Gender differences in risk factors for the 2 year development of sarcopenia in community-dwelling older adults

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Abstract

Background   Sarcopenia is an age-related chronic condition that can lead to mobility disabilities. This study aimed to evaluate the risk factors for incident sarcopenia in older Korean adults.
Methods   The Korean Frailty and Aging Cohort Study (KFACS) is a multicentre prospective study with a baseline examination in 2016–2017. A prospective follow-up study was conducted in 2018–2019. Changes in muscle-related variables were evaluated for subjects aged 70–84 years lacking sarcopenia at baseline. Sarcopenia was diagnosed according to the 2019 updated Asian Working Group for Sarcopenia consensus.
Results   Among the 1636 participants (54.4% women, age 75.9 ± 3.7) who did not have sarcopenia at baseline, 101 men (13.5%) and 104 women (11.7%) developed sarcopenia by the follow-up. Those who developed sarcopenia were older (men, 77.9 ± 3.9 vs. 75.7 ± 3.5, $P < 0.001$; women, 77.5 ± 4.0 vs. 75.5 ± 3.6, $P < 0.001$) with a lower body mass index at baseline (men, 23.9 ± 2.4 vs. 24.5 ± 2.9 kg/m^2, $P = 0.025$; women, 23.7 ± 2.8 vs. 25.2 ± 2.9 kg/m^2, $P < 0.001$) compared with older adults who remained nonsarcopenic; levels of glycated haemoglobin (men, 6.2 ± 1.0% vs. 5.9 ± 0.8%, $P = 0.029$) and the homeostasis model assessment of insulin resistance (men, 2.0 ± 1.3 vs. 1.7 ± 1.2, $P = 0.022$) were higher in men who progressed to sarcopenia but not in women. Development of sarcopenia was associated with older age and the frequency of resistance training (≥2 per week) after adjusting for potential risk factors in men [age, odds ratio (OR) 1.17, 95% confidence interval (CI) 1.10–1.25; frequent resistance training, OR 0.50, 95% CI 0.30–0.82]. In women, advanced age, poor nutritional status, and physical inactivity contributed to the development of sarcopenia (age, OR 1.14, 95% CI 1.08–1.21; mini nutritional assessment short form, OR 0.79, 95% CI 0.70–0.90; moderate to high physical activity, OR 0.57, 95% CI 0.34–0.95).
Conclusions   In this 2 year KFACS follow-up, modifiable risk factors for incident sarcopenia differed between genders. Resistance training (≥2 per week) helped to prevent sarcopenia in these community-dwelling older men. In older women, adequate nutritional support and being physically active might play a role in preventing progression to sarcopenia.

Keywords   Sarcopenia; Resistance training; Insulin resistance; Malnutrition; Exercise

Introduction

Over the past several decades, there has been a major demographic shift to older population distributions. The percentage of elderly persons of 65 years or older in Korea has more than doubled since 2000 and exceeded 16% in 2020.[1] Sarcopenia is defined as age-related progressive reduction in skeletal muscle mass and strength, leading to poor musculoskeletal health outcomes.[2] It interferes with successful aging and impairs the quality of life, in addition to generating a profound health-related effect on aging communities.[3] To date, there are no specific drugs approved for the treatment of sarcopenia. Once it develops, it becomes extremely challenging to counteract the loss of muscle mass and progressive functional decline.

Therefore, it is of utmost importance to recognize persons who are vulnerable to developing sarcopenia and to assess the factors contributing to its development. The incidence of sarcopenia increases with aging, and pathologic conditions closely linked to cachexia are regarded as an epiphenomenon of sarcopenia.[4] Other frequent underlying causes of sarcopenia include nutritional factors, circumstances associated with inactivity, and iatrogenic situations such as drug-related problems or hospital admission. Because sarcopenia is multifactorial in aetiology, equally sarcopenic individuals could be characterized by markedly different risk factor profiles depending on gender and ethnicity. It is unarguable that primary interventions to prevent the progression to sarcopenia should focus on amendable components regarding these factors.

It is generally acknowledged that men lose skeletal muscle mass and strength twice as rapidly as women during the aging process,[5–8] but to date, there are few longitudinal studies that explored the remediable risk factors for sarcopenia by gender. In this study, we have assessed the 2 year follow-up data of the Korean Frailty and Aging Cohort Study (KFACS) to evaluate the preventable measures in progression to new onset sarcopenia according to gender in older Korean men and women.

Methods

Study population

The KFACS is a multicentre, longitudinal study, with the baseline survey and examination conducted in 2016–2017 and the first follow-up examination in 2018–2019. The KFACS cohort consisted of community-dwelling older adults aged 70–84 years stratified by age and gender, recruited from 10 urban, suburban, and rural regions nationwide. Details on enrolment into the KFACS have been described.[9,10]

Of the 3014 enrolled participants, 2403 whose appendicular skeletal muscle mass (ASM) was measured by dual-energy X-ray absorptiometry (DXA) were included initially in the cross-sectional analysis, after excluding 611 participants from 2 centres that measured ASM using bioelectrical impedance analysis, not DXA.[10] Those exclusions were made considering the systematic bias in appendicular lean mass measurements between the two methods. Of these, 1983 participants were followed up after excluding 409 participants who were lost to follow-up, or who did not have the follow-up DXA or hand grip strength (HGS) measurement data (*Figure* 1). This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1607/354-402), and informed consent was obtained from all participants included in the study.

