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Original article

Nonalcoholic fatty liver disease and sarcopenia in a Western population (NHANES III): The importance of sarcopenia definition

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SUMMARY

Background: Recent epidemiological studies have shown that sarcopenia is associated with non-alcoholic fatty liver disease (NAFLD) and advanced fibrosis in an Asian population. We investigated whether NAFLD is associated with a higher risk of sarcopenia using a different definition in elderly patients.

Methods: A population-based cross-sectional survey of US patients was conducted, involving 2551 participants aged 60–75 years. NAFLD was measured by ultrasound. Sarcopenia was defined by both a low muscle mass and poor muscle function. In addition, the skeletal muscle index (SMI) was calculated as the absolute muscle mass (kilograms) divided by height^2 (meters) or total body mass (kilograms). A multivariable logistic regression was conducted to estimate the relationship between sarcopenia and NAFLD in the elderly.

Results: After adjusting for age, sex, and race/ethnicity, severe hepatic steatosis was associated with a decreased risk of sarcopenia as defined by the height-adjusted SMI (odds ratio (OR) 0.63; 95% confidence interval (CI) 0.46–0.87). In contrast, severe hepatic steatosis was associated with an increased risk of sarcopenia as defined by the weight-adjusted SMI (OR 1.73; 95% CI 1.31–2.28). These significant associations remained after further adjustments for other potential confounding variables.

Conclusions: NAFLD is associated with a lower risk of sarcopenia when using the height-adjusted SMI. In contrast, it showed the opposite result when using the weight-adjusted SMI. The definition of sarcopenia may be an important factor when examining its relationship with NAFLD.

1. Introduction

Sarcopenia is a geriatric syndrome [1] characterized by a progressive and generalized loss of skeletal mass and function with aging, and it is associated with adverse outcomes, such as falling [2], functional deterioration [3] and mortality [4,5]. Sarcopenia is also related to increased insulin resistance [6] and common inflammatory markers [7], including those that are defined as risk factors of non-alcoholic fatty liver disease (NAFLD) [8]. Recently, several studies have investigated the relationship between a low muscle mass and NAFLD in adults in Asian and Italian populations. In the Korean Sarcopenic Obesity Study [9], a low muscle mass was associated with an increased incidence of liver attenuation index-defined NAFLD in middle-aged participants. A limited number of studies investigating NAFLD via biopsies showed an association between a low muscle mass and nonalcoholic steatohepatitis (NASH) [10,11]. However, sarcopenia, which is defined as a low

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SMI, skeletal muscle index; CRP, C-reactive protein; NHANES III, National Health and Nutrition Examination Survey III; OR, odds ratio; BMI, body mass index; CI, confidence interval; BIA, bioimpedance analysis.

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muscle mass with weak muscle strength or low physical performance, is a more established and precise term than low muscle mass. Studies examining the relationship between NAFLD and sarcopenia, which is defined as the age-related loss of muscle mass and strength [12], in the elderly are scarce. In addition, controversy remains regarding whether height- or weight-adjusted skeletal muscle mass (SM/Ht^2 or SM/Wt) has a better predictive ability in defining sarcopenia [13]. More studies are needed to better validate the relationship between NAFLD and sarcopenia. To address these issues, we examined the impact of NAFLD on the risk of sarcopenia as defined by a low muscle mass and poor muscle function in the elderly using National Health and Nutrition Examination Survey III (NHANES III) data.

2. Materials and methods

2.1. Study population

The current study used data from the NHANES III, which was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) in the United States. We initially included 14,797 participants ≥20 years of age who were ethnically non-Hispanic black, non-Hispanic white, Mexican–American or other. We then excluded participants lacking data regarding hepatic steatosis, bioimpedance analysis (BIA), or gait speed data and those who reported excessive alcohol consumption (>14 drinks per week for women and average >21 drinks per week for men), iron overload (transferrin saturation >50%), positive hepatitis B surface antigen, and positive hepatitis C antibodies; in total, 2551 participants (1240 men and 1311 women) were included in the statistical analyses. The NHANES survey was approved by the Institutional Review Board at the National Center for Health Statistics. All participants provided written informed consent prior to completing any study-related activities. The analysis reported in this article was considered exempt from our local institutional review board.

