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Grip strength mediates the relationship between muscle mass and frailty

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Abstract

Background Although sarcopenia and frailty are important diseases in geriatrics, few studies have investigated the association between the two diseases. Thus, this study aimed to examine the relationship between two components of sarcopenia (muscle mass and muscle function) and frailty.

Methods In total, 997 Korean older adults (456 men and 541 women) were included in this cross-sectional observational study. We used a polynomial linear regression analysis to obtain standardized sex, age, and height-adjusted appendicular skeletal muscle mass (zASM), as well as to standardized sex, age, and height-adjusted grip strength (zGS). We then performed a causal mediation analysis to confirm the relationship between zASM and frailty.

Results In both men and women, zGS mediated the relationship between zASM and frailty (average causal mediation effect in men: −0.096 {−0.159 to −0.050}; in women: −0.053 {−0.098 to −0.010}). For every one-point increase in zGS score, the relative risk of a one-point increase in frailty was reduced by 21% in men ($e^{-0.238}$ = 0.788) and by 11% in women ($e^{-0.113}$ = 0.893).

Conclusions In this study on Korean older adults, muscle mass did not have a direct effect on frailty but had an indirect effect through altered muscle function.

Keywords Sarcopenia; Grip strength; Appendicular skeletal muscle; Frailty

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Introduction

Sarcopenia and frailty are important geriatric syndromes that become increasingly prevalent with age and may co-occur. Sarcopenia is defined as an age-related decline of skeletal muscle mass and function.[1,2] The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project defined sarcopenia as low lean muscle mass and low muscle strength.[1] The Asian Working Group for Sarcopenia (AWGS), which is based on the European Working Group on Sarcopenia in Older People,[3] also developed criteria for the diagnosis of sarcopenia in the Asian population.[2] The AWGS recommended that sarcopenia be defined as low muscle mass combined with low muscle strength and/or low physical performance (gait speed). These criteria use appendicular skeletal muscle mass (ASM) adjusted by body mass index (ASM/BMI) or height squared (ASM/height^2) as parameters of muscle mass, and grip strength (GS) as a parameter of muscle strength. However, ASM/BMI and ASM/height^2 is positively correlated with height, so shorter people tend to be included in the low muscle mass group,[4] and GS is also affected by height.[5,6] Furthermore, muscle mass and GS decline with advancing age.[5,7] Although muscle mass and GS are affected by age and height, investigations for adjusting these factors are lacking.

Frailty is an another significant issue in geriatrics, and it is defined as a geriatric syndrome characterized by multisystem

impairment, which results in increased vulnerability to external and internal stressor events.[8] There are many different criteria for frailty, and those criteria evaluate the general condition of individuals with various indicators, such as weight loss, weakness, low physical performance, exhaustion, depression, incontinence, and cognitive impairment.[8–10] Although each criterion focused on a slightly different aspect and risk for older people, there is general agreement that the impairment of physical function plays an important role in frailty.[11]

Physical function impairment (weakness) is a core condition of both sarcopenia and frailty, and these syndromes can be linked to GS, which is an objective measurement of weakness. However, not many studies have investigated the association between sarcopenia and frailty and their common characteristics. Therefore, we conducted this study for two reasons. First, we aimed to obtain the standardized sex, age, and height-adjusted appendicular skeletal masses (zASM), and grip strengths (zGS) of Korean older adults. Second, we examined the effects of zASM and zGS on frailty, with focus on the mediating effect of GS.

Methods

Study population

The study participants consisted 997 Korean older adults (456 men and 541 women), 60–90 years of age, who participated in the *Bitgoeul senior health examination*.[4] The Bitgoeul senior health examination participant was recruited from the Bitgoeul Senior Health Town, a retirement community for senior citizens located in Gwangju, Korea. We explained the purpose of the study to the participants and signed consent forms were obtained. Between 1 February 2015 and 30 August 2015, two trained nurses who were in attendance at the Bitgoeul Senior Health Town helped participants to fill out the questionnaires and performed physical measurements under the supervision of the study investigator. This study was performed by reanalyzing the data of subjects between 60 and 90 years of age in the Bitgoeul senior health examination. The requirement to obtain full ethical approval for reanalysis of the data collected during the Bitgoeul senior health examination was waived by Chonnam National University Hwasun Hospital Institutional Review Board (CNUHH-2018-183).

Measurements of ASM, GS, zASM, and zGS

To measure body composition, direct segmental multifrequency bioelectrical impedance analysis (BIA) (Inbody 720, Biospace, Seoul, Korea) was used. The body position of participants was supervised by a trained nursed to keep an upright posture with relaxed and opened arms and legs; the fingers, palm, and sole were evenly contacted with the electrodes. Participants were advised to go to the toilet for urination or defecation before the test and to avoid vigorous exercise, meals, or bathing before the test. ASM was defined as the sum of the skeletal muscle masses of the upper and lower extremities. GS was measured using a dynamometer (Hand Grip Metre No. 6103, Tanita, Tokyo, Japan). Each participant was asked to grip the dynamometer twice, using the dominant arm in a lowered straight position. The higher value was used in the analysis and calculations of zASM and zGS. The Z-score and the T-score have been used to diagnose osteoporosis. In a bone mineral density test, the T-score signifies the "Difference in number of Standard Deviations (SD) between the value for the individual and mean value of group of young adults of the same sex," while the Z-score signifies the "Difference in number of SD between the value for the individual and mean value of group of the same sex and age".[12] Because height has a positive influence on ASM and GS, we considered height as another covariate and adjusted for it as well as for age and sex

$$\mathrm{zASM} = \frac{\mathrm{ASM} - \mathrm{ASM_{adj}}}{\mathrm{SD\ of}\ \left(\mathrm{ASM} - \mathrm{ASM_{adj}}\right)}$$

$$\mathrm{zGS} = \frac{\mathrm{GS} - \mathrm{GS_{adj}}}{\mathrm{SD\ of}\ \left(\mathrm{GS} - \mathrm{GS_{adj}}\right)}.$$