Definition of disease status

Sarcopenia

Each subject's ASM was assessed by DXA. Muscle strength was evaluated using HGS measured on a digital grip strength dynamometer (TTK-5401, Takei Ltd, Tokyo, Japan) as described.[10] The short physical performance battery (SPPB) comprised the sum of scorings obtained from three tests: standing-balance measures, chair-stand time measures, and gait speed.[11] For the chair-stand time test, participants were instructed to fully sit on the chair between each stand five times without using their arms. A timed up and go (TUG) test was also performed to assess physical performance.

Diagnosis of sarcopenia was made based on the updated definition of the Asian Working Group for Sarcopenia (AWGS) 2019.[12] Sarcopenia is defined as a combination of low ASM index and low muscle strength or physical performance. Specifically, a low ASM index was defined as ASM/height^2 < 7.0 kg/m^2 for men and <5.4 kg/m^2 for women. HGS values of <28 kg for men and <18 kg for women were used as cut-offs for defining low muscle strength. Low physical performance was defined as a usual gait speed of <1.0 m/s, five-times sit-to-stand test of ≥12 s, or an SPPB score of ≤9 for both genders.

Comorbidities

To assess for comorbidity, the Charlson comorbidity index (CCI), a well-validated prognostic indicator for 1 year mortality, was applied.[13] The CCI comprised 17 comorbid conditions, of which the individual comorbid diseases were divided into 10 classes: myocardial, vascular, pulmonary, neurologic, endocrine, renal, liver, gastrointestinal, cancer/immune, and miscellaneous, including rheumatologic and dis-
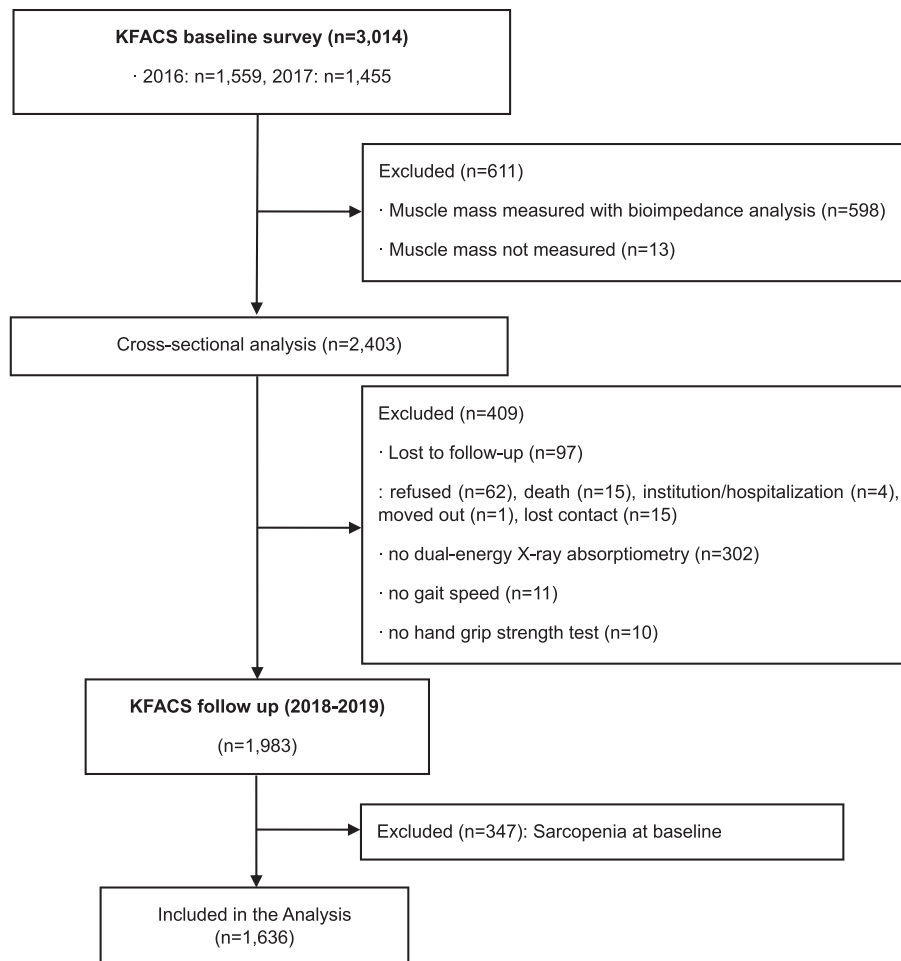
Figure 1 Consort diagram of participants enrolled in the Korean Frailty and Aging Cohort Study (KFACS).

eases involving coagulopathy. Additional weights in the CCI were assigned according to disease severity.

