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(Osteo)sarcopenia & sarcopenic obesity, volume II

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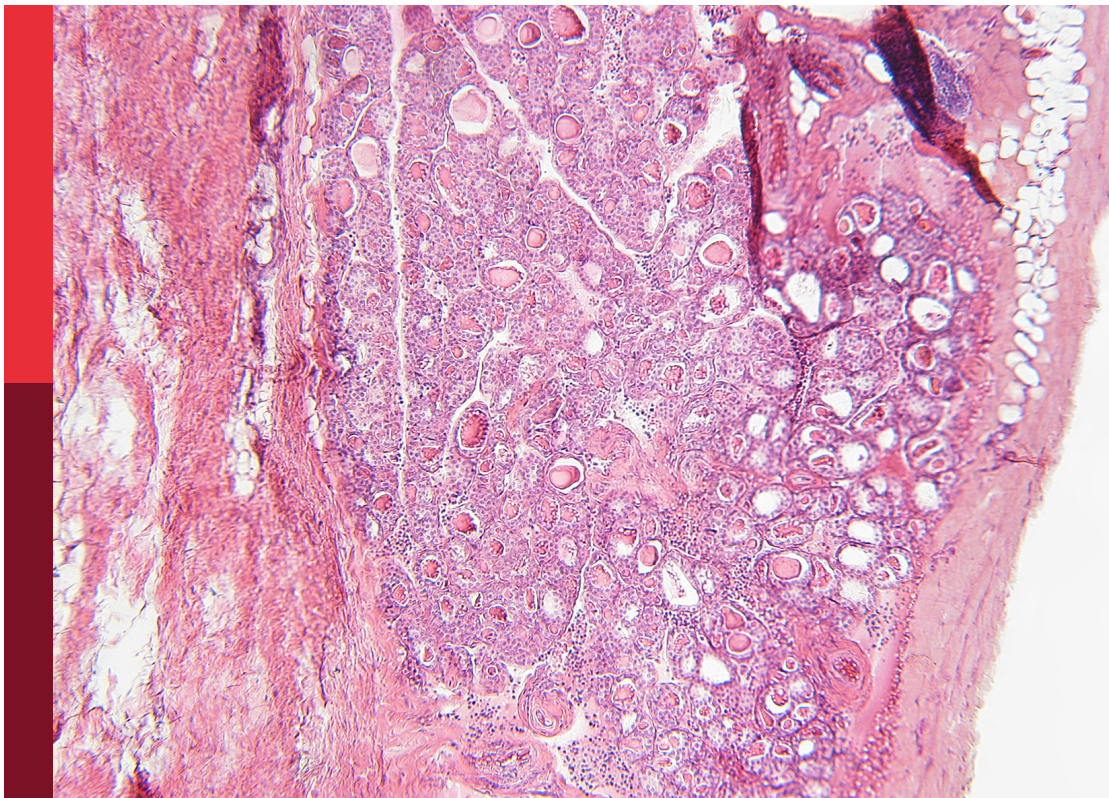

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(Osteo)sarcopenia & sarcopenic obesity, volume II

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Editorial: (Osteo)sarcopenia & sarcopenic obesity, volume II

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sarcopenia, sarcopenic obesity, exercise, diagnosis, osteoporosis

Editorial on the Research Topic
(Osteo)sarcopenia & sarcopenic obesity, volume II

Sarcopenia is characterized by the presence of low muscle mass, loss of muscle strength and compromised function and is recognized today as a characteristic of progressing age as well as an accompanying characteristic of many disease states (1–3). Sarcopenia is recognized today as a major determinant of poor health related to various comorbidities and its relationship with mortality is actively investigated (4–6). Our Research Topic aimed to identify various comorbidities related to sarcopenia and to identify the effect of exercise on sarcopenia. Sarcopenia may accompany obesity in the concept of sarcopenic obesity, a state characterized by many comorbidities and compromised quality of life (7, 8). Liu et al. investigated the role of obesity in sarcopenia and the optimal body composition to prevent against sarcopenia and obesity. They found a positive relationship between skeletal muscle mass and absolute fat mass but negative association with appendicular fat mass. Obesity was found to be a risk factor for sarcopenia.

Sarcopenia may accompany osteoporosis, may lead to falls and this combination may increase mortality (9, 10). In a study performed in China involving 9,006 individuals with a follow-up of over 7 years it was shown that sarcopenia is accompanied by an increased mortality risk Xiong et al. In particular, the odds ratio of sarcopenia for 7-year mortality was 1.41, whereas for severe sarcopenia the odds ratio was even greater. The study underlined the significant association of sarcopenia with mortality and stressed that low-hand grip and usual walking speed are significant indicators of mortality risk at least within the Chinese population. In a study performed in Italy Maccarone et al. investigated the prevalence of sarcopenia in a cohort of elderly patients, aged over 65, who were cared for in a rehabilitation center and had musculoskeletal complains. They found a high percentage of patients with overt sarcopenia and approximately 10% with severe sarcopenia. Patients with severe sarcopenia had lower body mass index (BMI) and in the assessment of nutritional status they rated low. Liu et al. examined the effect of sarcopenia, osteoporosis and osteosarcopenia on spine fractures in American adults with prediabetes by using data from the NHANES study 2009 to 2018. People with prediabetes were more likely to develop

sarcopenia than normal glucose tolerance subjects, while there was no significant increase of osteoporosis in prediabetes. Skeletal muscle mass was independently associated with osteoporosis in prediabetes adults. Sarcopenia and osteoporosis were positively associated with spine fracture in prediabetes.

In a study performed in West China, Xiang et al. explored the prevalence of sarcopenia, its association with osteoporosis and its effect on survival in patients on hemodialysis. In a group of 209 adult patients undergoing hemodialysis sarcopenia was diagnosed in 37.3%. Age, female sex, diabetes, serum magnesium and BMI were found to be independently associated with sarcopenia. The prevalence of osteosarcopenia was 22.3% and it was independently associated with all-cause mortality. They found that patients undergoing hemodialysis had a high incidence of sarcopenia and osteosarcopenia, the latter having a powerful association with mortality. Gong et al. investigated the relationship between lean body mass and cognitive function in old adults. They used data from the National Health and Nutrition Examination Survey (NHANES) 2011-2014. Their findings showed an association between predicted lean body mass and cognitive dysfunction in information processing speed.

Liu et al. investigated the relationship between COVID-19 and sarcopenia in a bidirectional Mendelian randomization analysis. Evidence suggested that COVID-19 patients were prone to skeletal muscle loss while sarcopenia may be associated with susceptibility, hospitalization, and severity of COVID-19. Using genetic data, the study explored the causal relationship between COVID-19 and sarcopenia related traits, but the results indicated that there was no such causal relationship. In an effort to identify the relationship between non-alcoholic fatty liver disease and sarcopenia Xu et al aimed to identify co-expressed genes in non-alcoholic fatty liver disease and sarcopenia. They conducted a complete transcription pattern mapping to identify core genes underlying biological mechanisms which regulate aging in non-alcoholic liver disease and sarcopenia patients.

Rosas-Carrasco et al. developed and validated a short new scale for the screening of sarcopenia, which they named Sarcopenia Geriatric Scale (SARCO-GS). The short scale was developed to be affordable, easy and accessible at all types of clinical settings and was found to be sensitive and to adequately predict functional dependence. The scale includes 7 items, five subjective questions and two measurements of strength and muscle mass. After validation, the scale, which was developed in Mexico, was adapted to English. Khalafi et al. performed a systematic review and meta-analysis of the effect of exercise training on body composition outcomes in postmenopausal women. They searched the main databases of medical literature, PubMed, Web of Science, CINAHL and Medline for randomized controlled trials on the effect of exercise training in postmenopausal women. The results showed that exercise training increased muscle mass and volume, muscle fat free mass and body and visceral fat and waist circumference. The results of the meta-analysis indicated that exercise training may improve body composition in postmenopausal women and that the combination of aerobic and resistance training may be an effective strategy for the improvement of body composition in the postmenopausal period.

Within our Research Topic we investigated further the relationship of sarcopenia with obesity, osteoporosis and spinal fractures and confirmed the positive relationship between sarcopenia, obesity, osteoporosis and spinal fractures. The relationship of sarcopenia with cognitive dysfunction was investigated and a positive correlation between sarcopenia and cognitive dysfunction was observed. A short new scale which aimed to be accessible at all clinical settings was developed for the screening of sarcopenia. The findings from the manuscripts included in the Research Topic underline the importance of various comorbidities associated with sarcopenia and the importance of exercise in its management. We feel the need to extend our gratitude to all the participants and contributors to the research projects and the papers included in this Research Topic and we are hopeful that the information presented will aid to the advancement of clinical practice and inspire further innovations in the future.

Author contributions

IK-A: Investigation, Writing – original draft, Writing – review & editing. LA: Conceptualization, Writing – original draft, Writing – review & editing. PA: Investigation, Software, Writing – original draft. SM: Supervision, Validation, Writing – review & editing. YD: Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The role of obesity in sarcopenia and the optimal body composition to prevent against sarcopenia and obesity

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Background: Elderly people with low lean and high fat mass, are diagnosed with sarcopenic obesity (SO), and often have poor clinical outcomes. This study aimed to explore the relationship between obesity and sarcopenia, and the optimal proportion of fat and muscle for old individuals.

Methods: Participants aged 60 years or above were instructed to perform bioelectrical impedance analysis to obtain the muscle and fat indicators, and handgrip strength was also performed. Sarcopenia was diagnosed according to predicted appendicular skeletal muscle mass and function. Body mass index (BMI) and body fat percentage (BF%) were used to define obesity. The association of muscle and fat indicators were analyzed by Pearson's correlation coefficient. Pearson Chi-Square test was utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) on the risk of sarcopenia according to obesity status.

Results: 1637 old subjects (74.8 $\pm$ 7.8 years) participated in this study. Not only fat mass, but also muscle indicators were positively correlated to BMI and body weight ($p < 0.05$). Absolute muscle and fat mass in different positions had positive associations ($p < 0.05$). Muscle mass and strength were negatively related to appendicular fat mass percentage ($p < 0.05$). When defined by BMI (OR = 0.69, 95% CI [0.56, 0.86]; p = 0.001), obesity was a protective factor for sarcopenia, whilst it was a risk factor when using BF% (OR = 1.38, 95% CI [1.13, 1.69]; p = 0.002) as the definition. The risk of sarcopenia reduced with the increase of BMI in both genders. It was increased with raised BF% in males but displayed a U-shaped curve for females. BF% 26.0–34.6% in old females and lower than 23.9% in old males are recommended for sarcopenia and obesity prevention.

Conclusion: Skeletal muscle mass had strong positive relationship with absolute fat mass but negative associations with the percentage of appendicular fat mass. Obesity was a risk factor of sarcopenia when defined by BF% instead of BMI. The management of BF% can accurately help elderly people prevent against both sarcopenia and obesity.

KEYWORDS

muscle, fat, sarcopenic obesity, aging, body mass index, body fat percentage

1 Introduction

The aging population has been an important challenge in public health and is posing a huge socioeconomic burden (1). A recent cohort study indicated that increased body mass index (BMI) was associated with lower all-cause and non-cardiovascular disease mortality in Chinese old people (2). This observation supports the "obesity paradox" again. However, gaining BMI can also have undesirable metabolic risks including excess adiposity accumulation, which leads to cardiovascular diseases and diabetes mellitus (3). Body composition analyses have also reported that excess body fat increases all-cause and disease-cause mortality, and people with low lean mass have been found to have higher death rates (4, 5). Therefore, the management of an optimal body composition for old people is important. It is well known that BMI only considers body mass rather than body composition, which may not be appropriate for old individuals (2), and understanding the optimal body composition to balance fat and lean mass is warranted (6).

Four main phenotypes have been classified with body adiposity and muscle mass composition, which are sarcopenia, obesity, sarcopenic obesity, and healthy status (7). Sarcopenia is an age-related muscle disorder, and is associated with increased risk of fall, fracture, and mortality (8, 9). The Asian Working Group for Sarcopenia (AWGS) 2019 consensus recommends using lower muscle mass with poorer grip strength or physical performance to define sarcopenia (10). On the other hand, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) revised consensus identifies sarcopenia in older adults with low grip strength and muscle mass, and those with a combination of poor physical performance are considered to have severe sarcopenia (11). It is known that lower BMI is commonly found in people with sarcopenia (12). Similar to BMI, body fat mass indicators including body fat percentage (BF%), are also used to diagnose obesity and estimate the risks of obesity-related diseases in older people (13, 14). Old individuals with both low muscle mass and high adiposity are sarcopenic obese (SO) which fail to benefit from the "obesity paradox" due to their higher risk of all-cause mortality (15). There has been evidence from pre-clinical studies indicating that adipose tissue damages muscle homeostasis, resulting in muscle atrophy and regeneration capacity reduction (16, 17). This finding was regarded as the pathogenic mechanism of sarcopenic obesity (17). Since sarcopenia, obesity, and sarcopenic obesity all lead to various adverse clinical outcomes of old people, it is necessary to establish the proper body indicator cut-offs for reference to decrease relevant risks. This cross-sectional study aims to explore i) the relationship between fat and muscle indicators in Asian elderly people, ii) the role of obesity in sarcopenia and muscle maintenance based on BMI- and BF%-defined obesity, and iii) the optimal BMI and BF% to prevent against both sarcopenia and obesity in old individuals.