$\mathrm{ASM_{adj}}$: sex, age, and height -adjusted ASM
$\mathrm{GS_{adj}}$: sex, age, and height -adjusted GS

Korean frailty index

The Korean frailty index (KFI) was developed by a functional assessment committee in the Korean Geriatric Society in 2010. The KFI comprises eight criteria (hospital admission, self-assessed health status, polypharmacy, weight loss, depressed mood, incontinence, visual or auditory problems, and timed up-and-go test), and the score ranges from 0 to 8.[10] In this study, we assumed that the sum of the KFI score would take on a negative binomial distribution.

Other covariates

The baseline characteristics of the study participants comprised age, height, weight, body fat percentage, waist circumference, household income, education level, smoking status, alcohol consumption, comorbidities, depression, and cognitive function. Comorbidities included ischemic heart disease, chronic obstructive pulmonary disease, diabetes, osteoarthritis, chronic renal failure, hypertension, congestive heart failure, peripheral artery disease, and cancer. Depression and cognitive function were assessed according to the Korean

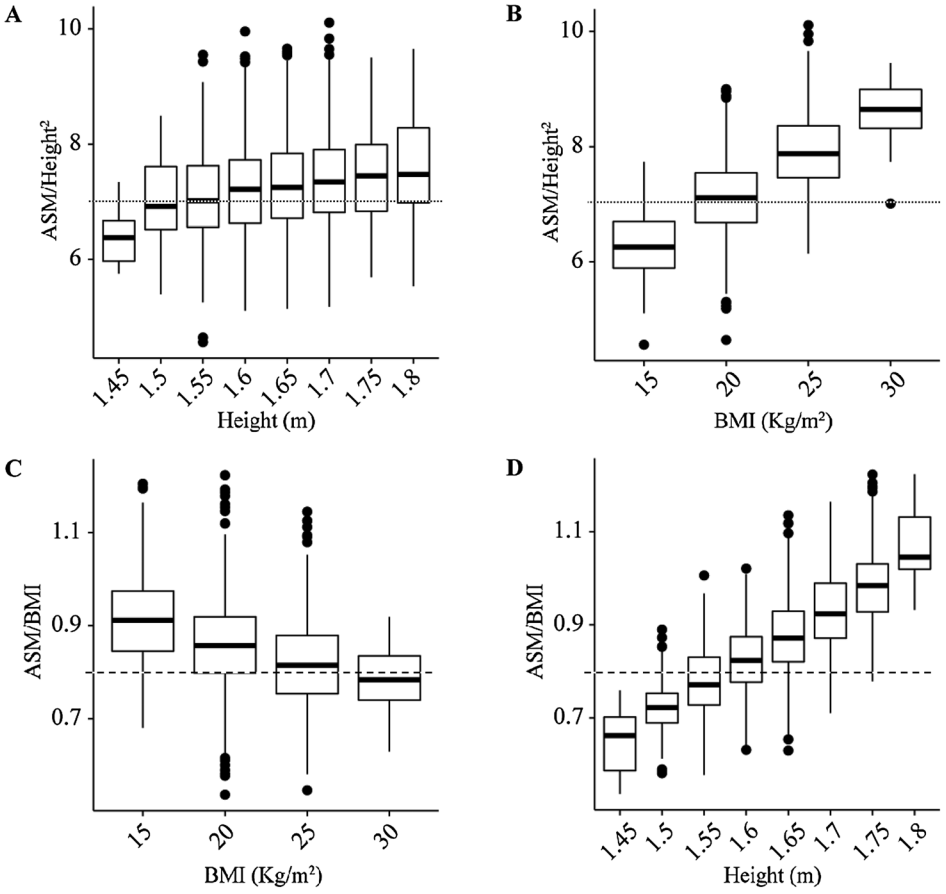
version of the Geriatric Depression Scale-Short form [13] and the Korean Dementia Screening Questionnaire-Cognition ,[14] respectively.

Statistical analysis

Before the main analysis, we described how ASM/height^2 and ASM/BMI, which are the most widely used indices for muscle mass, were distributed according to the height or BMI of 456 men participants in our study using a box-and-whisker plot (*Figure* 1). Then, we used national representative large-scale survey of Korean people to calculate zASM and zGS. The equation for zASM was developed using data from the 2008 to 2011 Korea National Health and Nutrition Examination Surveys IV and V (KNHANES IV and V, Korean Ministry of Health and Welfare; *N* = 5704: 2459 men and 3245 women). Changes in ASM according to changes in sex, age, and height were examined in a generalized additive model (GAM) analysis. Based on the GAM analysis results, zASM according to sex, age, and height was calculated using polynomial linear regression. The polynomial equation for zGS was obtained using the same method as that for zASM and both used data from the Survey on Health and Welfare Status of Elderly 2008 (Elderly Survey 2008, Korean Ministry of Health and Welfare; *N* = 13 573: 5651 men and 7922 women). After calculating the zASM and zGS for 997 Korean older adults (456 men and 541 women) in this study using the corresponding equations, the effects of zASM and zGS on the sum of frailty scores were analyzed using a negative binomial GAM. Finally, the mediating effects of zGS in the relationship between zASM and frailty were confirmed in a causal mediation analysis.