Measurements

Physical activity

The extent of physical activity was assessed based on the scoring of the short-form International Physical Activity Questionnaire (IPAQ).[14] The IPAQ comprises four sets of questions about the duration (in minutes) and frequency (times per week) of physical activities. Total physical activity level was determined by multiplying the duration (in minutes) and frequency of physical activities with the metabolic equivalent of task (MET), expressed as MET-min/week. Participants were classified into three levels of physical activities: low (<600 MET-min/week), moderate (600–2999 MET-min/week), and high activity (≥3000 MET-min/week). Moderate to high levels of physical activity on the IPAQ

score were considered to reflect subjects who were physically active.

Resistance training

The level of resistance training (RT) was determined by self-reported questionnaires. Those participants who engaged in at least two weekly sessions of exercising with weight machines (barbells, dumbbells, and/or elastic bands) or with free weights (push-ups, sit-ups, and/or squats) were defined to be active in RT.[15]

Nutritional assessment

The short-form version of the mini nutritional assessment (MNA-SF) screening score was used to assess nutritional status.[16,17] The six items in this well-validated MNA are used conventionally as a short screening tool in classifying geriatric patients at risk of malnutrition and malnutrition.

Laboratory measurements

All blood samples were obtained at around 8 AM after at least 8 h of overnight fasting and were analysed accordingly as described.[10,18] All blood tests were carried out in a core laboratory (Seegene Co., Seoul, Korea). The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin resistance. HOMA-IR was calculated as glucose (mg/dL) × insulin (μU/mL)/405.

Statistical analysis

Data are described as the mean ± standard deviation for continuous variables, and numbers and percentages for categorical variables. Differences in means and proportions by sarcopenia status were tested using Student's t-tests or analysis of variance for continuous variables and χ^2 test for categorical variables. In comparing three consecutive subgroups, P for trend was calculated using polynomial regression for continuous variables and the Cochran–Armitage test for categorical variables. For *post hoc* analysis, Tukey's honest significant difference method or Holm's adjustment was applied for continuous and categorical variables, respectively. For continuous variables that did not follow normal distribution, either logarithmic transformation (Ln) was applied to achieve normality or the Mann–Whitney non-parametric U-test was applied for comparison. To analyse longitudinal data by time and the status of sarcopenia, or by time and gender, generalized linear models were applied using generalized estimating equations.

Factors attributed to the development of sarcopenia in participants who did not have sarcopenia at baseline were assessed by binary logistic regression analysis. Univariable logistic regression analysis was performed to identify the potential risk factors for the onset of sarcopenia. Multivariable logistic regression analysis was followed to determine the independent association between the risk factors and incident sarcopenia. All following analyses were stratified by gender. All analyses were performed using IBM SPSS Statistics Version 27.0 (IBM Corp., Armonk, NY, USA) and R programming Version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). A two-sided P value of ≤0.05 was considered statistically significant.

Results

Baseline characteristics of participants who developed sarcopenia at the 2 year follow-up

Among the 1983 older adults with a complete 2 year follow-up, 194 men (20.4%) and 153 women (14.6%) had sarcopenia at baseline (*Figure* 1). Participants excluded for such underlying sarcopenia or follow-up loss were generally older, with lower body mass index (BMI) and muscle mass, and inferior muscle function (Supporting Information, *Table* S1).

For all participants with follow-up examination, biennial changes of muscle mass and function are described in *Table* S2. Of the 746 men and 890 women who did not have sarcopenia at baseline, 101 men (13.5%) and 104 women (11.7%) developed sarcopenia during the 2 years of follow-up (P = 0.292, men vs. women for incident sarcopenia; *Table* 1). Both genders who developed sarcopenia were older with a lower BMI at baseline. The men who developed sarcopenia had more comorbidities including hypertension, diabetes mellitus, and atherosclerotic cardiovascular disease compared with those who did not. Of note, none of the participants had disabled conditions leading to hemiplegia or paraplegia during the follow-up.

Whereas the total physical activity levels were higher in men than women regardless of progression to sarcopenia, the proportion of participants in the moderate to high physical activity group was significantly lower only in women out of those who developed sarcopenia (*Tables* 1 and S3). The proportion of participants who reported to be engaged in RT twice or more per week were lower only in men out of those who developed sarcopenia. The baseline MNA-SF was lower only in women who developed sarcopenia compared with those who remained nonsarcopenic.

Notably, the men who developed sarcopenia at follow-up had higher fasting glucose, glycated haemoglobin (HbA1c), and HOMA-IR values at baseline. In contrast, these variables were similar in women regardless of any development of sarcopenia at follow-up (*Table* 1).

Comparison of the changes in muscle mass and function according to incident sarcopenia

In conformity with the definition of sarcopenia, participants who developed sarcopenia at the 2 year follow-up had lower muscle mass and strength at baseline (*Table* 2). In men, those who developed sarcopenia at follow-up had had worse scores on all physical performances including gait speed, SPPB, TUG test, and five-times sit-to-stand test at baseline. In women, gait speed, TUG test, and five-times sit-to-stand test had been significantly inferior at baseline in those who developed sarcopenia at the follow-up.