2.2. Definition of sarcopenia

The BIA was measured using a bio-resistance body composition analyzer (Valhalla Medical, San Diego, CA, USA). The whole-body BIA was measured between the right wrist and ankle with the participants in a supine position. All participants completed this exam after fasting for a minimum of 6 h. We used the following validated equation derived by Janssen et al. [14] to assess the muscle mass in each participant: skeletal muscle mass (kilograms) = [(height^2/BIA resistance × 0.401) + (gender × 3.825) + (age × −0.071)] + 5.102, where height is recorded in centimeters, BIA resistance is recorded in ohms, gender is coded as 1 for men and 0 for women, and age is recorded in years. The skeletal muscle index (SMI) was calculated as the absolute muscle mass (kilograms) divided by height^2 (meters) or total body mass (kilograms). The cutoff values for low muscle mass were defined by the height-adjusted SMI (<10.76 kg/m^2 for men and <6.75 kg/m^2 for women) [15]. In addition, the cutoff values for low muscle mass were defined by the weight-adjusted SMI (<37.0% for men and <28% for women) [16]. Participants with both a low muscle mass and slow gait speed (≤0.8 m/s) were diagnosed with sarcopenia.

2.3. Definition of NAFLD

Hepatic steatosis was examined by ultrasound. Using previously recorded hepatobiliary ultrasound videos obtained as a part of the NHANES III, an images assessment was performed between 2009 and 2010 to classified the presence of fat in the hepatic parenchyma. Data concerning the presence of liver-to-kidney contrast, brightness of liver parenchymal, brightness of the intrahepatic vessels wall, deep beam attenuation, and the definition of the gallbladder walls was evaluated. Quality assurance and quality control process were performed by NCHS to standardize the readings from 3 ultrasound readers, who were educated, observed, and confirmed by a skilled radiologist. Furthermore, NHANES III study set up a robust algorithm based on the publication by Hamaguchi et al. [17] The hepatic parenchyma was graded as none, mild, moderate, or severe hepatic steatosis.

2.4. Other variables

Other variables that could confound the association between sarcopenia and NAFLD were included in the analysis. All participants completed an interview to obtain information regarding their age, sex, race/ethnicity (including non-Hispanic white, non-Hispanic black, Mexican–American, and other). Participants who self-reported that they had smoked at least 100+ cigarettes during their lifetime were classified as smokers. Engaging in physical activities between 3 and 6 metabolic equivalents (METs) for ≥5 times/week or engaging in physical activities with above 6 METs for 3 times/week was classified as ideal. Engaging in no physically activity was classified as poor. A degree of activity between ideal physical activity and no physical activity was considered as intermediate physical activity. Standardized measurements of height, weight, and waist circumference were acquired. The level of C-reactive protein (CRP) was analyzed using a latex-enhanced Nephelometry Analyzer System. Serum uric acid and total cholesterol levels were measured by chemical analyses (Hitachi Model 737 Multichannel Analyzer; Boehringer-Mannheim Diagnostics, Indianapolis, IN, USA). Serum vitamin D was assayed using a radioimmunoassay method (DiaSorin Inc, Stillwater, MN). Glycated hemoglobin was assayed using an ion-exchange high-performance liquid chromatography method (the Diamat Analyzer System). Details regarding these laboratory procedures have been previously published [18].

2.5. Statistical analysis

We grouped participants on the basis of their degree of hepatic steatosis. Categorical variables corresponding to the baseline characteristics were compared using chi-square tests, the mean values of continuous variables with a normal distribution were compared using ANOVA tests and the mean values of continuous variables without a normal distribution were compared using Kruskal–Wallis tests. Low muscle mass was stratified based on either the height-adjusted SMI or weight-adjusted SMI. The relationship between sarcopenia and the hepatic steatosis severity was assessed using a multivariable logistic regression. Multiple models adjusted for potential confounding factors in progressive degrees were constructed as follows: Model 1 was adjusted for age, sex, and race/ethnicity; Model 2 was further adjusted for serum cholesterol, serum vitamin D, serum HbA1c, serum CRP, and serum uric acid; and Model 3 was additionally adjusted for smoking status and physical activity. The results are reported as odds ratios (ORs) with 95% confidence intervals (CI). In addition, subgroup analyses of SMI and gait speed were performed. The multivariable models were adjusted for covariates using the same method as that used in the sarcopenia analysis. For all analyses, a p-value <0.05 was considered statistically significant. All logistic regression models were confirmed for the goodness of fit using the Hosmer–Lemeshow goodness-of-fit test, and there was no evidence of a lack of fit ($p > 0.05$). All statistical analyses were performed using SPSS (Version 18.0 for Windows, SPSS, Inc., Chicago, IL, USA). All data are

unweighted to provide a description of the study cohort rather than nationally generalizable estimates.