R version 3.5.1 (R core team, 2018) was used for the analysis in this study. The mgcv (version 1.8–24) and itsadug (version 2.3) packages were used for the GAM analysis and a mediation (version 4.4.6) package was used for the causal mediation analysis. The value indicative of statistical significance was $P < 0.05$.

Figure 1 Appendicular muscle mass of men participants according to anthropometric variables. A, B: Dotted lines, a cut-off value (7.0 kg/m^2) of low muscle mass presented by The Asian Working Group for Sarcopenia; C, D: Dashed lines, a cut-off value (0.789) of low muscle mass presented by The Foundation for the National Institutes of Health Sarcopenia Project. ASM, appendicular skeletal muscle; BMI, body mass index.



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Results

Figure 1 as a box-and-whisker plot represents the distribution of ASM/height^2 and ASM/BMI according to the height and BMI among 456 Korean older men aged 60–90 years in this study. Using ASM/height^2 ($<$7.0 kg/m^2 by AWGS, dotted line in *Figure* 1A and 1B) for the diagnosis of sarcopenia increases the probability of diagnosing short and thin people with sarcopenia, while using ASM/BMI ($<$0.789 by FNIH, dashed line in *Figure* 1C and 1D) increases the probability of diagnosing short and obese people with sarcopenia.

Table 1 shows the general characteristics of the participants in this study. ASM according to sex, age, and height was obtained based on the results of the GAM analysis using the KNHANES IV and V. The results showed that ASM decreased with decreasing height and advancing age in both men and women (*Figure* 2A and 2F). In both men and women, ASM decreased in a curvilinear manner and the difference in ASM according to height decreased with advancing age (*Figure* 2B and 2G). ASM increased linearly with height in both men and women and the difference in ASM according to age increased with increasing height (*Figure* 2C and 2H). Considering these patterns, the polynomial regression equation that is most reflective of ASM_{adj} in men is

$$\begin{aligned}\mathrm{ASM_{adj}} \approx \mathrm{height\ (m)} \times \big(&-0.00002 \times \mathrm{age}^3 + 0.00343 \times \mathrm{age}^2 \\ &- 0.44536 \times \mathrm{age} + 48.92696\big) \\ &+ 0.00004 \times \mathrm{age}^3 - 0.00595 \times \mathrm{age}^2 \\ &+ 0.62077 \times \mathrm{age} - 52.47251.\end{aligned}$$

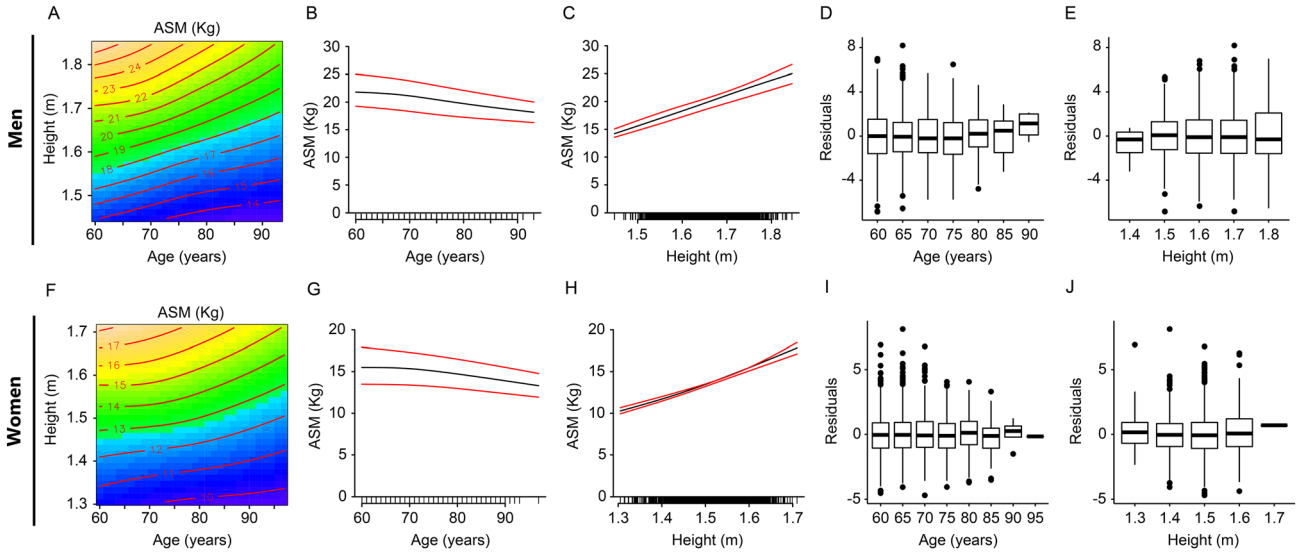
The standard deviation (SD) of ($ASM - ASM_{adj}$) was 2.2, and the SD was robust against age and height (*Figure* 2D and 2E). Therefore,