The extent of muscle mass decline was considerably higher in participants who developed sarcopenia compared with those who did not (*Figure* 2 and *Table* 2). All muscle function parameters deteriorated more expeditiously in men with incident sarcopenia compared with men without; HGS, gait speed, and TUG test retrogressed more significantly in women who developed sarcopenia compared with women who did not develop sarcopenia, but the SPPB and five-times sit-to-stand test did not. Intriguingly, the rate of muscle mass

Table 1 Baseline characteristics of subjects according to incident sarcopenia

	Men (N = 746)			Women (N = 890)		
	Sarcopenia (+) N = 101	Sarcopenia (−) N = 645	P	Sarcopenia (+) N = 104	Sarcopenia (−) N = 786	P
Age	77.9 ± 3.9	75.7 ± 3.5	<0.001	77.5 ± 4.0	75.5 ± 3.6	<0.001
Height (cm)	163.9 ± 4.8	165.4 ± 5.4	0.009	150.5 ± 5.0	152.5 ± 5.2	<0.001
Weight (kg)	64.2 ± 7.0	67.0 ± 8.6	<0.001	53.7 ± 7.2	58.7 ± 8.0	<0.001
BMI (kg/m^2)	23.9 ± 2.4	24.5 ± 2.9	0.025	23.7 ± 2.8	25.2 ± 2.9	<0.001
Waist circumference (cm)	88.0 ± 7.8	89.3 ± 8.2	0.139	84.1 ± 7.9	87.6 ± 8.3	<0.001
Hypertension (%)	64 (63.4)	326 (50.6)	0.017	65 (62.5)	460 (58.5)	0.439
SBP (mmHg)	129.7 ± 14.0	131.4 ± 15.0	0.287	130.5 ± 16.4	131.6 ± 15.3	0.512
DBP (mmHg)	76.4 ± 9.5	78.6 ± 8.8	0.019	75.5 ± 9.2	77.4 ± 9.0	0.044
Diabetes mellitus (%)	40 (40.0)	177 (27.5)	0.010	31 (29.8)	189 (24.1)	0.206
Dyslipidaemia (%)	24 (24.0)	158 (24.7)	0.882	37 (35.9)	322 (42.8)	0.182
ASCVD (%)	26 (25.7)	92 (14.3)	0.003	12 (11.5)	79 (10.1)	0.644
Charlson comorbidity index	0.94 ± 1.16	0.69 ± 0.99	0.024	0.93 ± 0.98	0.81 ± 0.94	0.206
MNA-SF	13.16 ± 1.05	13.07 ± 1.39	0.540	12.36 ± 1.91	13.02 ± 1.34	0.013
Alcohol (%)	60 (68.9)	459 (76.5)	0.163	10 (0.2)	155 (3.5)	0.072
Current smoker (%)	12 (17.2)	61 (12.2)	0.330	2 (0.0)	4 (0.0)	0.148
Moderate to high physical activity (%)	85 (85.0)	573 (90.2)	0.112	74 (72.5)	652 (83.5)	0.007
Resistance training (≥2 per week)	26 (25.7)	272 (42.2)	0.002	17 (16.3)	186 (23.7)	0.093
Biochemical variables						
Fasting glucose (mg/dL)	110 ± 28	104 ± 21	0.032	102 ± 20	102 ± 21	0.895
HbA1c (%)	6.15 ± 0.97	5.93 ± 0.77	0.029	6.07 ± 0.81	6.04 ± 0.79	0.698
HOMA-IR	1.97 ± 1.29	1.72 ± 1.24	0.022[a]	2.01 ± 1.34	2.15 ± 1.42	0.347[a]
Total cholesterol (mg/dL)	163 ± 33	168 ± 35	0.168	179 ± 38	181 ± 35	0.544
Triglyceride (mg/dL)	121 ± 66	114 ± 64	0.295	124 ± 57	124 ± 58	0.896
HDL-C (mg/dL)	47 ± 13	51 ± 14	0.004	55 ± 15	54 ± 13	0.352
LDL-C (mg/dL)	102 ± 30	104 ± 32	0.453	109 ± 35	113 ± 33	0.236
BUN (mg/dL)	17.7 ± 5.1	16.8 ± 4.9	0.060	15.5 ± 4.4	15.9 ± 4.4	0.465
Creatinine (mg/dL)	1.00 ± 0.23	0.96 ± 0.35	0.292	0.74 ± 0.17	0.71 ± 0.16	0.207
AST (IU/L)	22.9 ± 6.9	23.8 ± 11.3	0.475	22.5 ± 10.7	22.0 ± 6.8	0.640
ALT (IU/L)	20.2 ± 12.0	20.6 ± 12.3	0.795	17.4 ± 10.8	18.6 ± 9.3	0.218
CRP (mg/L)	1.51 ± 2.38	1.52 ± 2.73	0.975	1.17 ± 1.57	1.33 ± 2.30	0.471

ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease, defined as myocardial infarction, angina pectoris, peripheral artery disease, or cerebrovascular disease; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MNA-SF, mini nutritional assessment-short form; SBP, systolic blood pressure.
Data are shown as mean ± standard deviation, interquartile ranges, or number (percentage). Alcohol (%), number (%) of men who drink alcohol one or more times a month; moderate to high physical activity was assessed using the International Physical Activity Questionnaire short form.
[a]P value is for the *T*-test of the log transformed value.

decline over the 2 years of follow-up was similar between genders in participants with incident sarcopenia. Similar findings were observed for physical performances except HGS.