2 Materials and methods

2.1 Study population

Elderly people were screened from the community or outpatient clinics at Prince of Wales Hospital in Hong Kong from 2019 to 2021. The inclusion criteria were 1) aged 60 years old or above, and 2) Chinese ethnicity. The exclusion criteria were: 1) severe foot deformity which is unable to acquire the BIA data, and 2) unable to communicate and understand the test instructions, e.g., severe dementia. This study was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Ref. CREC 2018.602).

2.2 Assessment of muscle and fat

All participants height were measured by an ultrasonic sensor (Clifford H.K. Co., Hong Kong). The whole-body skeletal muscle mass (SMM), body fat mass (BFM), arms fat mass (AFM), legs fat mass (LFM), and trunk fat mass (TFM), arms fat-free mass (AFFM), legs fat-free mass (LFFM), as well as waist-hip ratio (WHR) were assessed and directly obtained from the bioelectrical impedance analysis (BIA) system (InBody 120, Seoul, Korea). The tests were performed according to the manual instructions. In brief, subjects stood on the BIA device platform barefoot, and held the electrodes until the measurement was completed. Other body composition values were calculated as follows: fat mass index (FMI) = BFM/height^2, skeletal muscle mass index (SMI) = SMM/height^2, BF% = BFM/body weight, leg fat mass percentage (LFM%) = LFM/leg mass, arms fat mass percentage (AFM%) = AFM/arm mass, trunk fat mass percentage (TFM%) = TFM/trunk mass, leg fat-free mass percentage (LFFM%) = LFFM/leg mass, arm fat-free mass percentage (AFFM%) = AFFM/arm mass. We previously found that the value of muscle mass index detected by BIA (InBody 120) was 2.89 ± 0.38 kg/m^2 higher than measured by dual-energy X-ray absorptiometry (DXA) (Horizon, Hologic, Marlborough, MA, USA), which was considered the gold standard (18). Therefore, we recruited another 48 volunteers and utilized our previous method to establish a model to predict the DXA-measured appendicular skeletal muscle mass index (ASMI) based on BIA-measured SMI and demographic information *via* test- (n=32) and validation (n=16) groups (18). Multiple regression and Bland–Altman analyses were performed. SMI, age, sex, and anthropometric parameters including height, weight, and BMI were involved as potential contributions to establish the best model (18). The final prediction model is: ASMI (DXA) = 0.378 + 0.662 * (BIA SMI) – 0.003 * (Age) – 0.032 * (BMI); R^2 = 0.862. The mean difference between predicted and actual value was 0.04 ± 0.25 kg/m^2 in the validation group. Handgrip strength (HGS) was measured by the dynamometer (5030JI, JAMAR, Bolingbrook, IL, USA).

Participants seated with 90° elbow flexion and executed the test 3 trials per hand. The maximal reading was recorded (10).

2.3 Diagnosis of sarcopenia and obesity

Cut-off points according to the AWGS 2019 were used. Participants with both low muscle mass and strength was defined as sarcopenia. Male with ASMI (predicted) < 7.0 kg/m^2, and HGS < 28 kg, and female with ASMI (predicted) < 5.4 kg/m^2, and HGS < 18 kg were sarcopenic. Two criteria were used to diagnose obesity according to the previous studies of SO (19). The BMI ≥ 25 kg/m^2 was used to define obesity as recommended by WHO for East Asians (20); and BF% > 27% in male and 35% in female, which was used in previous SO studies for classification of obesity, and was close to the 60th percentile of BF% in our cohort (21–23).

2.4 Statistical analyses

Continuous variables were presented as mean ± standard error (SD), and categorical variables were expressed as number and percentage. Pearson's correlation coefficient was used to test the correlations between variables, including age, height, weight, muscle- and fat-related indicators. One-way ANOVA with *post-hoc* analysis by Bonferroni test was used to analyze the differences of body parameters between normal, only sarcopenic, only obese, and sarcopenic obese groups. The Pearson Chi-square test was performed to detect the role of obesity in sarcopenia *via* odds ratios (OR), as well as the proper values of BMI and BF% to prevent sarcopenia according to the fifth distributions of BMI and BF%. The age-related descent rate of muscle mass and strength in people with or without obesity, as well as the ASMI prediction model were estimated by using regression coefficient (β) from linear regression analysis. Python 3.10.1 and R 4.0.2 were utilized for the analyses. $p \leq 0.05$ was regarded as statistical significance in differences.

3 Results

3.1 The associations of fat and muscle indicators

1637 old subjects (age: 74.8 ± 7.8, range: 60–98 years; 83.6% female) were included without missing data (Table 1). After analyzing data from the whole cohort (both genders), the Pearson's correlations (Figure 1A) showed that age (≥ 60 years) was not related to BMI, WHR, and fat mass in different body positions ($p > 0.05$). Higher fat mass percentage in the whole and partial body, fat mass index, and lower weight, height, fat-free mass (FFM) in partial body, percentage of FFM, SMM, SMI, ASMI, and handgrip strength were related to increased age ($p < 0.05$). The percentage of fat mass in arms and legs were inversely correlated with SMM, SMI, and ASMI ($p < 0.05$). TFM% was positively related to SMI ($p < 0.001$), but not ASMI ($p > 0.05$). Higher TFM% was associated with reduced SMM and HGS ($p < 0.05$). BF% was weakly and negatively related to SMM and ASMI, but positively related to SMI ($p < 0.05$). Body weight, BMI, absolute fat mass, and WHR had similar trends to be positively associated with almost all muscle and fat parameters instead of fat-free mass percentage ($p < 0.05$). ASMI and HGS were both negatively related to the percentage of fat mass in limbs ($p < 0.05$). The correlation of muscle and fat indicators in females and males was shown Supplementary Figure 1. In males, SMI and WHR reduced with advanced age, which were not significant in females. SMM in both genders was negatively related to percentage of appendicular fat mass ($p < 0.05$), but positively associated with BF% in females. The inverse association between TFM% and HGS was only found in males rather than females. ASMI was inversely related to AFM% but not LFM% in both genders. In females, SMI increased with higher LFM%, and HGS increased with higher WHR, which were not found in males.

3.2 The characteristics of sarcopenia, obesity, and sarcopenic obesity in Asian old people

Subjects were divided into four groups based on sarcopenia and two obesity definitions (Table 1). More SO patients were detected when obesity was defined by BF% (25% in male, 17.3% in female, and 18.6% in total). If BMI ≥ 25 kg/m^2 was used to define obesity, the prevalence of SO was 14.2% in male, 11.8% in female, and 12.2% in total. Fat mass percentage in the trunk was similar between individuals with sarcopenia and non-sarcopenia when compared within the people with or without obesity, respectively ($p > 0.05$), except for males defined with obesity by BMI. WHR was similar or higher in the healthy group compared to only sarcopenic group, as well as in only obese group compared to sarcopenic obesity group. Appendicular fat mass was comparable or lower in sarcopenic groups with matched obesity status, but significantly higher when demonstrated by percentage. The highest percentage of arm and leg fat mass was found in SO ($p < 0.05$). Although BFM was similar between obese status-matched sarcopenic and non-sarcopenic groups, lower SMM was shown in the former groups (Figures 1B, C). With similar ASMI, BMI-defined SO had remarkedly higher BF% and lower HGS than the normal group ($p < 0.05$). There were no significant differences of ASMI and HGS between the two sarcopenic groups when obesity was defined by BF% ($p > 0.05$).

3.3 The role of obesity in sarcopenia and muscle maintenance

The ORs with 95% confidence interval (CI) showed the risk of sarcopenia in elderlies with obesity (Table 2). BMI- and BF% defined obesity had opposite roles in sarcopenia. When the population without obesity was regarded as the reference group (OR = 1.00), obesity defined by BMI was a protective factor of

TABLE 1 The prevalence, muscle and fat indicators in older people with normal status, sarcopenia, obesity, and SO.

	Obesity defined by BMI				Obesity defined by BF%			
	Normal	Sarcopenia	Obesity	SO	Normal	Sarcopenia	Obesity	SO
Male								
N (prevalence)	77(28.7%)	98(36.6%)	55(20.5%)	38(14.2%)	87(32.4%)	69(25.7%)	45(16.8%)	67(25.0%)
Age (years)	71.1 ± 4.8^{a}	79.5 ± 7.5^{b}	71.3 ± 5.5^{a}	77.5 ± 8.8^{b}	70.8 ± 4.9^{a}	78.5 ± 7.9^{b}	71.8 ± 5.5^{a}	79.3 ± 7.9^{b}
Height (cm)	166.6 ± 5.8^{a}	160.3 ± 6.9^{b}	165.1 ± 5.2^{a}	160.6 ± 7.7^{b}	167.0 ± 5.9^{ab}	161.7 ± 6.7^{cd}	164.0 ± 4.3^{ac}	159.0 ± 7.3^{d}
Weight (kg)	61.3 ± 6.5^{a}	55.9 ± 7.7^{b}	74.4 ± 6.3^{c}	70.9 ± 8.1^{c}	64.1 ± 8.9^{a}	55.8 ± 8.6^{b}	72.0 ± 7.2^{c}	64.5 ± 10.1^{a}
BMI (kg/m^2)	22.1 ± 2.0^{a}	21.7 ± 2.3^{a}	27.3 ± 2.0^{b}	27.4 ± 1.7^{b}	23.0 ± 2.8^{a}	21.3 ± 2.4^{b}	26.8 ± 2.7^{c}	25.4 ± 2.8^{c}
BF%	20.7 ± 5.2^{a}	24 ± 6.2^{b}	28.6 ± 4.4^{c}	33.2 ± 4.3^{d}	20.5 ± 4.2^{a}	21.0 ± 4.9^{a}	30.8 ± 3.1^{b}	32.3 ± 3.4^{b}
SMI (kg/m^2)	9.6 ± 0.8^{a}	8.9 ± 0.9^{b}	10.8 ± 0.9^{c}	10.0 ± 0.8^{a}	10.0 ± 1.0^{a}	9.1 ± 0.9^{b}	10.2 ± 1.0^{a}	9.3 ± 1.0^{b}
ASMI (kg/m^2)	5.8 ± 0.5^{a}	5.3 ± 0.5^{b}	6.4 ± 0.5^{c}	5.9 ± 0.5^{a}	6.1 ± 0.6^{a}	5.5 ± 0.6^{b}	6.1 ± 0.6^{a}	5.5 ± 0.6^{b}
HGS (kg)	31.7 ± 2.8^{a}	20.9 ± 4.9^{b}	31.6 ± 4.5^{a}	20.6 ± 4.5^{b}	32.0 ± 3.8^{a}	21.7 ± 4.6^{b}	31.1 ± 3.0^{a}	19.9 ± 4.8^{b}
FMI (kg/m^2)	4.6 ± 1.4^{a}	5.3 ± 1.7^{b}	7.8 ± 1.6^{c}	9.1 ± 1.5^{d}	4.8 ± 1.4^{a}	4.5 ± 1.4^{a}	8.3 ± 1.4^{b}	8.3 ± 1.6^{b}
WHR	0.83 ± 0.04^{a}	0.83 ± 0.04^{a}	0.90 ± 0.03^{b}	0.90 ± 0.03^{b}	0.84 ± 0.04^{a}	0.82 ± 0.04^{b}	0.90 ± 0.03^{c}	0.89 ± 0.03^{c}
AFFM (kg)	4.9 ± 0.8^{a}	4.1 ± 0.9^{b}	5.9 ± 0.9^{c}	4.9 ± 1.0^{a}	5.3 ± 1.0^{a}	4.2 ± 1.0^{b}	5.4 ± 0.8^{a}	4.4 ± 1.0^{b}
LFFM (kg)	15.1 ± 1.9^{a}	12.5 ± 2.3^{b}	16.3 ± 1.7^{c}	14.3 ± 2.5^{a}	15.7 ± 2.1^{a}	13.1 ± 2.4^{b}	15.3 ± 1.5^{a}	12.9 ± 2.7^{b}
AFM (kg)	1.5 ± 0.6^{a}	1.8 ± 0.6^{a}	2.8 ± 0.8^{b}	3.4 ± 0.7^{c}	1.5 ± 0.5^{a}	1.5 ± 0.5^{a}	3.0 ± 0.7^{b}	2.9 ± 0.8^{b}
LFM (kg)	4.1 ± 1.1^{a}	4.3 ± 1.2^{a}	6.3 ± 1.2^{b}	7.1 ± 1.3^{c}	4.2 ± 1.0^{a}	3.8 ± 1.0^{a}	6.7 ± 1.1^{b}	6.4 ± 1.4^{b}
TF (kg)	6.2 ± 2.2^{a}	6.6 ± 2.4^{a}	11.0 ± 2.0^{b}	11.8 ± 1.9^{b}	6.5 ± 2.4^{a}	5.6 ± 2.2^{a}	11.4 ± 1.9^{b}	10.5 ± 2.3^{b}
AFFM%	76.5 ± 7.2^{a}	70.1 ± 8.3^{b}	68.1 ± 7.2^{b}	59.3 ± 7.2^{c}	77.6 ± 5.3^{a}	74.0 ± 6.4^{b}	64.1 ± 5.1^{c}	60.0 ± 6.0^{d}
LFFM%	78.8 ± 4.7^{a}	74.6 ± 6.0^{b}	72.1 ± 4.3^{c}	66.6 ± 5.0^{d}	79.1 ± 3.8^{a}	77.6 ± 4.6^{a}	70.0 ± 2.9^{b}	67.0 ± 3.9^{c}
AFM%	23.5 ± 7.2^{a}	29.9 ± 8.3^{b}	31.9 ± 7.2^{b}	40.7 ± 7.2^{c}	22.4 ± 5.3^{a}	26.0 ± 6.4^{b}	35.9 ± 5.1^{c}	40.0 ± 6.0^{d}
LFM%	21.2 ± 4.7^{a}	25.40 ± 6.0^{b}	27.9 ± 4.3^{c}	33.4 ± 5.0^{d}	20.9 ± 3.8^{a}	22.4 ± 4.6^{a}	30.0 ± 2.9^{b}	33.0 ± 3.9^{c}
TFM%	22.6 ± 6.4^{a}	26.1 ± 7.5^{b}	31.9 ± 4.3^{c}	36.9 ± 4.1^{d}	22.6 ± 5.6^{a}	22.7 ± 6.3^{a}	34.0 ± 3.0^{b}	35.7 ± 3.6^{b}
Female								
N (prevalence)	518(37.8%)	424(31.0%)	265(19.4%)	162(11.8%)	512(37.4%)	349(25.5%)	271(19.8%)	237(17.3%)
Age (years)	72.1 ± 6.4^{a}	76.8 ± 8.6^{b}	73.8 ± 7.0^{c}	79.3 ± 7.5^{d}	72.4 ± 6.6^{a}	76.7 ± 8.6^{b}	73.2 ± 6.7^{a}	78.7 ± 7.8^{c}
Height (cm)	153.5 ± 6^{a}	150.1 ± 6.2^{b}	151.5 ± 6.0^{c}	147.6 ± 6.3^{d}	153.7 ± 5.8^{a}	150.3 ± 6.3^{b}	151.1 ± 6.1^{b}	148.1 ± 6.2^{c}