Table 1 General characteristics of study participants

	Men (N = 456)	Women (N = 541)
Age (years)	72.69 ± 5.08	70.47 ± 4.71
Height (cm)	166.65 ± 5.42	154.42 ± 5.07
Weight (kg)	66.89 ± 8.19	59.22 ± 7.7
BMI (kg/m^2)	24.07 ± 2.60	24.82 ± 2.91
Fat %	25.27 ± 5.87	34.75 ± 5.60
Waist circumference (cm)	87.26 ± 7.52	83.36 ± 7.61
ASM (kg)	21.00 ± 2.56	15.08 ± 2.02
zASM	0.53 ± 0.78	0.57 ± 0.93
GS (kg)	30.40 ± 5.78	19.43 ± 3.98
zGS	0.09 ± 0.79	0.01 ± 0.80
SGDS-K	2(0–4)	2(1–5)
KDSQ-C	3(2–5)	5(3–6)
Household income (×10 000 Korean Won)		
0–50	151(33.11)	240(44.36)
51–100	50(10.97)	73(13.49)
101–200	53(11.62)	76(14.05)
≥201	202(44.30)	152(28.10)
Education level		
Undergraduate	1(0.22)	23(4.25)
Elementary school	21(4.61)	161(29.76)
Middle school	59(12.94)	163(30.13)
High school	151(33.11)	141(26.06)
College or higher	224(49.12)	53(9.80)
Current or ex-smoker	319(69.96)	9(1.66)
Alcohol		
Abstainer	214(46.93)	413(76.34)
1–2 drinks per occasion	83(18.20)	105(19.41)
≥3 drinks per occasion	159(34.87)	23(4.25)
Comorbidity		
Ischemic heart disease	32(7.02)	25(4.62)
COPD	17(3.73)	10(1.84)
Diabetes	106(23.25)	75(13.86)
Osteoarthritis	42(9.21)	151(27.91)
Chronic renal failure	5(1.10)	5(0.92)
Hypertension	229(50.22)	240(44.36)
Congestive heart failure	12(2.63)	12(2.22)
Peripheral artery disease	7(1.54)	5(0.92)
Cancer	44(9.65)	52(9.61)

Data are represented as mean ± standard deviations, medians (25–75%), or numbers (percentages).
ASM, appendicular skeletal muscle; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Fat %, body fat percentage; GS, grip strength; KDSQ-C, Korean Dementia Screening Questionnaire-Cognition; SGDS-K, Geriatric Depression Scale-Short form (Korean version); zASM, standardized sex, age, and height-adjusted appendicular skeletal muscle; zGS, standardized sex, age, and height-adjusted grip strength.

Figure 2 Distribution of appendicular muscle mass according to age and height. A: Mean value of ASM according to age and height in men; B: Changes in ASM according to age at constant heights (heights are 1.8, 1.7, and 1.6 m from top to bottom); C: Changes in ASM according to height at constant ages (ages are 75, 65, and 55 years from top to bottom); D: Distribution of (ASM − ASM_{adj}) according to age; E: Distribution of (ASM − ASM_{adj}) according to height; F: Mean value of ASM according to age and height in women; G: Changes in ASM according to age at constant heights (heights are 1.7, 1.6, and 1.5 m from top to bottom); H: Changes in ASM according to height at constant ages (ages are 75, 65, and 55 years from top to bottom); I: Distribution of (ASM − ASM_{adj}) according to age; J: Distribution of (ASM − ASM_{adj}). according to height. ASM, appendicular skeletal muscle mass.



$$zASM_{men} = {}^{1}/_{2.2} \times (ASM - ASM_{adj}).$$

The polynomial regression equation that is most reflective of ASM_{adj} in women is

$$\begin{aligned} ASM_{adj} \approx\ & height\ (m) \times (-0.00008 \times age^3 + 0.01963 \times age^2 \\ & - 1.86536 \times age + 79.70974) \\ & + 0.00012 \times age^3 - 0.03089 \times age^2 \\ & + 2.89576 \times age - 107.30373. \end{aligned}$$

The SD of (ASM − ASM_{adj}) was 1.5 and was robust against age and height (*Figure* 2I and 2J). Therefore,

$$zASM_{women} = {}^{1}/_{1.5} \times (ASM - ASM_{adj}).$$

Grip strength according to sex, age, and height was examined based on the results of the GAM analysis using the Elderly Survey 2008. The results showed that GS decreased with decreasing height and advancing age in both men and women (*Figure* 3A and 3F). In both men and women, GS decreased linearly and the difference of GS according to height decreased with advancing age. (*Figure* 3B and 3G). GS increased in a curvilinear manner in both men and women and the difference in GS according to age increased with increasing height (*Figure* 3C and 3H). Considering these patterns, the polynomial regression equation that is most reflective of GS_{adj} in men is

$$\begin{aligned} GS_{adj} \approx\ & age \times 44.18679 \times height\ (m)^6 - 426.87449 \\ & \times height^5 + 1704.78746 \times height^4 - 3602.32804 \\ & \times height^3 + 4248.95776 \times height^2 - 2655.20088 \\ & \times height + 688.00603. - 5396.12853 \\ & \times height^6 + 52737.20702 \times height^5 - 213208.12071 \\ & \times height^4 + 456366.12877 \times height^3 - 545582.02527 \\ & \times height^2 + 345684.04352 \times height - 90800.34206. \end{aligned}$$