The only parameter that differed in the magnitude of reduction between men and women was HGS; it was greater in men than women with incident sarcopenia (P = 0.013; *Table* 2).

Risk factors for the development of sarcopenia

To investigate the potential determinants of sarcopenia, logistic regression was performed with the variables presumed to contribute to the progression to sarcopenia along with the established risk factors.[2] The following variables were selected for analysis: age, CCI, MNA-SF, moderate to high physical activity, active RT, Ln(HOMA-IR), and HbA1c. In the univariable analysis, age, CCI, active RT, Ln(HOMA-IR), and

HbA1c contributed to the development of sarcopenia in men (*Table* 3). In women, age, MNA-SF, and moderate to high physical activity were associated with incident sarcopenia, but not CCI, active RT, or Ln(HOMA-IR).

When concurrently adjusted for multiple variables, the significance for CCI, Ln(HOMA-IR), and HbA1c were attenuated, and only age and active RT were significant in men (*Table* 3). In women, age, MNA-SF, and moderate to high physical activity all remained as independent risk factors for progression to sarcopenia in the fully adjusted model.

Next, we classified the men without sarcopenia at baseline based on the frequency of RT: individuals who performed one or less sessions of RT per week as the 'Infrequent RT' group (n = 453, 60%) and those who engaged in two or more sessions per week as the 'Frequent RT' group (n = 302, 40%) (*Figure* 3 and *Table* S4). Men in the Infrequent RT group had lower HGS, SPPB scores, and functional mobility measured by the five-times sit-to-stand test whereas their muscle masses

Table 2 Biennial changes in muscle mass, strength, and physical performance

| | Incident sarcopenia (+) | | | Incident sarcopenia (−) | | | | |
	2016–2017	2018–2019	P^a	2016–2017	2018–2019	P^a	P^b	P^c
Men								
ASM/height^2 (kg/m^2)	7.04 ± 0.75	6.31 ± 0.55	<0.001	7.31 ± 0.80	7.03 ± 0.75	<0.001	<0.001	0.111
Hand grip strength (kg)	30.4 ± 4.2	28.2 ± 5.2	<0.001	34.4 ± 5.1	34.4 ± 5.2	0.635	<0.001	0.013
Gait speed (m/s)	1.07 ± 0.21	0.99 ± 0.21	<0.001	1.25 ± 0.25	1.23 ± 0.20	0.058	0.006	0.785
SPPB (score)	11.0 ± 1.2	10.7 ± 1.4	0.015	11.4 ± 0.9	11.5 ± 0.9	0.229	0.007	0.536
Timed up and go test (s)	10.5 ± 2.3	12.5 ± 2.9	0.015	9.6 ± 2.1	10.0 ± 2.3	<0.001	<0.001	0.782
Five-times sit-to-stand test (s)	10.8 ± 2.8	11.5 ± 3.3	0.034	10.0 ± 2.9	9.5 ± 2.7	<0.001	0.004	0.852
Women								
ASM/height^2 (kg/m^2)	5.58 ± 0.55	4.99 ± 0.33	<0.001	6.02 ± 0.68	5.83 ± 0.63	<0.001	<0.001	—
Hand grip strength (kg)	19.2 ± 3.7	18.2 ± 3.3	0.002	22.0 ± 3.7	21.9 ± 3.9	0.305	0.008	—
Gait speed (m/s)	1.03 ± 0.20	0.94 ± 0.19	<0.001	1.13 ± 0.23	1.11 ± 0.21	0.003	0.003	—
SPPB (score)	10.8 ± 1.5	10.4 ± 1.6	0.031	10.9 ± 1.4	10.9 ± 1.5	0.614	0.135	—
Timed up and go test (s)	11.2 ± 3.5	13.0 ± 4.6	<0.001	10.1 ± 2.3	10.8 ± 2.8	<0.001	<0.001	—
Five-times sit-to-stand test (s)	12.4 ± 4.7	13.1 ± 5.8	0.127	11.4 ± 3.5	11.1 ± 3.7	0.040	0.073	—

ASM, appendicular skeletal muscle mass; SPPB, short physical performance battery.

Data are shown as mean ± standard deviation.

[a] P statistical significance between the baseline value (2016–2017) and the follow-up value (2018–2019).

[b] P for interaction of time and sarcopenic status.