3. Results

The baseline demographics and characteristics of the 2551 participants included in the analysis (Fig. 1) were stratified according to the degrees of hepatic steatosis, and the results are presented in Table 1. The mean age of the participants was 66.71 years, and 48.6% of the participants were men. Higher degrees of hepatic steatosis were associated with increased levels of glycated hemoglobin and serum uric acid and lower levels of serum vitamin D and physical activity (Table 1). Participates were also separated into four categories based on body mass index (BMI): underweight (BMI <18.5 kg/m^2), normal weight (BMI ≥18.5–24.9 kg/m^2), overweight (BMI ≥25.0–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Severe hepatic steatosis status increased significantly by increased BMI (Supplemental Table S1). In addition, the weight-adjusted SMI was lower in the high-BMI group.

According to the height-adjusted SMI and gait speeds of the 2551 participants, 1792 (70.2%) participants were normal, and 759 (29.8%) participants had sarcopenia. In contrast, according to the weight-adjusted SMI and gait speeds, 1566 (61.4%) participants were normal, and 985 (38.6%) participants had sarcopenia. The distribution of sarcopenia diagnosis defining SMI by SM/Ht^2 or SM/Wt is shown in Fig. 2. With respect of the height-adjusted and weight-adjusted SMI, 468 participants had the same diagnosis of sarcopenia. The BMIs of the participants with sarcopenia (as assessed using the height-adjusted SMI) were lower than those of the participants in the normal group. In contrast, the BMIs of the participants with sarcopenia (as assessed using the weight-adjusted SMI) were higher than those of the participants in the normal group (Table 2). In addition, the association of sarcopenia (in %) over SMI based on height and body mass are shown in Supplemental Figs. S1–4.

The age-, sex-, and race/ethnicity-adjusted ORs (95% CI) for incident sarcopenia (using the height-adjusted SMI) comparing participants with mild, moderate, and severe hepatic steatosis to those without hepatic steatosis were 0.94 (95% CI 0.72–1.23), 0.73 (95% CI 0.57–0.93), and 0.63 (95% CI 0.46–0.87), respectively. These associations persisted after further adjusting for serum cholesterol, serum vitamin D, serum HbA1c, serum CRP, serum uric acid, smoking status, and physical activity (OR 0.92, 95% CI 0.70–1.21; OR 0.72, 95% CI 0.56–0.92; OR 0.64, and 95% CI 0.46–0.90, respectively). In contrast, in the age-, sex-, and race/ethnicity–adjusted model, the OR (95% CI) for incident sarcopenia (using the weight-adjusted SMI) was 1.73 (95% CI 1.31–2.28) in the severe hepatic steatosis group. After adjusting for potential confounding factors (including serum cholesterol, serum vitamin D, serum HbA1c, serum CRP, serum uric acid, smoking status, and physical activity), the OR remained statistically significant at 1.52 (95% CI 1.14–2.04) in the severe hepatic steatosis group (Table 3).

To assess the reliability of the effect of NAFLD on sarcopenia, we performed subgroup analyses of SMI and gait speed. After adjusting for demographic and metabolic-related characteristics, the ORs in the severe hepatic steatosis group were 0.44 (95% CI 0.32–0.61) for sarcopenia using the height-adjusted SMI and 2.30 (95% CI 1.66–3.17) using the weight-adjusted SMI. The association between NAFLD and a slow gait speed was not statistically significant (Table 4).