The SD of (GS − GS_{adj}) was 6.5, and SD was robust against age and height (*Figure* 3D and 3E). Therefore,

$$zGS_{men} = {}^{1}/_{6.5} \times (GS - GS_{adj}).$$

The polynomial regression equation that is most reflective of GS_{adj} in women is

$$\begin{aligned} GS_{adj} \approx\ & age \times (-5.063696 \times height(m)^6 + 52.742862 \\ & \times height^5 - 227.704356 \times height^4 + 521.235911 \\ & \times height^3 - 666.723158 \times height^2 + 451.069190 \\ & \times height - 125.969329) + 531.884081 \\ & \times height^6 - 5525.917951 \times height^5 + 23797.266981 \\ & \times height^4 - 54341.367369 \times height^3 + 69344.197398 \\ & \times height^2 - 46805.053570 \times height + 13050.891212. \end{aligned}$$

The SD of (GS − GS_{adj}) was 4.5, and SD was robust against age and height (*Figure* 3I and 3J). Therefore,

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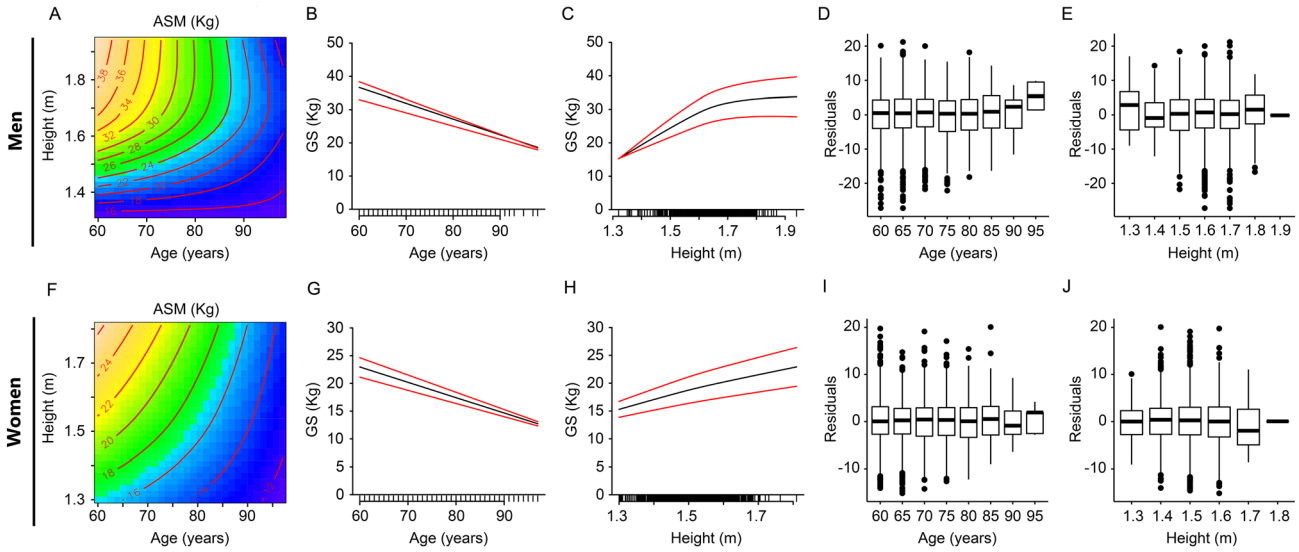
Figure 3 Distribution of grip strength according to age and height. A: Mean value of GS according to age and height; B: Changes in GS according to age at constant heights (Heights are 1.8, 1.7, and 1.6 m from top to bottom); C: Changes in GS according to height at constant ages (ages are 75, 65, and 55 years from top to bottom); D: Distribution of (GS − GS_{adj}) with age; E: Distribution of (GS − GS_{adj}) according to height; F: Mean value of GS according to age and height; G: Changes in GS according to age at constant heights (heights are 1.7, 1.6, and 1.5 m from top to bottom); H: Changes in GS according to height at constant ages (ages are 75, 65, and 55 years from top to bottom); I: Distribution of (GS − GS_{adj}) with age; J: Distribution of (GS − GS_{adj}) according to height. GS, grip strength.



$$zGS_{women} = {}^{1}/_{4.5} \times (GS - GS_{adj}).$$

A multivariate negative binomial GAM to analyze the effects of muscle mass and grip strength on frailty showed that zASM was not statistically significant among men or women (men: P = 0.855; women: P = 0.564); however, zGS was linearly associated with frailty in both men and women [men: estimated degrees of freedom = 1.000; $P < 0.001$; women: estimated degrees of freedom = 1.001; P = 0.025]. The slope for men was −0.238 (95% confidence interval: −0.360 to −0.116), which indicates that with every 1-point increase in zGS score (1 SD increase in GS), the probability that the frailty score would increase by 1 point is reduced by 21% ($e^{-0.238}$ = 0.788). The slope for women was −0.113 (95% confidence interval: −0.212 to −0.015), which indicates that with every 1-point increase in zGS score, the probability of the frailty score increasing by 1 point is reduced by 11% ($e^{-0.113}$ = 0.893) (*Table* 2, *Figure* 4). Figure 5 shows the results of the causal mediation analysis. Although zASM did not have a significant total effect on frailty (c in the left diagram) in men or women (men: P = 0.260; women: P = 0.066), it affected frailty with zGS as a mediator in the model that included zGS (average causal mediation effect $a \times b$ in the left diagram for men: −0.096 {−0.159 to −0.050}; for women: −0.053 {−0.098 to −0.010}). The average direct effect (c' in the left diagram), which represents the difference between total effect and average causal mediation effect, was not statistically significant in either men or women.