(Continued)

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TABLE 1 Continued

	Obesity defined by BMI				Obesity defined by BF%			
	Normal	Sarcopenia	Obesity	SO	Normal	Sarcopenia	Obesity	SO
Weight (kg)	50.9 ± 6.4[a]	47.6 ± 6.7[b]	65.6 ± 8.3[c]	59.5 ± 6.4[d]	51.9 ± 7.4[a]	46.8 ± 6.8[b]	63.3 ± 10.0[c]	56.8 ± 7.1[d]
BMI (kg/m^2)	21.6 ± 2.2[a]	21.1 ± 2.6[b]	28.6 ± 3.1[c]	27.3 ± 2.2[d]	21.9 ± 2.7[a]	20.7 ± 2.6[b]	27.7 ± 3.8[c]	25.9 ± 2.8[d]
BF%	28.7 ± 6.1[a]	29.3 ± 6.6[a]	38.3 ± 4.7[b]	40.1 ± 4.3[c]	28.1 ± 5.4[a]	27.4 ± 5.7[a]	39.4 ± 3.5[b]	39.5 ± 3.8[b]
SMI (kg/m^2)	8.1 ± 0.7[a]	7.7 ± 0.7[b]	9.4 ± 0.8[c]	8.6 ± 0.5[d]	8.4 ± 0.8[a]	7.8 ± 0.7[b]	8.9 ± 1.0[c]	8.2 ± 0.7[a]
ASMI (kg/m^2)	4.8 ± 0.4[a]	4.6 ± 0.4[b]	5.5 ± 0.5[c]	5.0 ± 0.3[d]	5.0 ± 0.5[a]	4.7 ± 0.4[b]	5.2 ± 0.6[c]	4.7 ± 0.4[b]
HGS (kg)	20.7 ± 2.8[a]	13.9 ± 3.4[b]	19.7 ± 4.4[c]	13.9 ± 3.1[b]	20.5 ± 3.1[a]	13.8 ± 3.4[b]	20.1 ± 3.9[a]	13.9 ± 3.1[b]
FMI (kg/m^2)	6.3 ± 1.8[a]	6.3 ± 2.0[a]	11.0 ± 2.5[b]	11.0 ± 2.0[b]	6.3 ± 1.7[a]	5.8 ± 1.7[b]	11.0 ± 2.5[c]	10.3 ± 2.0[d]
WHR	0.83 ± 0.04[a]	0.82 ± 0.05[b]	0.93 ± 0.04[c]	0.92 ± 0.04[d]	0.84 ± 0.05[a]	0.82 ± 0.05[b]	0.92 ± 0.05[c]	0.90 ± 0.04[d]
AFFM (kg)	3.2 ± 0.6[a]	2.8 ± 0.6[b]	4.1 ± 0.7[c]	3.4 ± 0.7[d]	3.4 ± 0.7[a]	2.8 ± 0.6[b]	3.8 ± 0.8[c]	3.2 ± 0.7[d]
LFFM (kg)	10.2 ± 1.7[a]	9.0 ± 1.6[a]	11.3 ± 1.8[b]	9.7 ± 2.8[c]	10.5 ± 1.8[a]	9.2 ± 1.6[b]	10.7 ± 2[a]	9.3 ± 2.5[b]
AFM (kg)	2.0 ± 0.6[a]	2.0 ± 0.7[a]	3.8 ± 1.2[b]	3.6 ± 1.0[c]	2.0 ± 0.6[a]	1.8 ± 0.5[b]	3.8 ± 1.2[c]	3.4 ± 0.9[d]
LFM (kg)	4.7 ± 1.2[a]	4.6 ± 1.3[a]	7.6 ± 1.8[b]	7.5 ± 2.7[b]	4.7 ± 1.2[a]	4.2 ± 1.1[b]	7.6 ± 1.8[c]	7.0 ± 2.4[d]
TF (kg)	7.1 ± 2.3[a]	6.7 ± 2.6[a]	12.7 ± 2.6[b]	11.8 ± 2.4[c]	7.1 ± 2.4[a]	6.1 ± 2.3[b]	12.5 ± 2.7[c]	11.1 ± 2.4[d]
AFFM%	61.5 ± 7.8[a]	58.7 ± 8.0[b]	52.3 ± 6.8[c]	48.9 ± 6.9[d]	62.8 ± 6.6[a]	61.1 ± 6.7[b]	50.0 ± 5.0[c]	48.5 ± 5.9[d]
LFFM%	68.5 ± 6.0[a]	66.7 ± 6.6[b]	59.8 ± 5.0[c]	56.7 ± 4.7[d]	69.3 ± 5.2[a]	68.6 ± 5.6[a]	58.6 ± 4.0[b]	57.1 ± 4.2[c]
AFM%	38.5 ± 7.8[a]	41.4 ± 8.0[b]	47.7 ± 6.8[c]	51.1 ± 6.9[d]	37.2 ± 6.6[a]	39.0 ± 6.6[b]	50.0 ± 5.0[c]	51.5 ± 5.9[d]
LFM%	31.5 ± 6.0[a]	33.3 ± 6.6[b]	40.2 ± 5.0[c]	43.3 ± 4.7[d]	30.7 ± 5.2[a]	31.4 ± 5.6[a]	41.4 ± 4.0[b]	42.9 ± 4.2[c]
TFM%	31.0 ± 7.3[a]	31.6 ± 8.1[a]	41.5 ± 4.3[b]	43.1 ± 5.0[b]	30.4 ± 6.7[a]	29.4 ± 7.3[a]	42.5 ± 3.3[b]	42.6 ± 4.3[b]

a, b, c, d: variables in groups with different letters were significantly different ($p < 0.05$).

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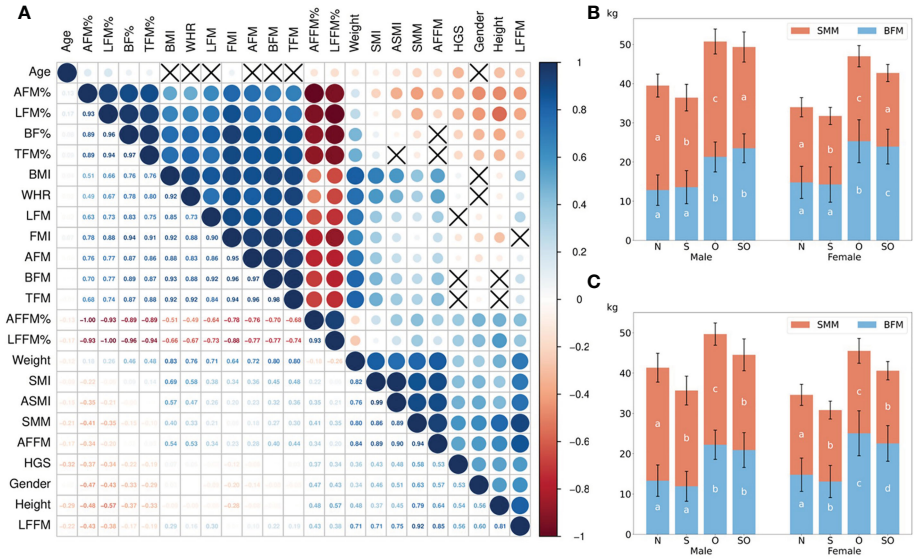

FIGURE 1
The correlation between muscle and fat indicators and the differences between normal, sarcopenic, obese, and sarcopenic obese groups. In **(A)**, the dark blue showed the strong positive correlation (correlation coefficient = 1), while the dark red showed the strong negative correlation (correlation coefficient = −1). Black cross was shown if there was no statistical significance (P > 0.05). The correlation coefficient was displayed in the lower half of the square. Female=0, male=1 for gender. **(B, C)** showed the differences of SMM and BFM in four groups according to BMI- and BF%-defined obesity. The *post-hoc* results were shown as a, b, c, d on the bars with same color; the results in groups with inconsistent letters were significantly different (P < 0.05). AFM%, arm fat mass percentage; LFM%, leg fat mass percentage; BF%, body fat percentage; TFM%, trunk fat mass percentage; BMI, body fat index; WHR, waist to hip ratio; LFM, leg fat mass; FMI, fat mass index; AFM, arm fat mass; BFM, body fat mass; TFM, trunk fat mass; AFFM%, arm fat-free mass percentage; LFFM%, leg fat-free mass percentage; SMI, skeletal muscle mass index; ASMI, appendicular skeletal muscle mass index; SMM, skeletal muscle mass; AFFM, arm fat-free mass; HGS, handgrip strength; LFFM, leg fat-free mass; N, normal group; S, only sarcopenic group; O, only obese group; SO, sarcopenic obese group.

sarcopenia in both male and female (ORs < 1.00, p < 0.05), while BF %-defined obesity was a risk factor (ORs > 1.00, p < 0.05). We also estimated the annual rate of muscle mass and strength decline based on obesity status in the elderly females (Figures 2A–D) and males (Figures 3A–D). For females, individuals with obesity had a steeper slope of ASMI (β: -0.017 vs. -0.006) and HGS (β: -0.238 vs. -0.206) decline when defined by BMI. Similar trends were also found in BF %-defined females with obesity, with the regression coefficient (β: -0.013 vs. -0.004) in ASMI, and in HGS (β: -0.253 vs. -0.189). Faster decline of ASMI in BMI-defined male with obesity was identified (β: -0.041 vs. -0.037). Other indicators in male without obesity declined more than male with obesity. Supplementary Table 1 showed the corresponding regression equations.

