frailty.[5,6] The causal mechanisms underlying sarcopenia can be oxidative stress, dysregulation of inflammatory cytokines and hormones, malnutrition,

Table 3
Independent Relationship Between Each Level of Frailty and Cognitive Decline or Sarcopenia

Domains	Univariate Analysis						Multivariate Analysis					
	Frailty Score						Frailty Score					
	≤1		≤2		≤3		≤1		≤2		≤3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Cognitive decline	1.76 (0.56–5.51)	.331	1.43 (0.54–3.84)	.473	3.73 (1.23–11.4)	.020*	2.48 (0.68–9.07)	.168	1.63 (0.56–4.72)	.371	4.61 (1.27–16.8)	.020*
Sarcopenia	5.33 (1.22–23.3)	.026*	9.07 (3.22–25.5)	<.001†	13.1 (4.98–34.2)	<.001†	5.47 (1.21–24.6)	.027*	8.75 (3.00–25.5)	<.001†	10.0 (3.40–29.6)	<.001†

The multivariate analyses were adjusted for age and medications.
*$P < .05$.
†$P < .01$.

physical inactivity, and muscle apoptosis, all of which have been hypothesized to contribute to frailty through interactive pathways.[32,33] Recently, the definition of sarcopenia has been the coexistence of low muscle mass and low physical performance,[5,20,34] which are contained in frailty domains. Thus, the association of sarcopenia with even prefrailty seems reasonable. Overlapping intervention strategies (eg, nutritional supplementation and exercise) may be required to prevent both frailty and sarcopenia.

During recent years, the definition of frailty has been changing. Frailty has been considered to include other aspects, for instance social aspects and comorbidities.[15] In addition to these aspects, poor cognition needs to be included in the definition of frailty, as shown in previous studies[4,8] and by this study. Furthermore, this study indicated that poor cognition was associated with frailty and that sarcopenia was associated even with prefrailty. The results indicate that we need to understand the consecutive mechanism as well as the association of prefrailty and frailty with cognitive decline, sarcopenia, and other adverse health outcomes. Interventions may need to be tailored to the level of frailty to effectively prevent various functional declines. Future studies should investigate these intervention strategies.

There were several limitations to this study. First, the cross-sectional design prevented us from establishing causal associations between frailty and cognitive decline or sarcopenia. Second, the findings in this study should be considered preliminary owing to the relatively small sample size, which may introduce some error of inference, reduce the power of analysis, and limit generalization. Third, the design of this study was not a population sampling, and participants in this study were independent in activities of daily living. This may lead to an underestimation of the prevalence of frailty, cognitive decline, and sarcopenia, as the participants were relatively healthy elderly persons.

In conclusion, our results indicate that there were differences in the association between physical frailty and cognitive decline, memory decline, and sarcopenia according to the level of frailty. Cognitive decline and memory decline were associated with frailty. Sarcopenia was associated with prefrailty and frailty. Further studies are required to understand these associations including biological mechanisms.

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ORIGINAL ARTICLE

Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40 to 79 years-of-age

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Aim: The age-dependent loss of skeletal muscle mass is highly concerning in diverse aging populations. However, age-dependent changes in muscle mass and the visceral fat area have not been well documented in Asian populations. The aim of the present study was to evaluate the age-dependent changes in skeletal muscle mass and the visceral fat area in Japanese adults from 40 to 79 years-of-age.

Methods: This was a cross-sectional study. Healthy men (n = 16 379) and women (n = 21 660) aged 40–79 years participated in the present study. The skeletal muscle mass and visceral fat area were measured in the study participants by bioelectrical impedance. The muscle mass data were converted into the skeletal muscle mass index (SMI) by dividing the weight by the height squared (kg/m^2).

Results: The SMI showed an age-dependent decrease in both sexes. Between 40 and 79 years, the total SMI decreased by 10.8% in men and by 6.4% in women. The arm SMI decreased by 12.6% in men and 4.1% in women, and the leg SMI decreased by 10.1% in men and by 7.1% in women in the same period. In contrast, the visceral fat area showed an age-dependent increase in both sexes. The visceral fat area increased by 42.9% in men and by 65.3% in women. The multiple regression analysis showed that the SMI was negatively associated with visceral obesity in both sexes.

Conclusions: In Japanese adults, sex-specific changes in skeletal muscle mass are more prominent in the arm than in the leg. Furthermore, the age-dependent increases in visceral adipose tissue might lead to loss of skeletal muscle mass. **Geriatr Gerontol Int 2014; 14 (Suppl. 1): 8–14.**

Keywords: age-dependent, Japanese, skeletal muscle mass, visceral fat area.