Discussion

Thus far, most studies on sarcopenia have been conducted using ASM/height^2 and ASM/BMI. ASM/height^2 is commonly read "height square adjusted ASM," which suggests that dividing ASM by the square of the height would make the value robust against height. However, this expectation was not met in this study, as shown in *Figure* 1. ASM/height^2 was low among shorter individuals and high among taller individuals. Therefore, using ASM/height^2 to diagnose sarcopenia without additional adjustments for height would increase the probability of shorter people being diagnosed with sarcopenia. Things were similar with respect to ASM/BMI, because simply dividing ASM by BMI does not make the value robust against BMI. Using ASM/height^2 increases the probability of diagnosing short and thin people with sarcopenia, while using ASM/BMI increases the probability of diagnosing short and obese people with sarcopenia. For this reason, people diagnosed with sarcopenia based on ASM/height^2 differed from those diagnosed with sarcopenia based on ASM/BMI in studies[15,16] that used both ASM/height^2 and ASM/BMI on the same target population. In our study, we proposed a new approach to evaluating muscle mass and muscle strength. Our findings indicated that GS mediated the relationship between muscle mass and frailty.

ASM literally refers to the skeletal muscle mass attached to the left and right upper and lower extremities. Assuming that arm and leg muscles take on a cylindrical shape,[17] arm and

Table 2 Univariate and multivariate negative binomial generalized additive model analysis results to determine the influence of muscle mass and grip strength on frailty

	Men						Women					
	Univariate			Multivariate			Univariate			Multivariate		
	EDF	χ^2	*P*-value	EDF	χ^2	*P*-value	EDF	χ^2	*P*-value	EDF	χ^2	*P*-value
Age (years)	1.000	12.050	<0.001	1.000	11.203	<0.001	2.138	34.100	<0.001	1.954	14.215	0.002
BMI (kg/m^2)	2.003	4.550	0.187				1.247	6.788	0.013			
Fat %	2.636	7.495	0.075	2.725	9.757	0.031	2.989	27.930	<0.001	1.586	4.521	0.095
Waist circumference (cm)	2.131	3.470	0.331				1.001	11.410	<0.001			
zASM	1.667	2.607	0.290	1.000	0.034	0.855	1.001	1.141	0.286	1.000	0.332	0.564
zGS	1.001	31.290	<0.001	1.000	14.533	<0.001	1.002	20.310	<0.001	1.001	5.073	0.025
log (SGDS-K + 1)	2.367	120.500	<0.001	1.103	41.158	<0.001	1.931	149.900	<0.001	1.664	35.828	<0.001
log (KDSQ-C + 1)	3.776	69.620	<0.001	1.001	13.686	<0.001	2.342	73.890	<0.001	3.442	28.369	<0.001
	Est	SE	*P*-value	Est	SE	*P*-value	Est	SE	*P*-value	Est	SE	*P*-value
Household income (×10,000 Korean Won)												
0–50		Reference			Reference			Reference			Reference	
51–100	−0.083	0.185	0.651	−0.244	0.149	0.101	0.008	0.110	0.941	−0.047	0.104	0.650
101–200	−0.376	0.194	0.052	−0.152	0.162	0.347	−0.376	0.123	0.002	−0.195	0.119	0.100
≥201	−0.459	0.128	<0.001	−0.135	0.113	0.233	−0.529	0.989	<0.001	−0.235	0.107	0.027
Education level												
Undergraduate		Reference						Reference			Reference	
Elementary school	0.452	1.277	0.723				−0.144	0.177	0.417	−0.038	0.157	0.811
Middle school	0.466	1.262	0.712				−0.382	0.180	0.033	−0.020	0.165	0.903
High school	0.159	1.258	0.900				−0.507	0.184	0.006	−0.026	0.173	0.881
College or higher	−0.013	1.257	0.991				−0.552	0.213	0.010	0.070	0.207	0.736
Current or ex-smoker	0.300	0.128	0.020	0.218	0.109	0.045	−0.141	0.324	0.663			
Alcohol												
Abstainer		Reference						Reference				
1–2 drinks	−0.236	0.160	0.141				−0.101	0.103	0.324			
≥3 drinks	−0.158	0.123	0.214				0.031	0.192	0.871			
Comorbidity												
Ischemic heart disease	0.239	0.21	0.255				0.216	0.174	0.215			
COPD	0.446	0.268	0.098	0.087	0.206	0.673	0.272	0.264	0.303			
Diabetes	0.420	0.125	<0.001	0.308	0.102	0.002	0.551	0.094	<0.001	0.424	0.088	<0.001
Osteoarthritis	0.555	0.172	0.001	0.295	0.135	0.029	0.371	0.081	<0.001	0.183	0.076	0.016
Chronic renal failure	0.656	0.462	0.156				−0.247	0.453	0.586			
Hypertension	0.158	0.114	0.162				0.301	0.078	<0.001	0.166	0.076	0.028
Congestive heart failure	0.806	0.290	0.005	0.500	0.212	0.019	0.184	0.25	0.462			
Peripheral artery disease	0.562	0.400	0.160				0.044	0.404	0.914			
Cancer	0.005	0.192	0.978				0.059	0.131	0.655			

BMI, body mass index; COPD, chronic obstructive pulmonary disease; EDF, estimated degrees of freedom; Est, estimate of coefficient; Fat %, body fat percentage; KDSQ-C, Korean Dementia Screening Questionnaire-Cognition; SE, standard error; SGDS-K, Geriatric Depression Scale-Short form (Korean version); zASM, standardized sex, age, and height-adjusted appendicular skeletal muscle; zGS, standardized sex, age, and height-adjusted grip strength; χ^2, chi-square statistics of spline model.