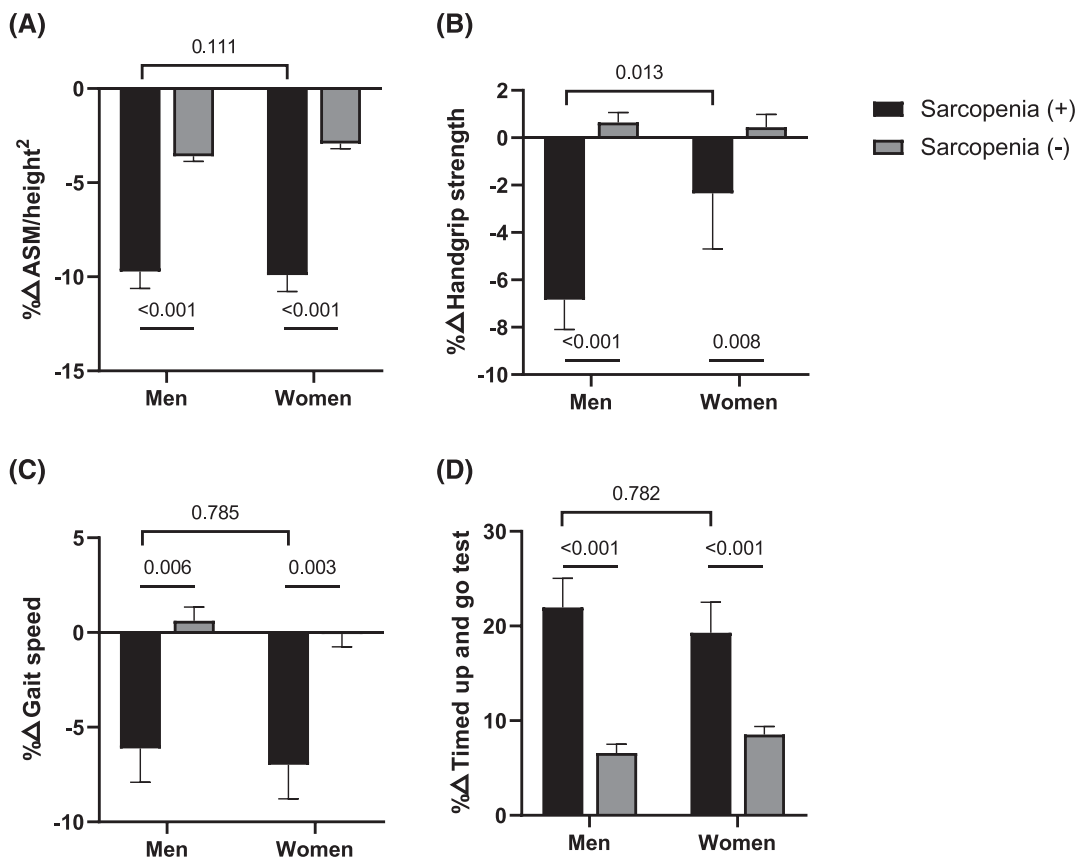[c] P for interaction of time and sex in participants with incident sarcopenia.

Figure 2 Changes in muscle mass and function according to the development of incident sarcopenia by gender. Black rectangles and grey rectangles indicate incident sarcopenia and no sarcopenia, respectively. (A) Relative percentage change of appendicular skeletal muscle mass (ASM) divided by height^2. (B) Relative percentage change of hand grip strength. (C) Relative percentage change of gait speed. (D) Relative percentage change in the timed up and go test.

Table 3 Logistic regression of variables associated with incident sarcopenia

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Men				
Age	1.18 (1.11–1.25)	<0.001	1.17 (1.10–1.25)	<0.001
Charlson comorbidity index	1.23 (1.02–1.48)	0.026	1.15 (0.94–1.42)	0.172
MNA-SF	1.05 (0.89–1.24)	0.539	1.04 (0.87–1.25)	0.678
Moderate to high physical activity	0.61 (0.33–1.13)	0.115	0.84 (0.43–1.63)	0.604
Resistance training (≥2 per week)	0.48 (0.30–0.76)	0.002	0.50 (0.30–0.82)	0.006
Ln(HOMA-IR)	1.45 (1.05–1.99)	0.022	1.26 (0.87–1.82)	0.222
HbA1c	1.35 (1.07–1.70)	0.010	1.15 (0.86–1.54)	0.335
Women				
Age	1.15 (1.09–1.21)	<0.001	1.14 (1.08–1.21)	<0.001
Charlson comorbidity index	1.14 (0.93–1.40)	0.207	1.08 (0.86–1.34)	0.507
MNA-SF	0.77 (0.68–0.87)	<0.001	0.79 (0.70–0.90)	<0.001
Moderate to high physical activity	0.52 (0.33–0.84)	0.007	0.57 (0.34–0.95)	0.030
Resistance training (≥2 per week)	0.63 (0.37–1.09)	0.096	0.72 (0.41–1.26)	0.249
Ln(HOMA-IR)	0.85 (0.61–1.19)	0.346	0.79 (0.54–1.16)	0.231
HbA1c	1.05 (0.82–1.35)	0.698	1.06 (0.80–1.40)	0.701

CI, confidence interval; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MNA-SF, mini nutritional assessment-short form; Moderate to high physical activity, 600 MET-min/week or higher score in the International Physical Activity Questionnaire short form; OR, odds ratio.

were similar at baseline, and they developed sarcopenia at a significantly higher rate compared with men in the Frequent RT group (16.7% vs. 8.7%; *P* = 0.002).