Introduction

Sarcopenia is an age-dependent loss of skeletal muscle mass, and is a serious medical concern in older populations.[1,2] Sarcopenia is characterized by an impaired state of health associated with mobility disorders, an increased risk of falls and fractures, an impaired ability to carry out activities of daily living, disabilities, and a loss of independence.[3–5]

Previous epidemiological studies of sarcopenia in several countries have shown a disease prevalence of 5–40% in older men and 7–70% in older women.[6–18] In general, the prevalence of sarcopenia is approximately 25% in older men and 20% in older women. Notably, previous work from this laboratory has shown that sarcopenia is highly prevalent among Japanese adults aged 80 years and older.[18] Because older adults have a greater potential for health problems than young adults, it is very important to begin prevention of sarcopenia early, possibly before the age of 65 years. Two previous studies from the USA and Europe have shown that the age-dependent loss of skeletal muscle mass starts at approximately 50 years-of-age, and that skeletal muscle mass declines by 6.6–23.3% until 79 years-of-age.[19,20] However, age-dependent changes in muscle mass in Asians are not well documented.

Visceral adiposity, which is the basis of metabolic syndrome and cardiovascular disease, is aggravated with age.[21] The visceral adipose tissue produces many inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6,[22] and expression of these inflammatory cytokines can lead to increased skeletal muscle breakdown.[23] Furthermore, previous studies have shown that increased visceral fat area is associated with decreased skeletal muscle mass in a

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small sample of older adults.[24] However, the association of skeletal muscle mass with age-dependent changes in visceral fat in a large population has not previously been shown.

The primary aim of the present study was to evaluate the age-dependent changes in skeletal muscle mass and visceral fat area using a large cross-sectional cohort of Japanese adults between 40 and 79 years-of-age. We also evaluated sex differences in skeletal muscle loss in the arms and legs. The secondary aim of the present study was to evaluate the association between the skeletal muscle mass and visceral fat area.

Methods

Participants

Participants were recruited by advertisements at several fitness and community centers. The participants in the present study were limited to visitors to these centers in the Kyoto, Osaka, and Hyogo prefectures in Japan. The inclusion criteria were an age of 40–79 years, living in the community and the ability to walk independently (including with a cane). The exclusion criteria were a certification of frailty status by the long-term care insurance service in Japan and artificial implants, such as cardiac pacemakers and replacement joints, which would interfere with accurate bioimpedance measurements. An interview was also used to identify those with the following exclusion criteria: severe cognitive impairment; severe cardiac, pulmonary, or musculoskeletal disorders; and comorbidities associated with greater risk of falls, such as Parkinson's disease or stroke. Because the purpose of the present study was to address physiological age-dependent changes in body composition, we excluded frail elderly and adults with those comorbidities. The present study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

Healthy men (n = 16 379) and women (n = 21 660) aged 40–79 years participated in the present study. The male participants were divided into eight groups according to age: 40–44 (n = 3697), 45–49 (n = 3151), 50–54 (n = 2202), 55–59 (n = 1952), 60–64 (n = 2274), 65–69 (n = 1683), 70–74 (n = 1030), and 75–79 (n = 390) years. The female participants were similarly divided into eight groups according to age: 40–44 (n = 3828), 45–49 (n = 3686), 50–54 (n = 3597), 55–59 (n = 3002), 60–64 (n = 3490), 65–69 (n = 2314), 70–74 (n = 1269), and 75–79 (n = 474) years.

Skeletal muscle mass index and visceral fat area

A bioelectrical impedance data acquisition system (Inbody 720; Biospace, Seoul, Korea) was used to determine bioelectrical impedance.[25] This system uses an electrical current at different frequencies (5, 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water in the body. The study participants stood on two metallic electrodes and held metallic grip electrodes. Using segmental body composition and muscle mass, a value for the appendicular skeletal muscle mass was determined and used for further analysis. The muscle mass was converted into the skeletal muscle mass index (SMI) by dividing the weight by the height squared (kg/m^2). This index has been used in several epidemiological studies.[6,26] Additionally, the SMI of the arms and legs was calculated. The visceral fat area was determined by evaluating a transverse cross-section of the fourth and fifth abdominal lumbar area.

Statistical analysis

Differences in the total SMI, arm SMI, leg SMI, and visceral fat area among the eight age groups were examined using an analysis of variance. Multiple regression models were applied to determine the relationship between the visceral fat area and the SMI, adjusted for age and weight in each sex. The data were managed and analyzed using SPSS (Windows version 18.0; SPSS, Chicago, IL, USA). A P-value of <0.05 was considered to show statistical significance for all analyses.