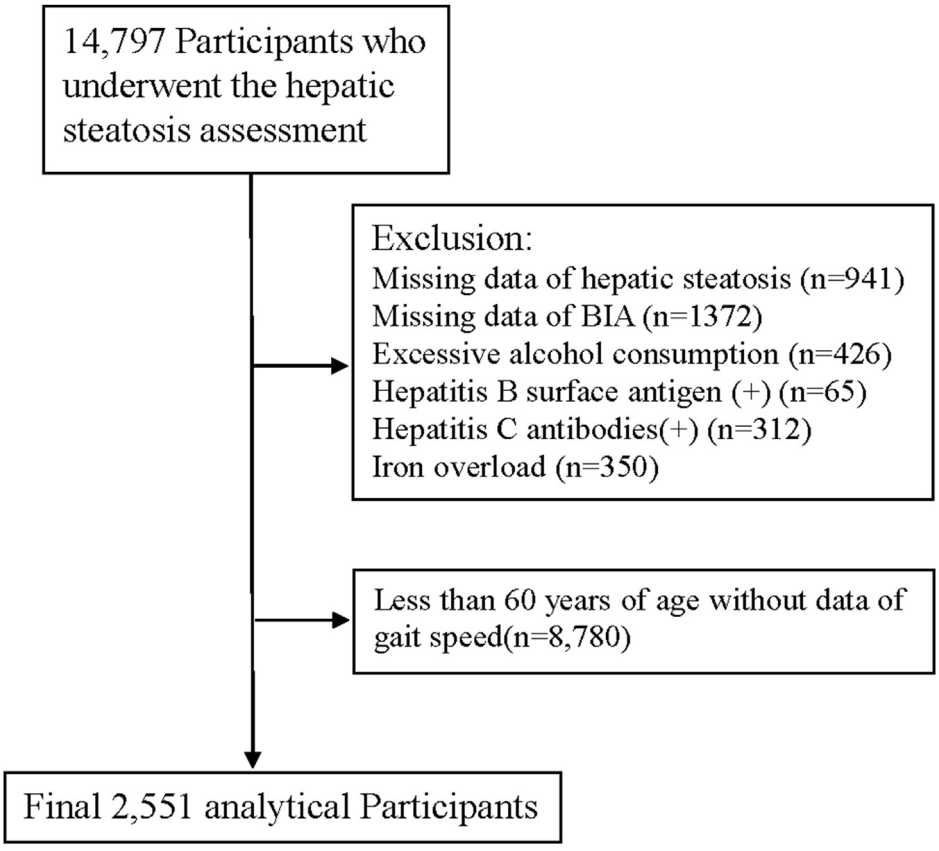

Fig. 1. Study participants flow chart.

Table 1
Baseline characteristics and demographic data according to hepatic steatosis status.

	Hepatic steatosis status				
	Normal (n = 1469)	Mild (n = 342)	Moderate (n = 480)	Severe (n = 260)	p
Age (years)	66.74 ± 4.34	66.64 ± 4.16	66.63 ± 4.31	66.75 ± 4.26	0.945
Male, N (%)	690(46.7)	187(54.4)	241(49.8)	129(49.4)	0.068
Race-ethnicity,N (%)					<0.001
Non-Hispanic white	737(50.2)	149(43.6)	241(50.2)	123(47.3)	
Non-Hispanic black	384(26.1)	72(21.1)	75(15.6)	58(22.3)	
Mexican American	299(20.4)	108(31.6)	152(31.7)	75(28.8)	
Other	49(3.3)	13(3.8)	12(2.5)	4(1.5)	
Serum cholesterol (mg/dL)	225.92 ± 43.05	222.31 ± 45.21	225.20 ± 42.42	222.12 ± 42.84	0.384
Serum vitamin D (ng/mL)	26.95 ± 10.76	26.31 ± 12.74	25.43 ± 10.03	25.24 ± 9.46	0.015
Glycated hemoglobin (%)	5.85 ± 1.21	6.1 ± 1.37	6.17 ± 1.43	6.40 ± 1.54	<0.001
Serum C-reactive protein (mg/dL)	0.53 ± 1.03	0.70 ± 1.34	0.59 ± 0.89	0.56 ± 0.79	<0.001
Serum uric acid (mg/dL)	5.43 ± 1.45	5.73 ± 1.55	5.84 ± 1.51	6.02 ± 1.47	<0.001
Alanine aminotransferase(U/L)	13.58 ± 9.15	15.48 ± 8.46	16.58 ± 8.16	19.59 ± 12.41	<0.001
Smoking status, N (%)					0.691
Non-smoker	833(56.7)	205(59.9)	277(57.7)	145(55.8)	
Smoker	636(43.3)	137(40.1)	203(42.3)	115(44.2)	
Physically active, N (%)					0.001
Ideal	520(35.4)	110(32.2)	140(29.7)	70(26.9)	
Intermediate	652(44.4)	137(40.1)	207(43.1)	122(46.9)	
Poor	297(20.2)	95(27.8)	133(27.7)	68(26.2)	
Gait speed (m/s)	0.76 ± 0.21	0.73 ± 0.21	0.74 ± 0.22	0.74 ± 0.20	0.010
Muscle mass (kg)					
Male	28.96 ± 3.95	29.97 ± 4.52	30.09 ± 4.17	30.42 ± 4.40	<0.001
Female	17.83 ± 2.96	18.54 ± 3.20	19.06 ± 3.11	19.05 ± 3.22	<0.001
Height-adjust SMI (kg/m^2)					
Male	9.74 ± 1.13	10.15 ± 1.33	10.13 ± 1.20	10.46 ± 1.31	<0.001
Female	7.03 ± 1.05	7.47 ± 1.12	7.64 ± 1.09	7.52 ± 1.14	<0.001
Weight-adjust SMI (%)					
Male	37.85 ± 4.38	36.50 ± 4.23	35.74 ± 4.58	36.15 ± 3.76	<0.001
Female	26.95 ± 3.72	25.44 ± 3.63	25.15 ± 3.24	24.97 ± 3.19	<0.001