3.4 Optimal BMI and BF% in the elderly to decrease risk of sarcopenia

To specify the optimal BMI and BF% that should be maintained in elderlies to prevent sarcopenia, the recommended classification of BMI (<18.5, 18.5–22.9, 23–24.9, 25–29.9, ≥30) (20), as well as the fifth distributions of BF% (<19.1, 19.1–23.8, 23.9–27.4, 27.5–31.5, >31.5 in males, <26.0, 26.0–30.9, 31.0–34.6, 34.7–38.2, >38.2 in females) were used to calculate the ORs of sarcopenic prevalence according to the intervals of BMI and BF% (Supplementary Table 2). BMI 18.5–22.9, and the lowest BF% (<19.1) were chosen as reference groups. With the increase of BMI, a trend of reduced risks of sarcopenia were found in both male and female (Figure 4A). The significant effect of

TABLE 2 The risk of sarcopenia according to the status of obesity.

Definition	Gender	OR non-obese	OR obese	95%CI		p-value
				lower	upper	
BMI	Male	1.00 (reference)	0.53	0.32	0.88	0.013
	Female	1.00 (reference)	0.73	0.58	0.92	0.007
	Total	1.00 (reference)	0.69	0.56	0.86	0.001
BF%	Male	1.00 (reference)	1.88	1.15	3.07	0.012
	Female	1.00 (reference)	1.28	1.03	1.60	0.027
	Total	1.00 (reference)	1.38	1.13	1.69	0.002

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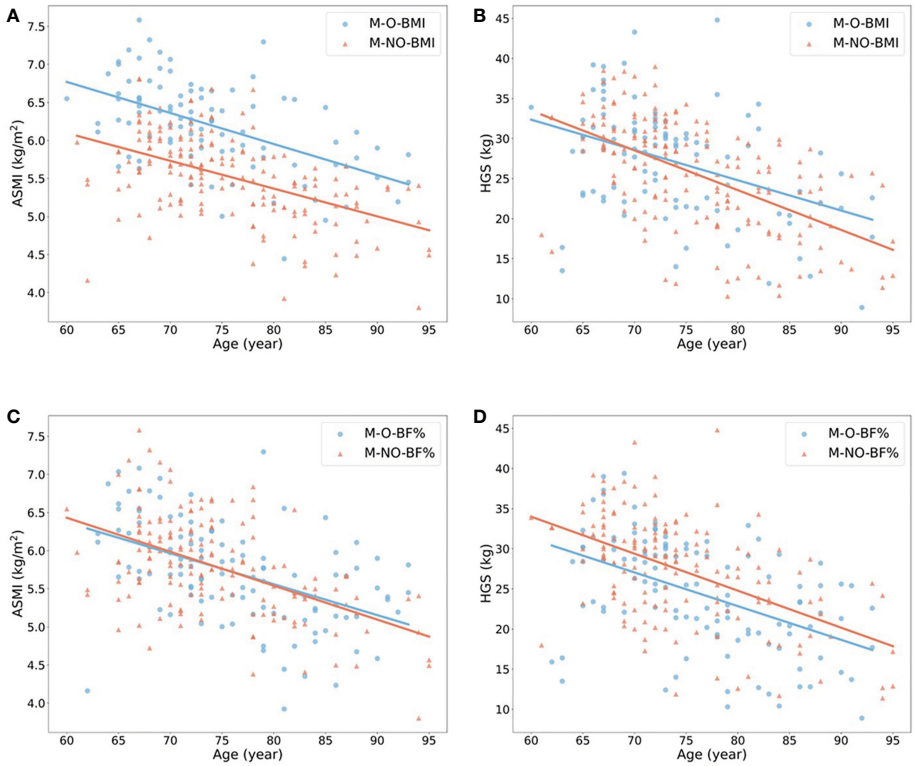

FIGURE 2
Linear regression model to show the annual rate of ASMI and HGS decline in females with (blue) or without (red) obesity. **(A, B)** showed the changes of ASMI and HGS according to age in females with or without obesity when obesity defined by BMI ≥ 25 kg/m2. **(C, D)** showed the changes of the above variables when obesity defined by body fat percentage > 35% in female. All p-value of regression models is ≤ 0.05. F, female; O, obese; NO, non-obese; BMI, body mass index; BF%, body fat percentage; ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength.

sarcopenia prevention was found in BMI 25–29.5 group in male ($p = 0.02$), and BMI ≥ 30 in female ($p = 0.001$). BMI <18.5 increased the risk of sarcopenia in female ($p = 0.05$). BF% and the risk of sarcopenia displayed a U-shaped curve in female, but the OR was lineally raised in male over 23.8% (Figure 4B). The significant protective effects were found in BF% 26.0–30.9% and 31.0–34.6% groups compared to the lowest BF% group in female ($p < 0.05$). Nevertheless, the risk of sarcopenia was comparable in the first four BF% groups, but significantly higher in the fifth group with BF% > 31.5 ($p < 0.01$) in male. To minimize the risk of sarcopenia, females should keep their BMI over 18.5 kg/m^2, as well as BF% between 26.0% and 34.6%. In males, higher BMI and BF% less than 23.9% were recommended.

4 Discussion

Muscle and fat are two widely studied tissues that contribute to a significant portion of our bodies. Without a large change of body composition, the increase of BMI is usually accompanied with both fat and muscle mass in adults. For old people, a lower BMI has become a predictor of sarcopenia (12). Various biomarkers for sarcopenia identification may be derived from this characteristic, such as lower triglycerides in sarcopenic patients (24). However, the gain of weight or BMI for elderly people without monitoring body composition is inadvisable, since older people have less lipid turnover and higher risks of metabolic diseases (25). A weak but significantly positive correlation between BF% and age was found in the elderly. This finding was also applicable in people from middle to old age (26). Although patients with sarcopenia have similar or even lower levels of absolute fat mass compared to non-sarcopenic people, their relative fat mass increased especially in limbs. Appendicular fat mass percentage was inversely related to ASMI and HGS when analyzed the whole cohort. Therefore, the fat deposition in limbs can be a potential diagnostic indicator of sarcopenia. Central obesity was associated with the development of metabolic complications and adverse clinical outcomes (27). We found higher TFM% was related to lower HGS in males, but to higher ASMI and SMI in females. Although WHR in non-sarcopenic individuals was also similar or higher compared to the sarcopenic ones, higher WHR in females was positively related to muscle mass and strength indicators. Previous studies also showed that females with central obesity but not males had lower prevalence of sarcopenia (28). This finding indicated there were greater adverse effects of fat accumulation and central obesity on the muscle of males. *In-vitro* studies showed that the coculture of mature adipocytes and skeletal muscle progenitor cells led to a reduction of nuclei number in myosin heavy chain (MHC)-positive myotubes (29). Fat deposition in extremities may play a role of muscle loss and dysfunction in sarcopenic patients *via* paracrine of adipokines and cytokines. Circulation lipid metabolites may also play roles in

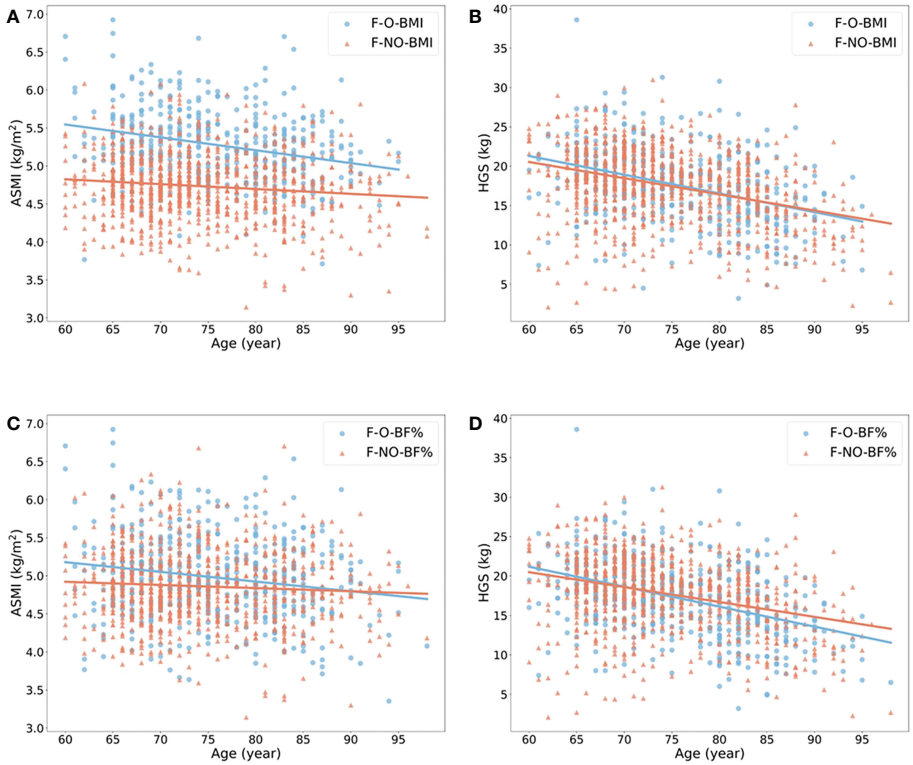

FIGURE 3
Linear regression model to show the annual rate of ASMI and HGS decline in males with (blue) or without (red) obesity. **(A, B)** showed the changes of ASMI and HGS according to age in males with or without obesity when obesity defined by BMI ≥ 25 kg/m2. **(C, D)** showed the changes of the above variables when obesity defined by body fat percentage > 27% in male. All p-value of regression models is < 0.05. M, male; O, obese; NO, non-obese; BMI, body mass index; BF%, body fat percentage; ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength.

aggravating muscle metabolism disorders, which mainly affects the energy metabolism and muscle function (30).

There is a well-known paradox that obesity is related to a lower risk of mortality (31). However, this finding depends on the definition of obesity by using BMI. When obesity was defined by BF%, obesity became related to higher death rate (14). Hence, the body composition may be the missing gap. According to the body composition, old individuals can be separated into sarcopenia, obesity, SO, and healthy status. Individuals with SO had lower muscle mass, strength, and higher adiposity, as well as higher all-cause mortality and worse surgical prognosis (17, 32). In our study, SO was more prevalent in males than females, and when obesity was defined by BF% than BMI. When defined by BMI, SO could be diagnosed dominantly by muscle function test since their muscle

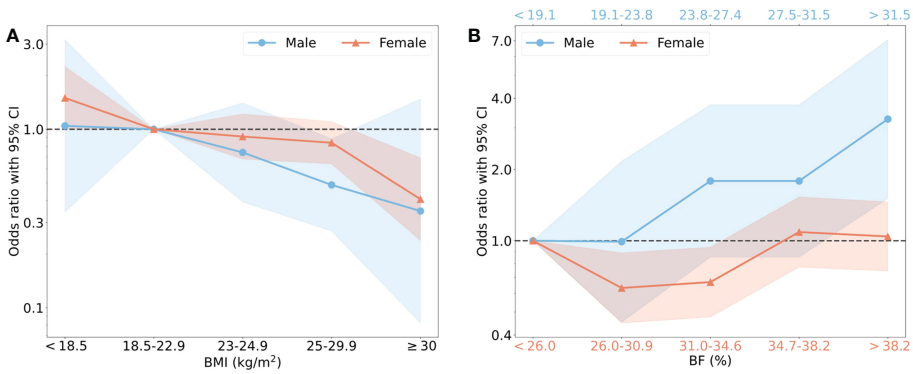

FIGURE 4
The risk of sarcopenia in males and females with different BMI and BF%. **(A)** showed that BMI was classified into 5 intervals based on the recommendation from WHO, the normal BMI (18.5–22.9) was regarded the reference group with OR=1.00. Blue points as OR values and blue shade as 95% CI represented male, and red represented female. **(B)** showed that BF% was classified into 5 intervals by quintile, the group with the lowest value of BF% was reference group. The specific interval of male (blue) was shown on the upper horizontal axis and female (red) on the lower horizontal axis.

mass was large. Although with higher BMI and absolute muscle mass than sarcopenia alone, SO patients had lower muscle quality, high risk of physical disability, as well as more metabolic issues, which may induce poor clinical outcomes (33). If defined by BF%, ASMI became comparable between simple sarcopenic and SO patients due to the shrunken discrepancies of BMI among groups. AFM% and LFM% were significantly higher in SO and may be biomarkers of this disease. In most cases, SO patients had different demographic features when diagnosed by different obesity definitions. A recommendation of the standard diagnostic criteria of SO should be noted in the future according to the risk of adverse events and outcomes with different definitions.