The decreasing trend in the prevalence of incident sarcopenia was observed for higher physical activity levels in both men and women, with statistical significance retained for women in the subgroup analysis (men, *P* for trend = 0.015; women, *P* for trend = 0.004; *Table* S5). Despite the decreasing trend for BMI and waist circumference with higher physical activity levels, baseline muscle mass indices as well as MNA-SF screening scores were similar between the groups. Baseline muscle strength and physical performances were better preserved in men and women with higher physical activity levels. When women were categorized according to the MNA-SF screening score of 12 or higher (Well-nourished) and <12 (Malnutrition at risk), the latter indubitably demonstrated lower BMI values; however, similar baseline muscle mass indices were observed between the two groups (*Table* S6). In line with other indices, baseline muscle strength and physical performance were inferior for women in the Malnutrition at risk group and were antecedents of incident sarcopenia.

Discussion

Sarcopenia poses a serious threat to independence and quality of life in elderly populations, which could lead to major healthcare burdens. In this longitudinal cohort study at 2 year follow-up, we found 13.5% and 11.7% of incident sarcopenia in men and women. Amendable determinants differed for the development of new sarcopenia in older Korean persons by gender: thus, an RT of <2 times per week was a risk factor

for the development of sarcopenia in men; in women, malnutrition and physical inactivity played a role in the progression to sarcopenia.

Gender differences in the prevalence of sarcopenia using various definitions were reported recently using cross-sectional data of the KFACS cohort.[10,19,20] Accordingly, all analyses were stratified by gender in this study. However, studies on the prevalence of new onset sarcopenia are scarce, and to the best of our knowledge, none have investigated gender-based differences in incident sarcopenia. The cumulative incidence of sarcopenia was 13.7% during the 12 year follow-up of the English Longitudinal Study of Ageing (ELSA) with participants with a mean age of 69.1 ± 6.7 years,[21] 13.7% during the 4 year follow-up of the sarcopenia and physical impairment with advancing age (SarcoPhAge) cohort with participants with a mean age of 72.5 ± 5.8 years,[22] and 3.6% during the 6.7 year follow-up of Taiwanese participants with a mean age of 60.5 years.[23] The prevalence of incident sarcopenia varied considerably by age, ethnicity, comorbidities, and the follow-up duration. Of note, the threshold for diagnosing sarcopenia were heterogeneous: the sum of only the low HGS and low skeletal muscle mass was applied for the ELSA and the SarcoPhAge study. In the Taiwanese study, the diagnosis of sarcopenia was made based on an insurance claim database, which might explain the particularly low incidence rates of new onset sarcopenia, as the validity of the diagnosis codes for sarcopenia is unknown. The rate of 2 year incident sarcopenia using the AWGS 2019 criteria was 13.5% and 11.7% for men and women in this KFACS cohort, respectively, but this incidence did not differ between men and women during the 2 years of follow-up.

Here, the rate of decline in muscle mass did not differ between men and women who developed incident sarcopenia. This finding was contrary to those of previous longitudinal
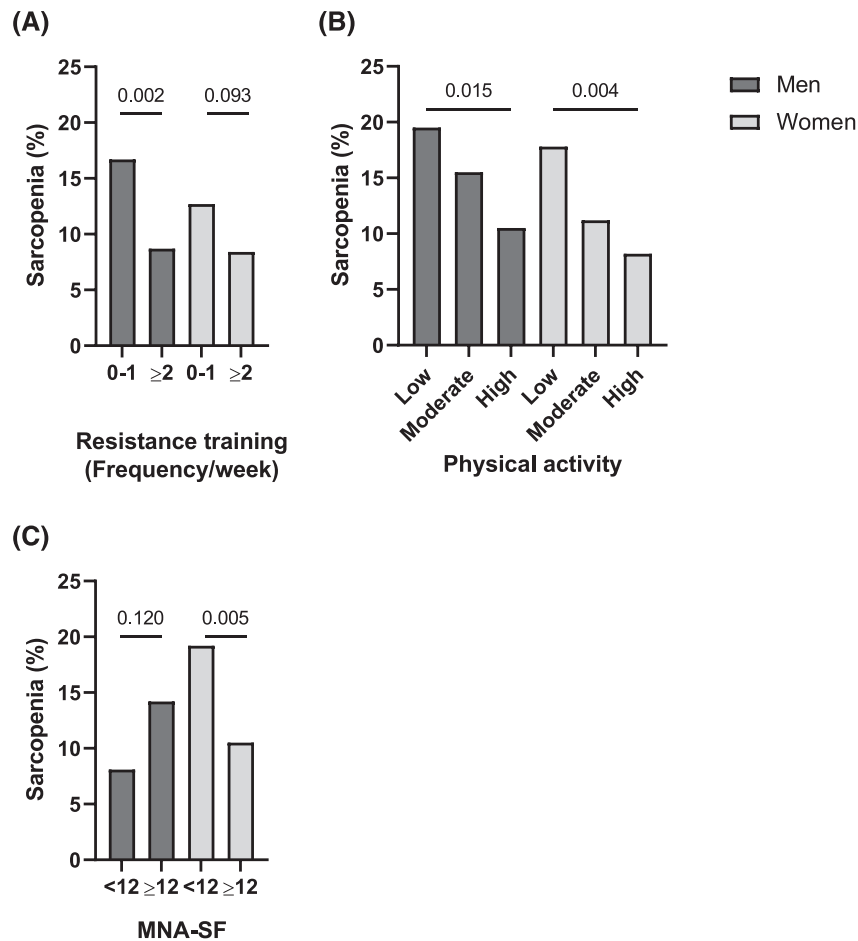
Figure 3 Incidence of sarcopenia according to risk factors by gender. Dark grey rectangles and light grey rectangles indicate men and women who developed incident sarcopenia, respectively. *(A)* Men who are engaged in resistance training for 0–1 times per week vs. ≥2 times per week. *(B)* Men and women grouped according to low/moderate/high levels of physical activity. *(C)* Women with mini nutritional assessment-short form (MNA-SF) of <12 vs. ≥12.