Data are presented as the mean ± standard deviation or N (percentage).
p Values represent comparisons among the 4 groups using a chi-squared, ANOVA, or Kruskal–Wallis test according to the type of variable.
SMI: skeletal muscle index.
Note: Baseline characteristics and demographic data according to body mass index were listed in the Supplementary Table S1.

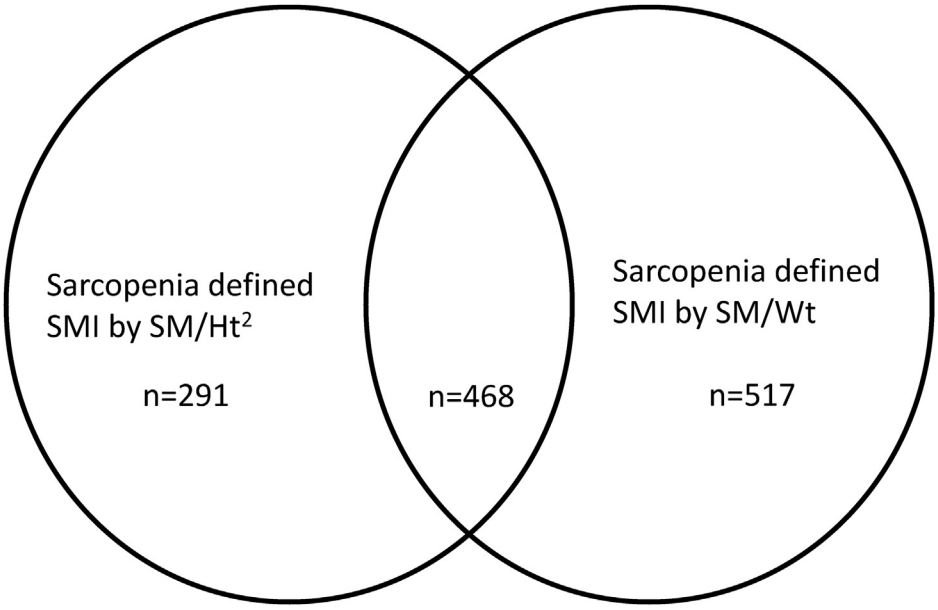

Fig. 2. The distribution of the sarcopenia defined SMI by SM/Ht^2 or SM/Wt.

Table 2
Characteristics based on different definition of sarcopenia.

	Sarcopenia defined SMI by SM/Ht^2			Sarcopenia defined SMI by SM/Wt		
	Normal (n = 1792)	Sarcopenia (n = 759)	p	Normal (n = 1566)	Sarcopenia (n = 985)	p
Age (years)	66.41 ± 4.25	67.42 ± 4.35	<0.001	66.45 ± 4.25	67.13 ± 4.35	<0.001
Male, N (%)	730(40.7)	510(67.2)	<0.001	884(56.4)	356(36.1)	<0.001
Body mass index (kg/m^2)	28.62 ± 5.35	25.42 ± 4.02	<0.001	26.07 ± 4.37	30.21 ± 5.41	<0.001
Waist (cm)	99.60 ± 12.98	95.24 ± 11.90	<0.001	94.84 ± 11.99	103.8 ± 12.17	<0.001
Serum cholesterol (mg/dL)	226.69 ± 44.29	220.70 ± 40.27	0.002	223.58 ± 44.39	227.03 ± 41.18	0.050
Serum vitamin D (ng/mL)	26.23 ± 10.95	26.8 ± 10.49	0.236	27.39 ± 10.72	24.82 ± 10.78	<0.001
Glycated hemoglobin (%)	6.01 ± 1.30	5.97 ± 1.37	0.514	5.92 ± 1.28	6.12 ± 1.39	<0.001
Serum C-reactive protein (mg/dL)	0.54 ± 0.93	0.65 ± 1.24	0.019	0.51 ± 1.00	0.67 ± 1.07	<0.001
Serum uric acid (mg/dL)	5.57 ± 1.47	5.71 ± 1.54	0.033	5.52 ± 1.46	5.76 ± 1.54	<0.001
Physically active, N (%)			<0.001			<0.001
Ideal	568(36.3)	272(27.6)		609(34)	231(30.4)	
Intermediate	723(46.2)	395(40.1)		807(45)	311(41)	
Poor	275(17.6)	318(32.3)		376(21)	217(28.6)	