When obesity was defined by BMI, we found that it was a protective factor of sarcopenia despite the various metabolic problems that can occur (34). On the contrary, pre-clinical studies reported that obesity impaired muscle glucose tolerance, imbalanced protein synthesis and degradation, and oxidative stress which ultimately led to muscle atrophy, especially in old animals (16, 17). This may be caused by the severe obesity and exorbitant BF % in diet-induced obese animal models (35). In our study, we observed that obesity defined by BF% was a risk factor of sarcopenia which was consistent with pre-clinical findings. The ratio of body fat was not only associated with metabolic syndromes and adverse events but also with sarcopenia (36, 37). BF% contains the information of lean mass, fat mass, sarcopenia, and obesity, which is better than BMI that only contains body mass for elderly people. Similar to previous findings, in the elderly female group with obesity, a faster decline of muscle mass and strength with aging was observed (38). Although they had larger muscle storage, the muscle regeneration may be impaired (17). Nevertheless, the muscle decline in males was not as sensitive to obesity as in females. To explore the casual relationship between obesity and sarcopenia, a prospective study is needed. The management of body composition is important, and there are several strategies. Resistance training combined with nutrient supplementation, such as protein is preferable to maintain muscle mass (39). As for elderlies with obesity, the combination of caloric restriction (low-fat, proper high-protein diet with moderately decreased energy), as well as aerobic and resistance training have been recommended (40, 41).

In order to identify the optimal BMI and BF% to prevent sarcopenia, we divided the elderly population into 5 subgroups according to BMI and BF% distribution as previous methods (4). The differences caused by gender was apparent. For instance, lower BMI (<18.5 kg/m^2) dramatically increased the sarcopenia risk in females instead of males. In addition, the lowest interval of BF% in females also harmed muscle status. Adipose tissue is an essential endocrine organ that regulates hormonal levels. The lowest BMI and BF% resulted in low estrogen levels in menopausal female (42). It was reported that reduction of estradiol concentrations attenuated satellite cell proliferation, and the ability to maintain muscle mass and strength (43). The excess accumulation of fat also affects muscle phenotypes metabolically (17). Hence, we identified a range of BF% to prevent both sarcopenia and obesity in females. Males with the highest interval of BF% had three times greater risk of sarcopenia than the lowest subgroup. In a large cohort of men, increment of fat mass was associated with mortality, which may be associated with the high prevalence of sarcopenia (4). It is necessary to control the adiposity levels in old males due to the faster increasing trend of obesity compared to females (44). BMI was not as sensitive as BF% to simultaneously identify metabolic and sarcopenic risks. From our results, it is recommended for females to have a BMI between 18.5 kg/m^2 and 25 kg/m^2, and BF% between 26.0% and 34.6% to prevent sarcopenia and obesity. For males, the BMI should be lower than 25 kg/m^2 and BF% lower than 23.9%. Those with high BF% warrants early attention due to the higher potential to suffer both muscle and metabolic disorders. Since muscle disorders are associated with high risk of mortality, the reservation of muscle mass and strength is important (9). At present, numerous home-based, economical body fat percentage analysis instruments have been utilized for general body composition supervision, which old people will greatly benefit from. We also recommend that annual health examinations can consider to include BF% in elderlies, and body composition can be maintained through regular exercise and nutrition supplements.

Our study has several strengths. This study exhibited the correlation between various muscle and fat indicators comprehensively. We compared the role of obesity in sarcopenia with two different obesity definitions, and found that higher body fat percentage is related to the increased risk of sarcopenia, but higher BMI is associated with the lower risk of sarcopenia. Our findings indicate that body composition should be focused on in the elderly to observe the risks of both sarcopenia and obesity. The optimal range of BMI and BF% to resist sarcopenia for elderly individuals has also been shown in this study.

There are some limitations in this study. We diagnosed sarcopenia based on the AWGS 2019 consensus with only ASMI and HGS. This is due to the fact that the EWGSOP2 consensus only requires these two parameters for diagnosis, and the addition of physical performance defines severity. We wanted to avoid confusion from readers worldwide. However, as recommended by AWGS 2019 consensus, physical performance parameters such as 6-metre walk, short physical performance battery (SPPB), or 5-time chair stand test should also be evaluated in future studies. In addition, we used a prediction model to estimate ASMI, so that an error from the true value may be present. The sample size of male participants was smaller which may cause the false-negative results. The blood samples as well as comorbidity information were not collected for further analyses. This was a cross-sectional study which only showed the relative risk instead of revealing the causal relationship between obesity and sarcopenia, and thus prospective studies are warranted.

Our study revealed that muscle mass and strength elevated along with BMI and absolute fat mass increment. Obesity is a protective factor of sarcopenia when defined by BMI but is a risk factor when defined by BF%. As for the fat distribution, appendicular fat mass percentage was inversely relevant to muscle mass in both genders, and trunk fat mass percentage was negatively related to muscle strength only in males. The prevalence of SO in Chinese old people was higher if obesity was defined by BF% than BMI. In females with obesity, the annual rate of muscle mass and strength decline was faster than the non-obese group, but this finding did not present in males. The lowest incidence of sarcopenia

was found in females with the BF% 26.0–34.6%, and BMI over 18.5 kg/m^2. A trend showed that BF% less than 23.9% in males was better for sarcopenia prevention. Due to the negative effects of adipose tissue on muscle in pre-clinical studies, a longitudinal obese cohort to explore the alterations of muscle and its function with advanced age is warranted to elucidate the role of fat in muscle clinically.

Data availability statement

The datasets presented in this article are not readily available unless a valid and reasonable purpose is given. Requests to access the datasets should be directed to louischeung@cuhk.edu.hk.

Ethics statement

The studies involving human participants were reviewed and approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Ref. CREC 2018.602). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CL: writing-original draft and editing; conceptualization; methodology. KY-KC: investigation; data curation. XT: statistical analysis; data visualization. W-HC: supervision; writing-review and editing. SK-HC: supervision; writing-review and editing. SL: conceptualization; validation. RW: conceptualization; investigation; supervision; writing-review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1077255/full#supplementary-material

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Exploration of the core gene signatures and mechanisms between NAFLD and sarcopenia through transcriptomic level

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Introduction: The increased prevalence of non-alcoholic fatty liver disease (NAFLD) and sarcopenia among the elderly are facing a significant challenge to the world's health systems. Our study aims to identify the coexpressed genes in NAFLD and sarcopenia patients.

Methods: We downloaded the transcriptome data of NAFLD tissue from patients, as well as muscle tissues from sarcopenia patients, from the GEO database in order to investigate the shared transcriptional regulation mechanisms between these two diseases. Then, focusing on the genes that were frequently expressed in these diseases, together with GSVA and WGCNA, we utilized a range of analysis methods to identify the main co-expressed genes in both diseases by taking intersections. We investigated these changes after learning that they mostly affected lipid metabolism and oxidative stress injury pathways.

Results: By analyzing these genes and their interactions with transcription factors and proteins, we were able to identify 8 genes that share common patterns. From these 8 genes, we were possible to forecast potential future medicines. Our research raises the possibility of NAFLD and sarcopenia transcriptome regulatory pathways in aging populations.

Discussion: In conclusion, a complete transcription pattern mapping was carried out in order to identify the core genes, underlying biological mechanisms, and possible therapeutic targets that regulate aging in NAFLD and sarcopenia patients. It provides novel insights and proof in favor of decreasing the increased prevalence of sarcopenia in the elderly caused by NAFLD.

KEYWORDS

NAFLD (non-alcoholic fatty liver disease), sarcopenia, high throughput sequencing, bioinformatics analyses, co-expressed genes

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of lipids in the liver, which may further lead to the deterioration of liver fibrosis (1), cirrhosis and even liver cancer (2). According to statistics, about 25% of the world population is suffered from NAFLD, and patients attacked by NAFLD are becoming younger (3). Therefore, it is imperative to underlying the mechanisms of NAFLD and develop an effective treatment for it. Hepatic steatosis is age-related and associated with metabolic syndromes such as high-fat diet (4), flora disorders(5) and hyperlipidemia, as well as various toxins, drugs, and diseases. The pathogenesis of NAFLD is well established as a two-strike and multiple-strike theory but the molecular mechanism of the occurrence and development of NAFLD remains uncovered. (6). However, other aging diseases interrelated with lipid metabolism and fibrosis can aggravate the exacerbation of NAFLD.

Skeletal muscle accounts for 40% of the body weight, undertake 30% of the basic energy metabolism, and maintains behavioral functions. In adults, muscle loss begins at age 30 and accelerates after age 50. By age 60, muscle loss can reach 30 percent. The degeneration of muscle with the increase of age is defined as sarcopenia, which is accompanied by a series of pathological changes such as decreased muscle mass, fibrosis, and fat infiltration, seriously affecting the functional activities of the elderly and reducing life expectancy(7). The prevalence of sarcopenia in people over 80 years of age is as high as 50% and becoming a novel condition with direct life-threatening within the developing world (8) (9). Multiple factors are responsible for muscle glycolipid-metabolism disorder with aging. Reduced oxidative capacity or physical activity with aging both increases the proportion of lipids in body composition, and causes activation of inflammation and insulin resistance(10, 11). Numerous pro-inflammatory cascades are conjunct within muscle and visceral fat, which approach less muscle mass. Additionally, impaired insulin sensitivity can be further increased by muscle catabolism, resulting in abundant ectopic fat deposition within the muscle. Interstitial fibrosis is the other major histopathological change during the progress of sarcopenia, which contributes to the recession of force generation and enhances muscle stiffness.

Glycolipid-metabolism and fibrogenesis appear to be the intersection joint of NAFLD and sarcopenia. With a high degree of functional sharing, crosstalk and mutual regulation, one's metabolic disorders can lead to compensatory or even systemic metabolic disorders (12). Studies have shown that sarcopenia is an important indicator of the severity of NAFLD (13). Therefore, investigating the association and verifying the shared pathways between them provides a prospective way of creating novel age-related disease treatment strategies. (14).

Transcriptome analysis can determine and quantify changes in transcription levels in various states(15). A large number of applications in the life sciences have made transcriptomics widely used (16; 17). As the needs have changed, new techniques for transcriptome studies targeting low cell numbers and even more accurately targeted sequencing have emerged (18). In disease research, transcriptome technology can help researchers more accurately understand the pathogenesis of diseases and the relationship between specific RNA and diseases. Based on clarifying the precise regulation of various genes in diseases, transcriptome technology can help in the development of new drugs and has important applications in the prevention and treatment of tumors. The integration and analysis of biological data by various bioinformatics tools are important means of life science research. For example, a network algorithm or Random Forest was used to predict patient-related biomarkers (19). Transcriptome data combined with dual disease analysis can be used to better understand the pathological molecular mechanisms between diseases and make more accurate drug predictions (20). The present study aimed to identify hub genes and a hot research topic to the link between NAFLD and Sarcopenia. Therefore, by obtaining transcriptome sequencing data from clinical patients of the two diseases from the GEO database, further joint analysis of their gene expression data was conducted. The differences and commonalities were preliminarily analyzed to clarify the disease characteristics of NAFLD and Sarcopenia. After that, the co-expressed genes of the two diseases were screened. Diversity statistical analysis methods were used to obtain the co-expressed genes and the pathways significantly associated with NAFLD and Sarcopenia. Finally, we integrate the results from the single analysis and intend to provide a basis for subsequent clinical-related research.

2 Materials and methods

2.1 Data processing

Two genome-wide transcriptome profiling using RNA-Seq (GSE167523, GSE167186) of NAFLD and sarcopenia samples were obtained from the GEO database by using Illumina high throughput sequencing platform. 98 NAFLD patients' gene expression profiles formed the GSE167523 data set. The 72 samples in the GSE167186 data set were patients with sarcopenia. The analytic workflow is shown in Figure 1.