Figure 4 Spline portion of multivariate negative binomial generalized additive model analysis. Fat %, body fat percentage; KDSQ, Korean Dementia Screening Questionnaire; SGDS, Geriatric Depression Scale-Short form; zASM, standardized sex, age, and height-adjusted appendicular skeletal muscle; zGS, standardized sex, age, and height-adjusted grip strength.

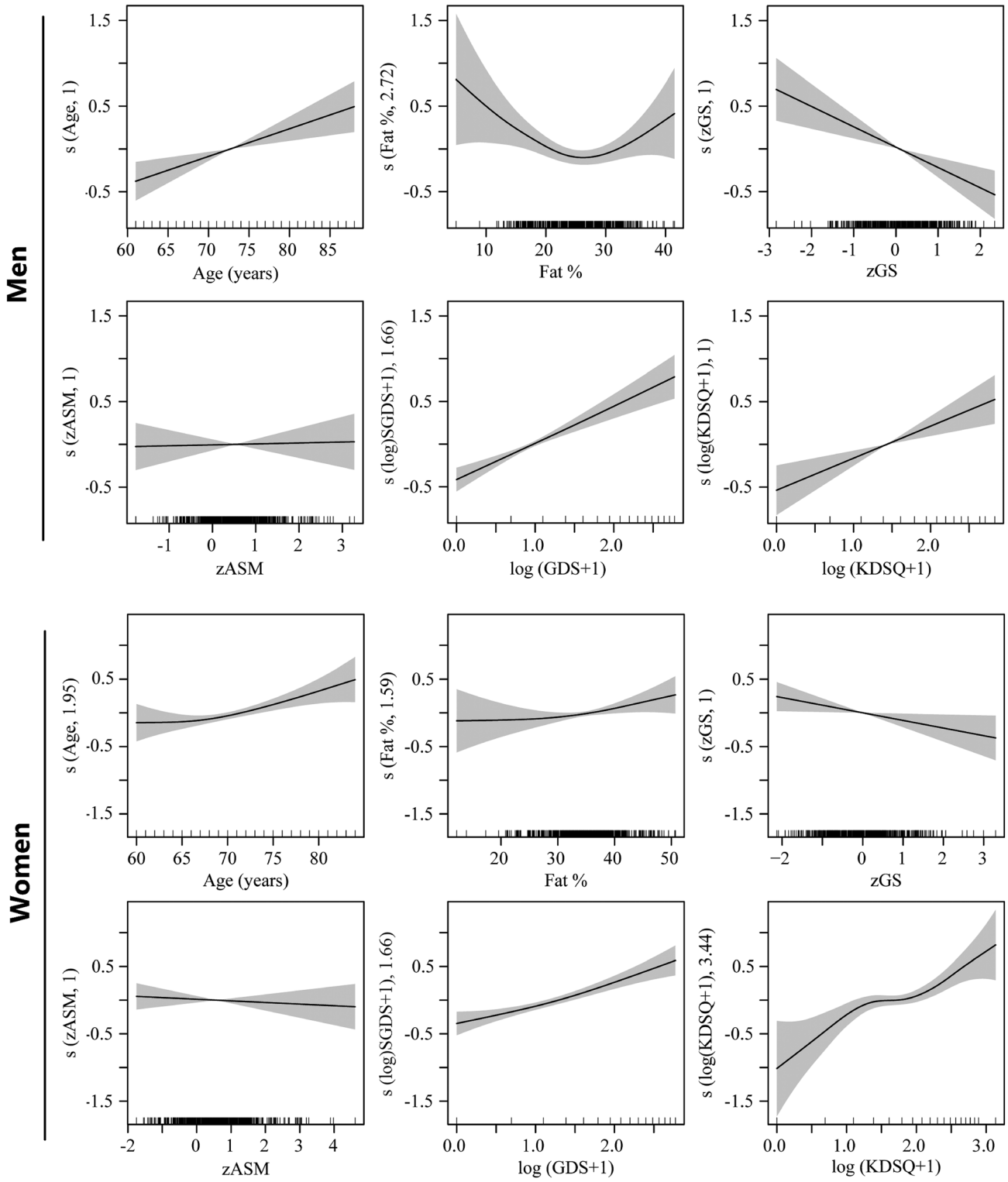


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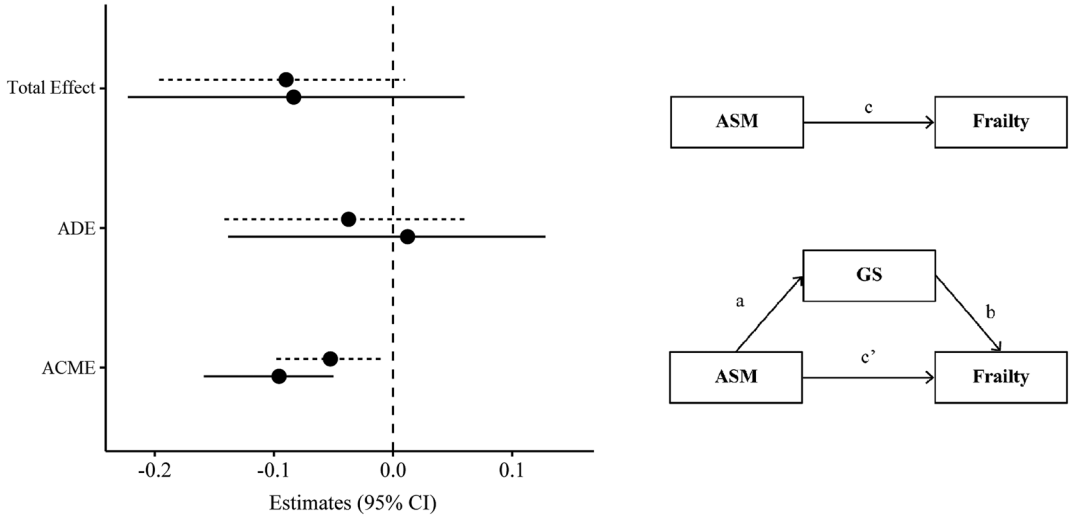
Figure 5 Causal mediation analysis result between muscle mass and frailty. Dashed line: estimates of women; Solid line: estimates of men. Total effect: *c* in the left diagram; ADE (average direct effect): *c*' in the left diagram; ACME (average causal mediation effect): *a* × *b* in the left diagram. ASM, appendicular skeletal muscle; CI, confidence interval; GS, grip strength.



leg muscle masses would be proportional to $\pi \times \text{radius}^2 \times$ length of the extremity. When radius is excluded, because it is intimately associated with the degree of sarcopenia, the volume of ASM becomes proportional to the length of the extremity. Thus, upper extremity skeletal muscle adjusted by upper extremity length and lower extremity skeletal muscle adjusted by lower extremity length should be calculated and combined for an accurate comparison of ASM. Because most cohort studies on aged persons did not measure the lengths of the upper and lower extremities separately, we adjusted for height with ASM assuming that height could represent the lengths of the upper and lower extremities in this study. However, it should be noted that even people who are the same height can have different arm and leg lengths depending on their ethnicity.[18,19] Additionally, height decreases with age due to kyphosis, concomitant without changes in the lengths of the arms and legs.

Grip strength is the maximal grip strength of the dominant hand specifically. Multiple studies confirmed that GS was associated with the size of the dominant hand[20] and forearm volume.[21,22] As we did for ASM, we adjusted GS for height, assuming that height could represent the sizes of the hand and forearm.[23,24] The resulting zGS values showed a linear relationship with frailty and that a 1-point increase in zGS score lowered the relative risk of a 1-point increase in frailty score by 21% in men and 11% in women. This risk reduction is greater than those reported in previous studies,[25,26] presumably due to the greater diagnostic clarity of GS owing to the additional adjustments for age and height.

Physical function impairment (weakness) evaluated by GS is the main definition of sarcopenia and frailty, and a well-known risk factor for mortality, morbidity, and disability in older individuals.[27] Although weakness was assessed with the timed up-and-go test in this study, not by GS, sarcopenia and frailty can be strongly linked to the concept of weakness. Furthermore, GS is considered as single marker of frailty in people of a similar age, more than chronological age alone[28] and proved to be valuable in predicting factors for frailty in older patients with hematologic malignancies.[29]