Data are presented as the mean ± standard deviation or N (percentage).
p Values represent comparisons among the 2 groups using a chi-squared, t-test according to the type of variable.

Table 3
Odds ratio (95% CI) for sarcopenia according to hepatic steatosis status.

	Hepatic steatosis status							
	Normal	Mild	p	Moderate	p	Severe	p	p for trend
Sarcopenia defined SMI by SM/Ht^2								
Unadjusted	1	1.05(0.82–1.36)	0.664	0.79(0.62–0.99)	0.047	0.68(0.50–0.93)	0.017	0.006
Model 1	1	0.94(0.72–1.23)	0.676	0.73(0.57–0.93)	0.012	0.63(0.46–0.87)	0.005	0.001
Model 2	1	0.95(0.72–1.24)	0.732	0.74(0.58–0.95)	0.022	0.67(0.48–0.93)	0.018	0.003
Model 3	1	0.92(0.70–1.21)	0.550	0.72(0.56–0.92)	0.010	0.64(0.46–0.90)	0.009	0.001
Sarcopenia defined SMI by SM/Wt								
Unadjusted	1	1.44(1.13–1.83)	0.003	1.94(1.57–2.39)	<0.001	1.67(1.27–2.18)	<0.001	<0.001
Model 1	1	1.51(1.18–1.95)	0.001	2.05(1.65–2.55)	<0.001	1.73(1.31–2.28)	<0.001	<0.001
Model 2	1	1.47(1.13–1.90)	0.003	1.93(1.54–2.42)	<0.001	1.55(1.16–2.07)	0.003	<0.001
Model 3	1	1.43(1.11–1.86)	0.006	1.88(1.50–2.37)	<0.001	1.52(1.14–2.04)	0.004	<0.001

CI: confidence interval.
Model 1: adjusted for age, gender, and race/ethnicity.
Model 2: adjusted for age, gender, race/ethnicity, serum cholesterol, serum vitamin D, serum HbA1c, serum C-reactive protein, and serum uric acid.
Model 3: adjusted for age, gender, race/ethnicity, serum cholesterol, serum vitamin D, serum HbA1c, serum C-reactive protein, serum uric acid, physical activity, and smoking status.
Note: Odds ratio (95% CI) for sarcopenia defined SMI by SM/BMI according to hepatic steatosis status were listed in the Supplementary Table S2. Odds ratio (95% CI) for sarcopenia defined by absolute muscle mass according to hepatic steatosis status were also listed in the Supplementary Table S2.

Table 4
Odds ratio (95% CI) for low SMI and slow gait speed according to hepatic steatosis status.