2.2 Top 1000 expressed genes selection and gene set variation analysis

Counts in NAFLD and Sarcopenia data sets (GSE167523, GSE167186) were normalized treatment. First, the two data sets were integrated according to gene name. Using the cpm function of package R edgeR (V.3.38.4), Counts per million (CPM) were calculated, and log2 was performed. After the log2 (cpm+1) value is arranged from the largest to the smallest, the first 1000 genes are selected as the top 1000 genes. These genes were analyzed by GSVA (Gene set variation analysis) using R package GSVA (V.1.44.5), The reference gene sets were selected from Homo sapiens C5 (ontology gene sets) in the MSigDB database. Use

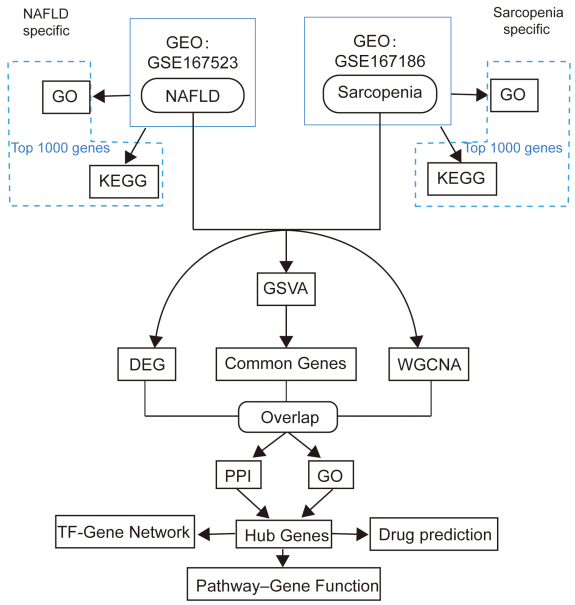


FIGURE 1
The framework of this study.

the GSVA function in the GSVA package. The analysis parameters are method="gsva", kcdf="Gaussian".

2.3 Analysis of inter-sample correlation and differentially expressed genes

When analyzing the correlation between samples, the vst function in package R DEseq2 (V.1.36.0) was first used to standardize the expression matrix. Then dist function was used to calculate the Pearson distance between samples, and the prcomp function was used for Principal Component Analysis (PCA). The DESeq function in using DEseq2 gene counts matrix analysis of differentially expressed genes, DEGs judgment standard for pvalue < 0.05 & (log2FoldChange > = 2 | log2FoldChange < = 2), The common genes are pvalue < 0.05 & (log2FoldChange >= -2 & log2FoldChange <= 2). For volcano mapping, the R package EnhancedVolcano (V.1.14.0) is used.

2.4 Weighted correlation network analysis

The log2 (cpm+1) matrix with an input file as the gene was constructed using an R package called "WGCNA". The power value was determined by the pickSoftThreshold function. Weight coexpression network uses the blockwiseModules function. The plotDendroAndColors function draws the clustering between samples. The labeledHeatmap function shows the correlation between the disease and gene Modules. The plotEigengeneNetworks function shows the correlation between each gene Module.

2.5 Gene Ontology and pathway enrichment analyses

GO is a database established by the Gene Ontology Consortium that provides simple annotations of gene products in terms of function, the biological pathways involved, and their location in the cell. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway is a database dedicated to storing information about genetic pathways in different species. KEGG's Orthopedic Annotated System (KOBAS) (http://kobas.cbi.pku.edu.cn) is a gene/protein functional annotation and functional enrichment Web server developed by Peking University, which collected functional annotation information of 4325 species. "GO terms" and "KEGG pathways" analyses use the "enrichGO" function and "enrichKEGG" function in the R package clusterProfiler (V.4.4.4), respectively, with the p-value cutoff set to 0.05. GO terms-genes network mapping uses the cnetplot function. The R packages GOplot (V.1.0.2) and ggplot2(V.3.3.6) are also used for visualization.

2.6 Determination and functional analysis of hub gene

Search Tool for the Retrieval of Interacting Genes (STRING; http://string-db.org)(11.0 version) Relationships between proteins of interest can be searched, such as direct binding relationships or co-existence of upstream and downstream regulatory pathways, to construct PPI networks with complex regulatory relationships. The TF-genes network is predicted by NetworkAnalyst software. DSigDB database was used to predict possible small-molecule drugs.

3 Results

3.1 GO and KEGG pathway analyses of NAFLD and sarcopenia

We conducted a preliminary analytic and statistical study on the disease data from NAFLD and sarcopenia. First, we performed enrichment analysis on the top 1000 genes from 98 NAFLD patients. The observations demonstrate a strong relationship between fat metabolism and energy metabolism in both molecular function, cellular component, and biological process (Figure 2A). And when we look at the KEGG data, we can see that these genes are related to some relevant metabolic pathways, such as liver alcoholic glycolysis degradation, fatty beta–alanine acid, cytochrome adducts P450, and other related metabolic pathways shown in Figure 2B. Genetic groups related to NAFLD were described.

Then we obtained transcriptome data from 81 patients with sarcopenia and selected the top 1000 genes for the enrichment analysis of GO and KEGG. Sarcopenia genes

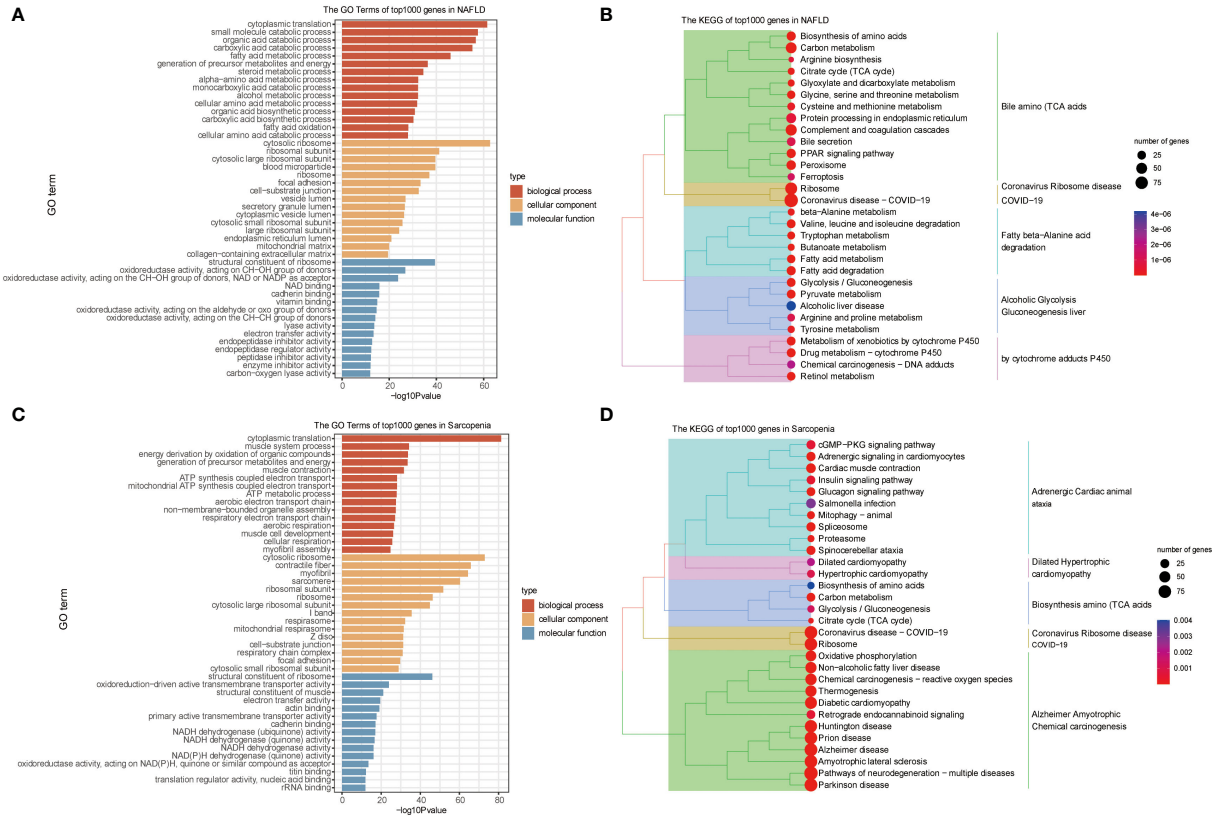


FIGURE 2
GO and KEGG Pathway Analyses of NAFLD and Sarcopenia. **(A)** The enriched GO terms of the top 1000 genes in NAFLD; **(B)** The KEGG of the top 1000 genes in NAFLD; **(C)** The enriched GO terms of the top 1000 genes in Sarcopenia; **(D)** The KEGG of the top 1000 genes in Sarcopenia.

were significantly correlated with energy metabolism and REDOX pathways in molecular function, cellular components, or biological processes (Figure 2C). Dilated Hypertrophic Cardiomyopathy, Biosynthesis of Amino Acids (TCA Acids), and Alzheimer's Amyotrophic Chemical Carcinogenesis were all strongly associated with KEGG enrichment (Figure 2D). This indicates that energy metabolism and redox pathways play a significant role in the disease features of NAFLD and sarcopenia, respectively.

3.2 Gene set variation analysis in NAFLD and sarcopenia

To further investigate the similarity between the two diseases, we integrated the genes of NAFLD and Sarcopenia. The enriched GSVA of the two diseases showed the main pathways as follows, according to the clustering analysis of the genes expressed in the two diseases: Purine nucleotide salvage, Fat-soluble vitamin catabolic process, Lipoxygenase pathway, Long-chain fatty acyl CoA biosynthetic process, Long-chain fatty acyl CoA metabolic process (Figure 3). A high similarity between the two diseases was identified by GSVA.

3.3 Differential gene expression in NAFLD and sarcopenia

Principal component analysis (PCA), which was used to further evaluate the transcriptome of these two diseases, revealed that the differences between the two diseases were more meaningful than the differences between the two diseases themselves (sFigure1A). The Pearson distance analysis, as shown in Figure 4A, further supported this result. Figure 4B indicates the variations in overall gene expression between the two diseases. The statistics show that there are numerous overlap genes between the two diseases, which will need to be further investigated. Searching at the differences between the two diseases and the differentially expressed genes in sarcopenia versus NAFLD, it is fairly obvious from GO terms that the majority of the genes associated with sarcopenia's high expression are those that are participated in muscle system processes, muscle contraction, muscle organ development, and other components of muscle development (Figure 4C). However, the metabolism of small molecules, sterols, alcohol, and other fat and disease-related metabolic pathways were all strongly expressed by NAFLD (Figure 4D). Similar results to those in the GO term were shown in the KEGG enrichment (sFigure 1C). Sarcopenia is mostly overexpressed in pathways

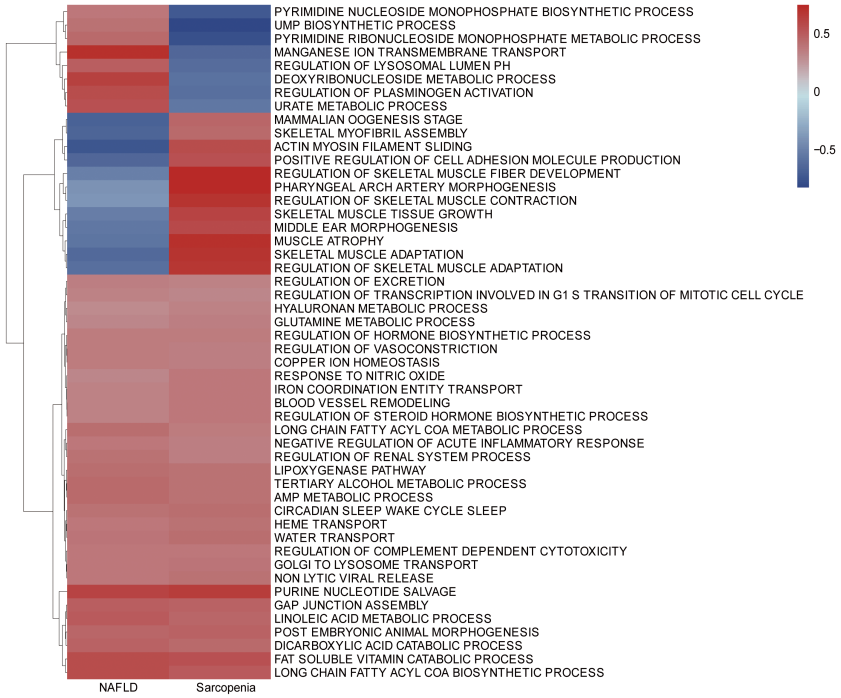
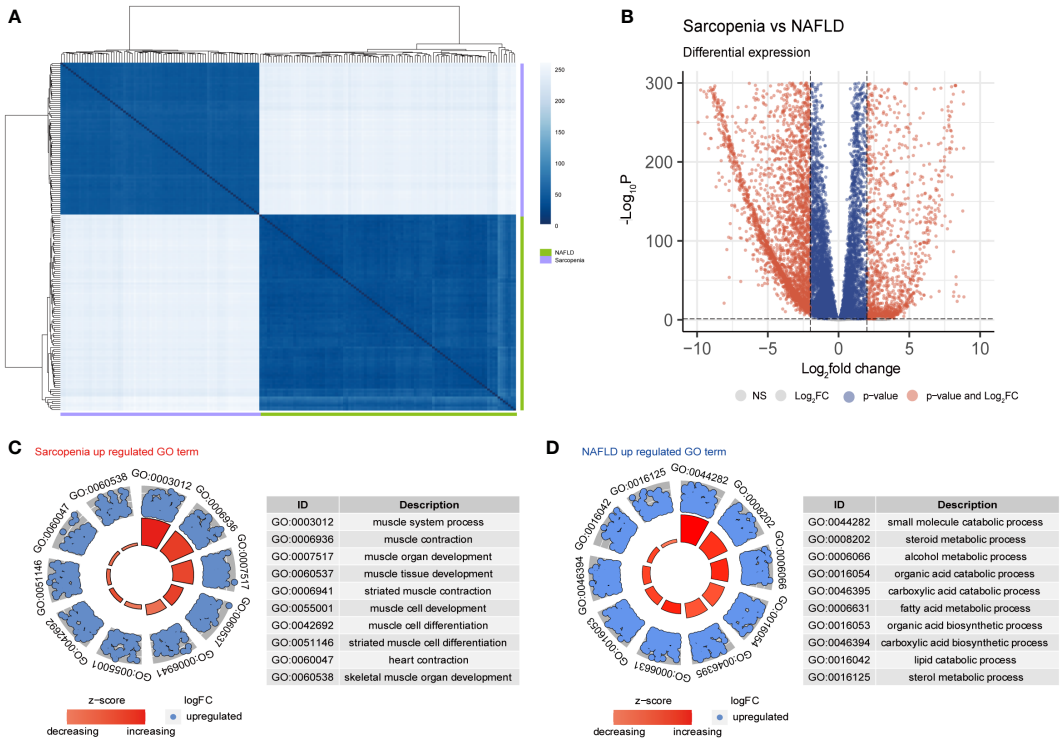