The causal mediation analysis using zASM and zGS and calculated via the described methods showed that muscle mass did not have a significant direct effect on frailty; however, the mediating effects of muscle strength in the relationship between muscle mass and frailty were statistically significant. Existing sarcopenia studies have assumed that outcomes were better with greater muscle mass and muscle strength. However, not many studies have investigated the outcomes of cases in which there was a large muscle mass, but the muscles were functionally impaired. This study showed, from a cross-sectional perspective, that only muscle mass associated with GS influenced frailty by a mediation effect, and muscle mass not related with GS cannot have an influence on frailty. These results could possibly be derived from the cross-sectional design. If a small amount of muscle mass is excessively worked to generate strength, the rate of strength reduction could be accelerated as the muscle mass shrinks with aging. Conversely, functionally impaired muscles that can protect against the reductions in strength associated with aging could lead to better outcomes longitudinally. Such a hypothesis could be addressed in a longitudinal study. Furthermore, considering that muscle changes caused by aging are not confined to reductions in muscle mass and that reductions in muscle mass are necessarily caused by aging,[30] diagnostic approaches to both muscle mass and muscle function would be needed in subsequent studies on sarcopenia.

Our study has some limitations. First, the equation for zASM in this study was derived from KNHANES survey data, which measured muscle mass via the dual energy x-ray absorptiometry method; however, the muscle mass of the actual study population was measured via the BIA method. Although BIA measurements can be influenced by body position or hydration status, the difference does not seem significant.[31,32] Additional research indicating the usefulness of dual energy x-ray absorptiometry and BIA to assess ASM is needed. Second, our new approach, which is zASM and zGS also do not accurately reflect arm and leg lengths. Although ASM is actually affected by the arm and leg lengths as mentioned earlier, we used height as a surrogated marker because surveys measuring the length of the limbs have not been adequately conducted. If the understanding of sarcopenia deepens, the need for more detailed and specific anthropometric measurements will emerge.

Despite this limitations, this study is meaningful in that it proposed a new approach to muscle mass and muscle strength and confirmed their associations with frailty.

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Conflict of interest

None declared by all authors.

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