	Hepatic steatosis status							
	Normal	Mild	p	Moderate	p	Severe	p	p for trend
Height-adjust SMI								
Unadjusted	1	0.74(0.58–0.93)	0.011	0.58(0.47–0.71)	<0.001	0.49(0.37–0.64)	<0.001	<0.001
Model 1	1	0.59(0.45–0.77)	<0.001	0.48(0.38–0.60)	<0.001	0.39(0.29–0.52)	<0.001	<0.001
Model 2	1	0.65(0.49–0.85)	0.002	0.53(0.42–0.68)	<0.001	0.45(0.33–0.62)	<0.001	<0.001
Model 3	1	0.63(0.48–0.83)	0.001	0.52(0.41–0.67)	<0.001	0.44(0.32–0.61)	<0.001	<0.001
Weight-adjust SMI								
Unadjusted	1	1.33(1.05–1.69)	0.021	2.15(1.71–2.69)	<0.001	2.33(1.73–3.14)	<0.001	<0.001
Model 1	1	1.47(1.14–1.88)	0.003	2.32(1.84–2.93)	<0.001	2.51(1.85–3.40)	<0.001	<0.001
Model 2	1	1.43(1.10–1.85)	0.007	2.24(1.76–2.86)	<0.001	2.33(1.69–3.21)	<0.001	<0.001
Model 3	1	1.41(1.09–1.83)	0.009	2.22(1.74–2.83)	<0.001	2.30(1.67–3.17)	<0.001	<0.001
Slow gait speed								
Unadjusted	1	1.29(1.01–1.65)	0.039	1.32(1.07–1.64)	0.01	1.15(0.88–1.50)	0.316	0.021
Model 1	1	1.26(0.98–1.61)	0.071	1.32(1.06–1.64)	0.013	1.12(0.85–1.48)	0.408	0.037
Model 2	1	1.07(0.82–1.39)	0.619	1.09(0.86–1.38)	0.475	0.88(0.66–1.19)	0.406	0.430
Model 3	1	1.12(0.86–1.45)	0.404	1.17(0.92–1.47)	0.197	0.94(0.70–1.25)	0.654	0.659

CI: confidence interval, SMI: skeletal muscle index.
Model 1: adjusted for age, gender, and race-ethnicity.
Model 2: adjusted for age, gender, race-ethnicity, serum cholesterol, serum vitamin D, serum HbA1c, serum C-reactive protein, and serum uric acid.
Model 3: adjusted for age, gender, race-ethnicity, serum cholesterol, serum vitamin D, serum HbA1c, serum C-reactive protein, serum uric acid, physical activity, and smoking status.

4. Discussion

To the best of our knowledge, this is the first study to consider low physical performance, an important component of the definition of sarcopenia, in addition to a low muscle mass to evaluate the association between NAFLD and sarcopenia in an elderly population. In addition, this is the first study to simultaneously consider low muscle mass as defined by both SM/Ht^2 and SM/Wt when exploring its association with NAFLD.

Previous literature shows that individuals with a low muscle mass have a higher risk of NAFLD [9–11]. Our findings on the association between sarcopenia and NAFLD are consistent with those reported in studies of Asian [9,10] and Western [11] populations that defined sarcopenia using an SM/Wt-derived cutoff point. Hong et al. [9] found a strong association between low muscle mass and NAFLD in middle-aged participants in the Korean Sarcopenic Obesity Study. Koo et al. [10] and Petta et al. [11] found an association between low muscle mass and NASH using biopsies. Nevertheless, these studies defined sarcopenia as low muscle mass without including a functional assessment. Physical function is important in understanding the relationship between NAFLD and sarcopenia. We expanded on the previous studies by finding an association between sarcopenia and NAFLD when sarcopenia was defined by both low muscle mass (SM/Wt) and decreased physical performance. In general, decreased gait speed has been associated with greater risk of disability [19] and mortality [20]. However, there are no previous investigation specifically focusing on the association between NAFLD and decreased gait speed. In a previous study, the level of alanine transferase, which is a major marker of NAFLD, was not associated with gait speed [21]. In our study, subgroup analyses of decreased gait speed also revealed an apparent lack of association with NAFLD. Thus, any potential role of NAFLD on gait speed is still unclear. Our findings need to be confirmed with further studies.

Participants with NAFLD were at a significantly higher risk of having sarcopenia, as defined by the weight-adjusted SMI, than participants without NAFLD. However, the opposite result was found when sarcopenia was defined by the height-adjusted SMI. These associations persisted even after further adjustments for traditional sarcopenia risk factors and metabolic factors. Our study directly compared NAFLD between groups identified as having sarcopenia using SM/Wt and SM/Ht^2 acquired from BIA-measured skeletal muscle mass. These observations suggest that the definition of sarcopenia may explain the conflicting results regarding the relationship between sarcopenia and NAFLD. The discrepancy between these results raises the question of how to define sarcopenia, and a universal index for identifying sarcopenia remains controversial. Most of the current sarcopenia studies in EWGSOP [22], SCWD [23], IWGS [24] and AWGS [25] use an SM/Ht^2-defined low muscle mass cutoff point to diagnose and assess sarcopenia. In previous studies assessing muscular function [26] and death [5] as outcomes of sarcopenia, SM/Ht^2 has been more universally used. However, when studying metabolic diseases, such as NAFLD, diabetes and metabolic syndrome [27], as the outcomes of sarcopenia, SM/Wt is more commonly used and is shown to be a better predictor than SM/Ht^2. The heterogeneous methods used to assess muscle mass may affect the prevalence of sarcopenia [28]. In our study, the different methods not only influenced the prevalence of sarcopenia but also the outcomes of sarcopenia. Further studies exploring the outcomes of sarcopenia must consider these differences.