FIGURE 3
Gene Set Variation Analysis (GSVA) in NAFLD and Sarcopenia. GSVA of top 1000 genes in NAFLD and Sarcopenia.



ID	Description
GO:0003012	muscle system process
GO:0006936	muscle contraction
GO:0007517	muscle organ development
GO:0060537	muscle tissue development
GO:0006941	striated muscle contraction
GO:0055001	muscle cell development
GO:0042692	muscle cell differentiation
GO:0051146	striated muscle cell differentiation
GO:0060047	heart contraction
GO:0060538	skeletal muscle organ development

ID	Description
GO:0044282	small molecule catabolic process
GO:0008202	steroid metabolic process
GO:0006066	alcohol metabolic process
GO:0016054	organic acid catabolic process
GO:0046395	carboxylic acid catabolic process
GO:0006631	fatty acid metabolic process
GO:0016053	organic acid biosynthetic process
GO:0046394	carboxylic acid biosynthetic process
GO:0016042	lipid catabolic process
GO:0016125	sterol metabolic process

FIGURE 4
Differential gene expression in NAFLD and Sarcopenia. **(A)** The correlation heatmap of NAFLD and Sarcopenia; **(B)** Volcanic map showing the differentially expressed genes of NAFLD and Sarcopenia; **(C)** The GO term of the up-regulated pathways in sarcopenia versus NAFLD; **(D)** The GO term of the up-regulated pathways in NAFLD versus sarcopenia.

linked to muscle growth relative to NAFLD; while compared to sarcopenia, NAFLD is overexpressed in lipid metabolism-related pathways.

3.4 Common genes analyses in NAFLD and sarcopenia

We further investigate the relationship between the two diseases in consideration of the common genes depicted in Figure 4B. The resulting Go term revealed the common genes of NAFLD and Sarcopenia, regardless of their molecular function, cellular component, or biological process, by clustering the shared genes. These mainly enriched processes involve ribonucleoprotein complex biogenesis, ribosome biogenesis, ncRNA processing, histone modification, rRNA metabolic process, transcription coregulator activity, On DNA binding transcription factor binding, and other pathways, which indicates that these two diseases are strongly connected to epigenetic changes (Figure 5A). After evaluating the KEGG enrichment of common genes, we observed that various relevant pathways were enrichment, as well as metabolic pathways of numerous significant diseases (Figure 5B). Two diseases associated with nucleic acid metabolism and epigenetic modifications by GO enrichment.

3.5 Weighted correlation network analysisof NAFLD and sarcopenia

The scale-free network, adjacency matrix, and topological overlap matrix (sFigure 2A) were all constructed after the two groups of data were clustered using the Pearson correlation coefficient. Removal of the outliers, a sample clustering tree (sFigure 2B) was established. Finally, Figure 6A displays 12 modules based on average hierarchical clustering and dynamic tree pruning (the grey module is often regarded as an undefined module). We found that the blue and turquoise modules, which were selected as clinically significant modules for further analysis, were significantly correlated with NAFLD and sarcopenia. We investigated the connection between characterizing genes. Information regarding the pairing relationships between gene co-expression modules can be obtained from characteristic genes. The characteristic genes were grouped. The results demonstrated that the 11 modules can be grouped into two clusters in Figure 6B and that each of the module combinations (blue and pink, and turquoise and yellow) exhibit a high level of interactive connectedness. We enriched the modules for GO terms by combining them with clinical characteristics (Figure 6C). Blue modules were found to be significantly correlated with histone modification and RNA splicing, whereas brown modules were associated with gastrointestinal diseases, green modules with olfactory dysfunction, gray modules with miRNA regulation, red modules with cofactor 2, and turquoise modules with lipid metabolism. Which, the turquoise module also indicated that the organic acid catabolic process, carboxylic acid catabolic process, small molecule catabolic process, cellular lipid catabolic process, and alcohol metabolic process were significantly correlated (Figure 6D). Blue module revealed that protein methylation, protein alkylation, RNA splicing, and RNA splicing *via* transesterification processes were all strongly related to both diseases (Figure 6E). WGCNA shows that metabolism-related processes and behaviors such as RNA shearing are closely associated with both diseases.

3.6 Protein-protein interaction network

Therefore, intersection analysis was conducted on the genes in the obtained GSVA, DEG of common genes, and the modules obtained by WGCNA. 126 genes were screened out from these

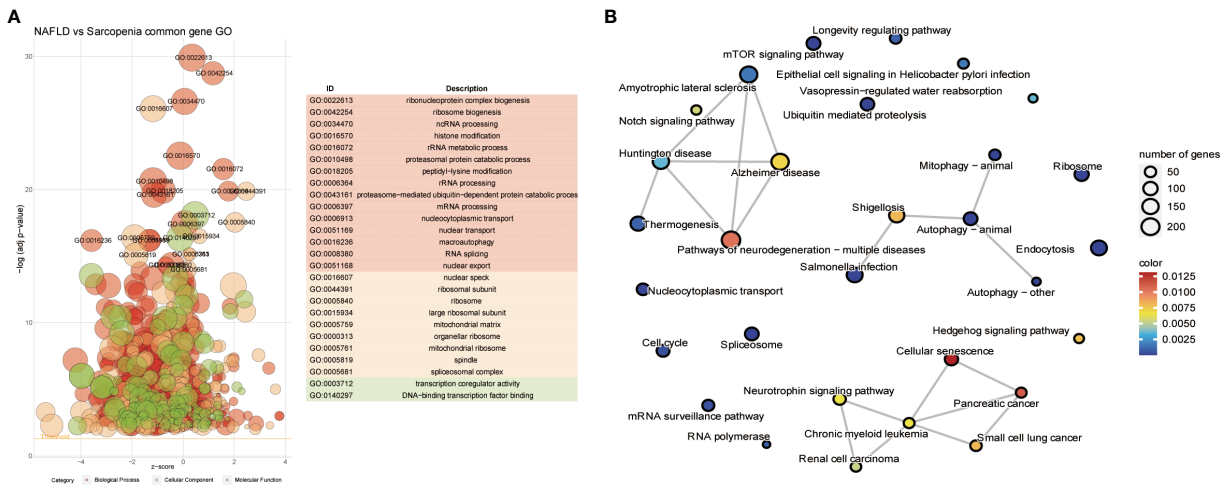


FIGURE 5
Common Genes Analyses in NAFLD and Sarcopenia. **(A)** The GO term of all common genes in NAFLD and Sarcopenia; **(B)** The KEGG of all common genes in NAFLD and Sarcopenia.

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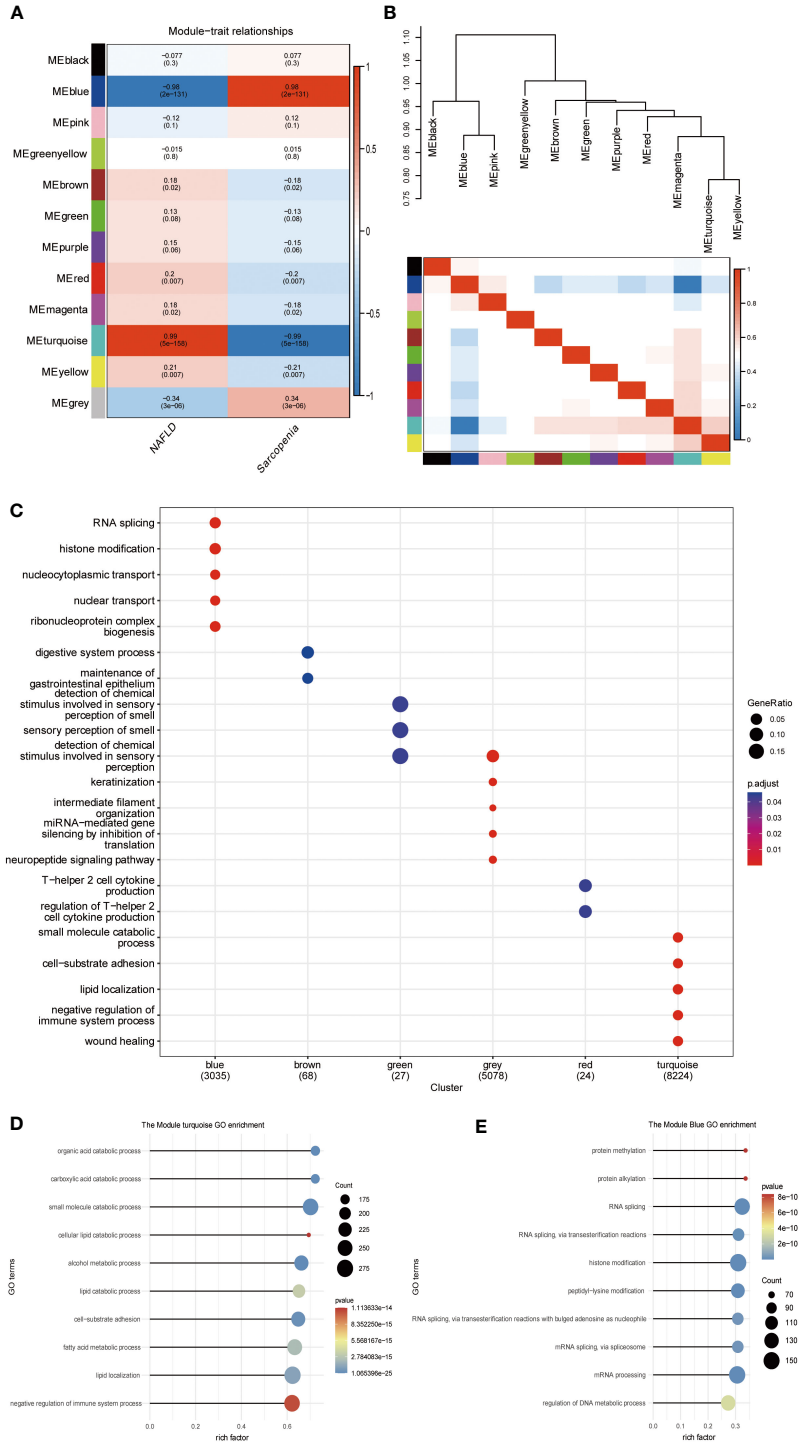


FIGURE 6
WGCNA of NAFLD and Sarcopenia. **(A)** Module−trait associations. Each row corresponds to a module, and each column corresponds to a trait. Each cell contains the corresponding correlation and P value. The table is color-coded by correlation according to the color legend; **(B)** Eigengene dendrogram and eigengene adjacency plot; **(C)** Gene Ontology analysis; **(D)** Gene Ontology analysis of the genes involved in the turquoise module; **(E)** Gene Ontology analysis of the genes involved in the blue module.