studies that demonstrated that age-related decline in height-adjusted muscle mass is less pronounced in women than in men.[24,25] Decreases in physical performances were also similar between men and women over the 2 years although a longer follow-up is warranted. Of note, the biennial decline in HGS was higher in men than in women. More expeditious hand grip weakness in men in comparison with women is in concordance with a 22 year follow-up study that evaluated the accelerated decline in HGS in men[26] and a 4 year prospective study from China that revealed a particularly faster decline in HGS compared with other measures for sarcopenia.[27]

While the effectiveness of RT to combat muscle wasting and weakness is legitimately underscored by a series of landmark randomized clinical studies,[28–30] few epidemiological studies conducted in the field of geriatric medicine have revealed RT as a major modifiable risk factor for preventing sarcopenia. A plausible explanation is that information regarding RT might not have been explored extensively

through cohort studies. Here, we demonstrated that the most important modifiable factor in the development of sarcopenia in elderly men was engaging in RT at least two times per week. Importance of RT is recently being revitalized, as it has been proposed that while aerobic exercise may attenuate the loss of skeletal muscle during energy restriction in obese adults, a single mode of aerobic exercise alone does not promote muscle hypertrophy to the same extent as RT.[31–35] Along the same line, while there was an increasing trend in the onset of sarcopenia according to a decrease in the physical activity level, this association was modest and did not independently contribute to the development of sarcopenia in men.

In the current study, men with or without the development of sarcopenia were relatively insulin sensitive and nonobese at baseline. That this cohort mainly consisted of metabolically healthy phenotypes partly explains why higher fasting glucose, HbA1c, and HOMA-IR values only demonstrated meagre roles in the progression to sarcopenia. Furthermore, we

adopted ASM/height^2 as a muscle mass index in this study, as recommended by the contemporary AWGS guidelines, but it has been implied that muscle mass index adjusted by body weight is more closely associated with insulin resistance when compared with ASM/height^2.[36] The effects of hyperglycaemia and insulin resistance were completely abolished after adjusting for potential risk factors that could negatively influence muscle mass and function, belying the apparent association shown with sarcopenia development in the crude analysis.

In women, insulin resistance, comorbidities, and engagement in RT had negligible effects on sarcopenia development. On the contrary, malnutrition conferred an appreciable risk, consistent with a previous cross-sectional study.[37] This is in line with a 9 week study that provided either an adequate-protein or a low-protein diet to groups of healthy elderly women.[38] Despite the small sample size, women fed with the low-protein diet had negative nitrogen balance and this resulted in worse functional capacity, while those in the adequate-protein diet group were able to maintain both a lean body mass and muscle function. In addition, accumulating evidence suggests that immobility induces anabolic resistance and that increasing physical activity might enhance the muscle protein anabolic response upon protein intake by improving blood flow and nutrient delivery to muscle.[39] In this cohort, self-reported physical activity levels were considerably lower in women than men. Whether there is a threshold level of physical inactivity that could impair functional capacity in older adults should be elucidated; however, there is a possibility that sedentary behaviour in older Korean women might have been closely linked to the deteriorations in muscle indices. Collectively, avoiding malnutrition and being physically active could be fundamental modifiable factors to preserve muscle mass and function in Korean older women.

It should be noted that in women, the rate of decline in SPPB and five-times sit-to-stand test did not differ regarding incident sarcopenia status. Musculoskeletal complaints linked to less competent use of knee extensor muscles may have overtaken the sole impact of sarcopenia on scoring of the SPPB and five-times sit-to-stand test. Indeed, the prevalence of osteoarthritis was higher in women compared with men in this study.[40]

This study had some inherent limitations. First, our analysis was conducted after the first biennial visit of this cohort, which made the duration of follow-up 2 years. A longer follow-up might distinguish the currently subtle gender-based differences in the annual deterioration rate of muscle mass and function, as well as detecting other potential factors that may contribute to the development of sarcopenia. Second, as most participants in this cohort had relatively low HOMA-IR values, the impact of insulin resistance might have been underestimated. Third, the frequency of RT and physical activity levels were based on a self-reported questionnaire, and individual intensities and durations of exercise may have been diverse. While admitting that the optimal intensity of RT is yet to be determined, RT, especially if performed by physically frail elderly persons who have been habitually sedentary, should be individualized periodically.

With these caveats in mind, we surmise that understanding gender-based differences of potential modifiable factors in progression to sarcopenia is imperative. An adequate amount of RT may be a safeguard to elderly men in retaining muscle mass and function. Performing moderate to high physical activity and improving nutritional status could be effective strategies for preventing incident sarcopenia in women.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest

None declared.

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