One potential explanation for the discrepancies found across studies may be characteristic discrepancies in the groups of individuals with sarcopenia. In our study, the sarcopenia group defined by SM/Wt had higher BMIs and waist circumferences. Studies in Taiwan [29] and Korea [27,30] that compared height- and weight-adjusted sarcopenia also found that BMIs were lower in the height-adjusted sarcopenia group than in the height-adjusted non-sarcopenia group. In contrast, the BMIs were higher in the weight-adjusted sarcopenia group than in the weight-adjusted non-sarcopenia group. Previous studies exploring the association between NAFLD and sarcopenia also found higher BMIs in the SM/Wt defined sarcopenia group [9,10]. Therefore, when muscle mass is adjusted by weight, more subjects identified as having sarcopenia will be overweight or obese. An individual with a high BMI in a weight-adjusted sarcopenia group with a low relative muscle mass may have a high relative fat mass, and the latter may be the root cause of NAFLD. When using SM/Wt for SMI, the SMI may decline when the body weight increases due to the increase in fat mass, regardless of an unchanged or decreased muscle mass. Therefore, an increased fat mass but unchanged or decreased muscle mass may explain the difference in the results found when comparing analyses using SM/Ht^2 and SM/Wt, as the denominator of SM/Wt is greatly influenced by the fat mass. Adjustment for muscle mass is crucial for accurately assessing low muscle mass. Although previous studies [9–11] have raised possible hypotheses to support the association of severe hepatic steatosis with an increased risk sarcopenia, in a recent prospective population-based study (InCHIANTI study), Vespasiani-Gentilucci et al. [31] found that low ALT levels, as a surrogate marker of less NAFLD, in older individuals were related to sarcopenia and was a predictor of adverse outcomes. We also found that low ALT levels are related to sarcopenia defined SMI by SM/Ht^2 in our result, which is the same as the finding reported by Umberto et al. This result supports our finding that NAFLD is associated with a lower risk of sarcopenia when using the height-adjusted SMI.

In addition, we also used the different parameter, BMI-adjusted SMI and absolute muscle mass (not corrected for body size), to further explore the relationship between NAFLD and sarcopenia (Supplemental Table S2). Participants with NAFLD were at a significantly higher risk of having sarcopenia, as defined by the BMI-adjusted SMI, than participants without NAFLD. BMI is the most common method used to diagnose overweight and obesity in clinical practice. In other words, BMI can be considered as one similar parameter of weight. Therefore, the association between BMI-adjusted SMI and NAFLD was the same as the association between weight-adjusted SMI and NAFLD. However, because the cutoff values for BMI-adjusted SMI and absolute muscle mass (not corrected for body size) in these analysis are arbitrary, we should interpret these result carefully.

Several limitations need to be considered when interpreting our findings. First, NHANES uses a cross-sectional design; thus, there are concerns regarding both reverse causation and residual confounding. Prospective studies are needed to determine whether NAFLD is longitudinally associated with sarcopenia. Second, the use of ultrasound is not as definite for the diagnosis of fatty liver as histology and cannot distinguish NAFLD from NASH. However, ultrasound is suitable for large population-based studies when acquiring liver biopsies from participants is not feasible. Third, the pathogenic processes underlying the relationship between NAFLD and sarcopenia could not be determined. Any current hypothesis will require further exploration. Fourth, no ideal diagnostic tool is available to accurately measure muscle mass. Thus, although we determined muscle mass using BIA methods adjusted for body size by height or weight, which are widely used in the literature, our results should be confirmed using other definitions. Despite these limitations, the large sample size and standardized procedures of the NHANES III survey add to the strengths and novelty of our findings.

In conclusion, our findings have potential clinical significance because the different operational methods used to calculate SMI

could substantially influence study results, particularly in relation to NAFLD. Strategies to assess the real effect of NAFLD on sarcopenia require further research.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Authors contributions

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All authors read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.11.021.

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