Results

The mean age of the study participants was 54.5 ± 9.9 years, and 21 660 (56.9%) of the participants were women. The total SMI showed an age-dependent decrease in both sexes (men, F = 251.1, P < 0.001; women, F = 135.6, P < 0.001; Table 1). The percentage change in the total SMI at 40–44 years showed an age-dependent decrease in both sexes (Fig. 1, Table 1). In those aged over 65 years, the percentage change in the total SMI was greater in men than in women. In addition, the 20th percentile of total SMI in men and women aged 65–79 years was 7.02 kg/m^2 and 5.61 kg/m^2, respectively (Table 2).

To compare the age-dependent changes in muscle mass in the upper and lower limbs in this cohort, we analyzed the arm and leg SMI. The arm SMI showed an age-dependent decrease in both sexes (men, F = 132.1, P < 0.001; women, F = 24.1, P < 0.001; Table 1). The percentage change in the arm SMI using the 40–44 years group as a reference also showed an age-dependent decrease in both sexes (Fig. 2, Table 1).

Similarly to the arm SMI, the leg SMI also showed an age-dependent decrease in both sexes (men, F = 273.2, P < 0.001; women, F = 192.2, P < 0.001; Table 1). The percentage change in the leg SMI also showed an

Table 1 Participant characteristics by age half decade

		Overall Men (n = 16 379) Women (n = 21 660)			40–44 years Men (n = 3697) Women (n = 3828)			45–49 years Men (n = 3151) Women (n = 3686)			50–54 years Men (n = 2202) Women (n = 3597)			55–59 Men (n = 1952) Women (n = 3002)		
		Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years
Total SMI (kg/m^2)	Men	7.97	0.73	–	8.20	0.78	–	8.11	0.66	−1.0	8.11	0.67	−1.1	7.98	0.64	−2.7
	Women	6.26	0.64	–	6.41	0.67	–	6.39	0.64	−0.3	6.33	0.64	−1.3	6.23	0.59	−2.8
Arm SMI (kg/m^2)	Men	2.08	0.28	–	2.14	0.31	–	2.11	0.26	−1.4	2.11	0.26	−1.2	2.08	0.24	−3.0
	Women	1.47	0.22	–	1.49	0.24	–	1.49	0.23	−0.5	1.47	0.22	−1.4	1.46	0.21	−2.3
Leg SMI (kg/m^2)	Men	7.98	0.73	–	6.06	0.51	–	6.00	0.46	−0.9	5.99	0.46	−1.1	5.91	0.45	−2.5
	Women	6.26	0.64	–	4.92	0.48	–	4.91	0.45	−0.3	4.85	0.46	−1.3	4.77	0.42	−3.0
Visceral fat area (cm^2)	Men	100.6	29.2	–	88.4	28.8	–	91.9	27.1	4.0	98.9	28.8	11.9	103.5	25.7	17.1
	Women	84.7	27.4	–	68.0	25.3	–	72.1	23.9	6.0	79.3	23.6	16.5	89.4	23.0	31.5

		60–64 years Men (n = 2274) Women (n = 3490)			65–69 years Men (n = 1683) Women (n = 2314)			70–74 years Men (n = 1030) Women (n = 1269)			75–79 years Men (n = 390) Women (n = 474)			ANOVA	
		Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	Mean	SD	% change over 40–44 years	F-value	P-value
Total SMI (kg/m^2)	Men	7.84	0.68	−4.3	7.64	0.67	−6.9	7.59	0.66	−7.4	7.32	0.62	−10.8	251.1	<0.001
	Women	6.14	0.61	−4.2	6.08	0.60	−5.2	6.09	0.55	−5.1	6.00	0.60	−6.4	135.6	<0.001
Arm SMI (kg/m^2)	Men	2.05	0.25	−4.4	1.99	0.25	−6.9	1.96	0.24	−8.5	1.87	0.26	−12.6	132.1	<0.001
	Women	1.45	0.22	−3.1	1.44	0.21	−3.6	1.46	0.20	−2.5	1.43	0.21	−4.1	24.1	<0.001
Leg SMI (kg/m^2)	Men	5.80	0.48	−4.3	5.64	0.46	−6.9	5.64	0.51	−7.0	5.45	0.45	−10.1	273.2	<0.001
	Women	4.69	0.43	−4.6	4.64	0.44	−5.7	4.63	0.41	−5.9	4.57	0.45	−7.1	192.2	<0.001
Visceral fat area (cm^2)	Men	108.3	26.2	22.5	113.0	25.7	27.8	122.3	25.1	38.3	126.4	25.2	42.9	376.9	<0.001
	Women	94.0	23.3	38.2	101.6	23.0	49.4	108.5	24.1	59.5	112.4	29.3	65.3	966.7	<0.001

Percentage change of 40–44 years = (absolute change value / 40–44 years value) × 100. SMI, skeletal muscle mass index.