intersection genes for subsequent analysis (Figure 7A). Therefore, The PPI network of the intersection DEGs was constructed using String (Figure 7B). We analyzed the enrichment top GO pathway by looking at the GO of intersection genes and found that these genes and blood vessel remodeling, regulation of transcription involved in G1/S transition of the mitotic cell cycle, regulation of hormone biosynthetic process, and other vascular regulation and hormone anabolic pathways (Figure 7C). Two pairs of genes with high and low expression were filtered out by combining the results of Figures 7B, C. The results showed that the PPI

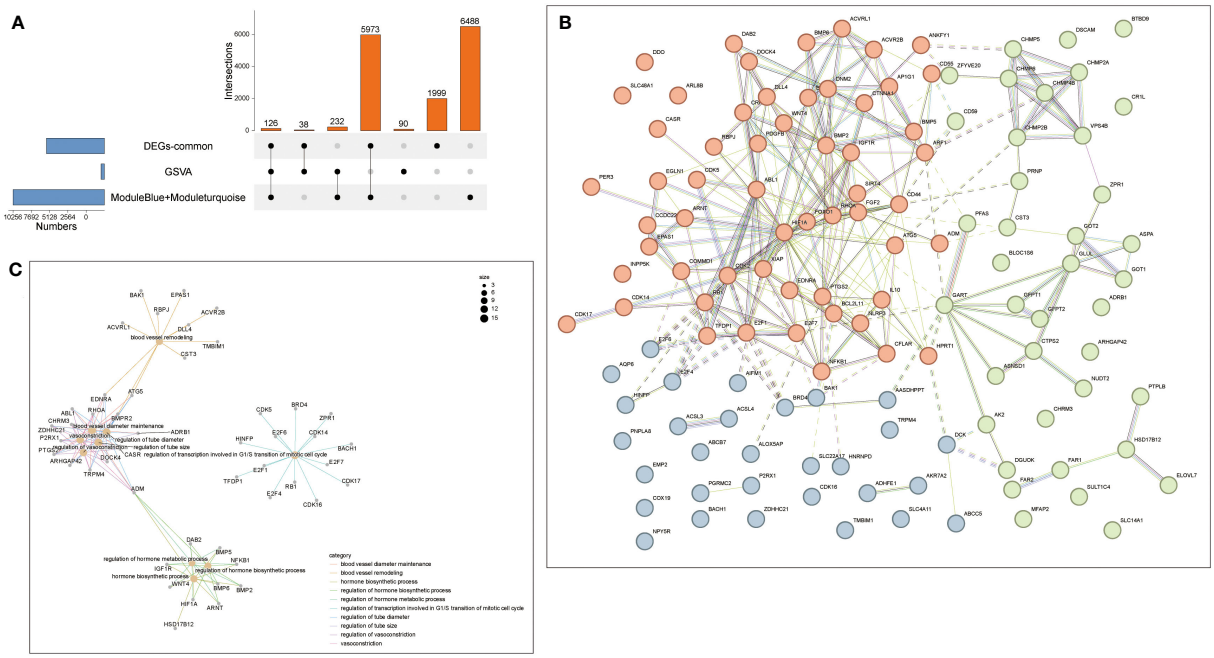


FIGURE 7
Protein-Protein Interaction Network (PPI). **(A)** The Venn diagram showed that seven algorithms have screened out 16 overlapping hub genes in NAFLD and Sarcopenia. **(B)** PPI network diagram. **(C)** The GO biological process analyses overlap genes from **(A)**.

network of these 126 genes correlated with energy, and hormone anabolism.

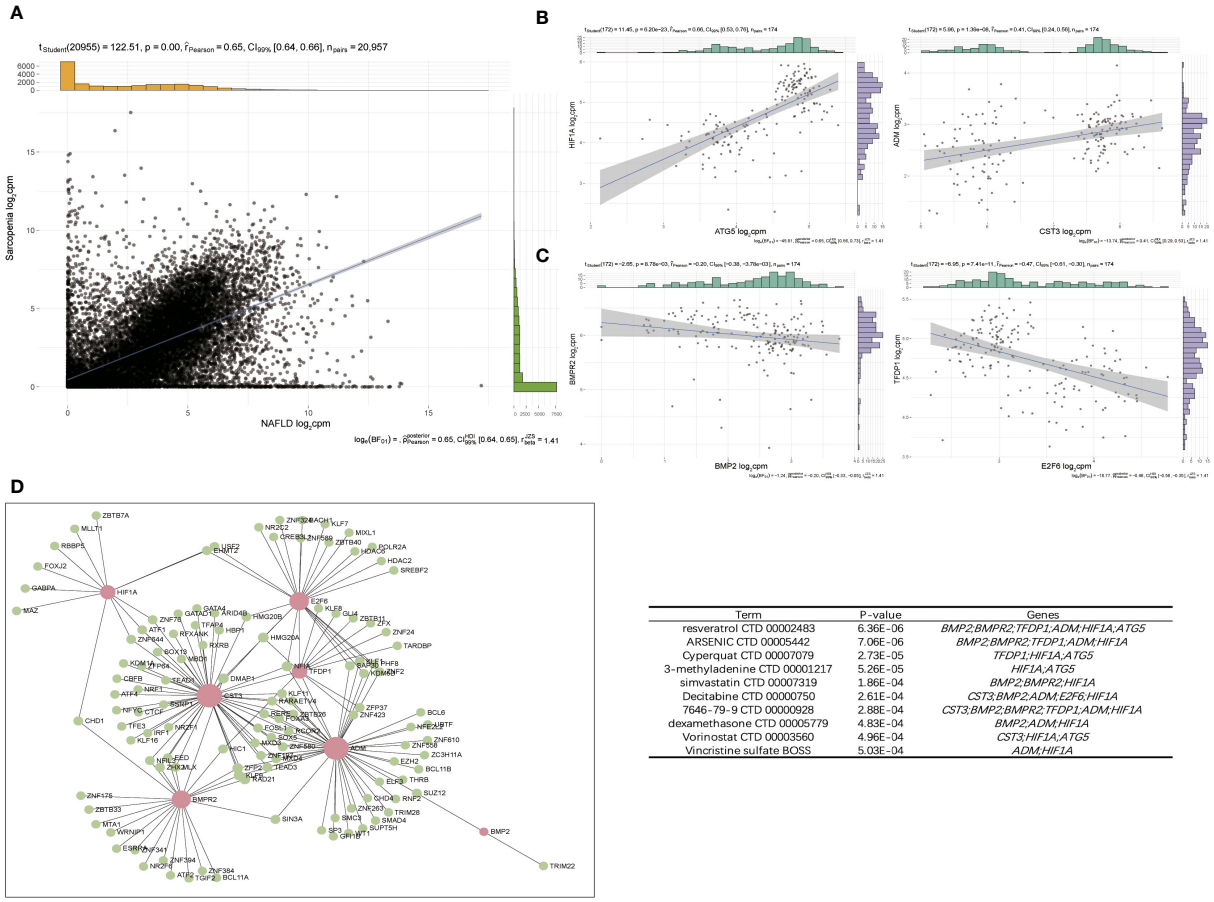
3.7 Pathway–gene functional network to screen hub gene

The expression patterns of NAFLD and Sarcopenia were found to be positively correlated after reviewing the expression values of all genes. This finding implies that the two diseases may be attached by a co-regulatory network and that further research into the co-regulatory mechanisms of the two diseases is essential (Figure 8A). Figure 8B shows the high expression of *HIF1A* and *ATG5*, as well as *ADM* and *CST3*, in the two diseases. *HIF1A* and *ATG5* were also strongly connected with the reoxidation-reduction of the disease. *ADM* and *CST3* were linked to hormonal disorders. The mutually compatible receptors *BMP2* and *BMPR2*, which are connected to protease hydrolysis, etc., were two pairs of genes with low expression in common. *TFDP1* and *E2F6* were two genes that also have significant regulatory functions in transcription and translation (Figure 8C). Additionally, we constructed a TF-target regulatory network diagram based on the eight-node genes, and Figure 8D clearly illustrates the correlation between the eight genes. With a high degree of linkage, *CST3*, *TFDP1*, *ADM*, and *BMPR2* could be especially noteworthy in the TF-target network. To give thorough treatment for patients who also have NAFLD and sarcopenia, several additional TFs were included, and medicines prediction was also done based on these genes. The top 10 potential medicines were displayed in Table 1. Future treatments for both diseases may be based on these 8 node genes.

4 Discussion

Investigating embryonic development, we learned that mesodermal differentiation is the principal source of muscle formation (21), while the liver consists of endoderm-derived hepatobiliary cell lineage and various mesodermal-derived cells (22), and liver development, from liver specification to liver maturation, requires close interaction with cells of mesodermal origin. This also implies that the progenitor cells of both organs have a strong commonality, and the origin from the same germ layer indicates that they are also functionally very closely related.

To better identify genes that are co-regulated in both diseases, we used the GSVA, common gene in DEGs analysis, and WGCNA analyses to jointly identify genes that are expressed in high abundance in both diseases and involved in disease development. Our research focused on the analysis of the co-expressed genes in both tissues to identify potential therapeutic strategies. We conducted an enrichment analysis for the top 1000 genes associated with each disease after homogenizing the obtained data. While Sarcopenia was more closely associated with energy metabolism and reoxidation reduction, we could see that the principal genes expressed in NAFLD were still associated with lipid metabolism, glycometabolism, and energy metabolism (Figure 2). As the body's primary metabolic organs, the liver and muscle can also be considered as potentially sharing some of the same functions (23). After realizing this commonality, we investigated the variations and consistency of the data in more detail. We proceeded by analyzing the differences between the two diseases and the co-expressed genes. We could see that sarcopenia and NAFLD were distinguishable in that sarcopenia had a higher



Term	P-value	Genes
resveratrol CTD 00002483	6.36E-06	*BMP2;BMPR2;TFDP1;ADM;HIF1A;ATG5*
ARSENIC CTD 00005442	7.06E-06	*BMP2;BMPR2;TFDP1;ADM;HIF1A*
Cyperquat CTD 00007079	2.73E-05	*TFDP1;HIF1A;ATG5*
3-methyladenine CTD 00001217	5.26E-05	*HIF1A;ATG5*
simvastatin CTD 00007319	1.86E-04	*BMP2;BMPR2;HIF1A*
Decitabine CTD 00000750	2.61E-04	*CST3;BMP2;ADM;E2F6;HIF1A*
7646-79-9 CTD 00000928	2.88E-04	*CST3;BMP2;BMPR2;TFDP1;ADM;HIF1A*
dexamethasone CTD 00005779	4.83E-04	*BMP2;ADM;HIF1A*
Vorinostat CTD 00003560	4.96E-04	*CST3;HIF1A;ATG5*
Vincristine sulfate BOSS	5.03E-04	*ADM;HIF1A*

FIGURE 8
Pathway–Gene Functional Network to screen hub gene. **(A)** Correlation of overlap genes in NAFLD and Sarcopenia. **(B)** Two pairs of genes that were positive-regulated expressed. **(C)** Two pairs of genes that were negative-regulated expressed. **(D)** The TF–target network of periimplantitis. TF, transcription factor.

expression of genes mainly related to muscle development. The high gene expression of NAFLD relative to sarcopenia was enriched in the adipose metabolism pathways associated with NAFLD illness itself (Figure 4E), which also reflected the specificities of each disease. This was associated with the gene expression of the muscle itself (Figure 4D). We were particularly interested in the relationship between the two diseases in our research. The major pathways of co-expressed enrichment of these two diseases were identified by GSVA, and the results revealed that the enrichment pathway was not only significantly related to epigenetics but also

TABLE 1 Top 10 drug predictions of hub genes.

Term	Overlap	P-value
resveratrol CTD 00002483	6/1602	6.36E-06
ARSENIC CTD 00005442	5/854	7.06E-06
Cyperquat CTD 00007079	3/160	2.73E-05
3-methyladenine CTD 00001217	2/028	5.26E-05
simvastatin CTD 00007319	3/305	1.86E-04
Decitabine CTD 00000750	5/1801	2.61E-04
7646-79-9 CTD 00000928	6/3095	2.88E-04
dexamethasone CTD 00005779	3/422	4.83E-04
Vorinostat CTD 00003560	3/426	4.96E-04
Vincristine sulfate BOSS	2/86	5.03E-04

involved in other metabolic diseases and immune-related pathways (Figure 3). This suggests that the gene expression of most metabolic diseases is very similar, and the cause of metabolic diseases may be related to REDOX-related pathways (24), epigenetic modification, or the mutual regulation of various RNAs (25, 26), as well as activating the immune system (27, 28).

WGCNA was used for further analysis to check the relationship between these two diseases in more depth. In the highly correlated turquoise and blue modules, we found that the key genes for the two diseases were still enriched in the epigenetic modification and lipid metabolism pathways (Figure 6D, E). Additionally, it is consistent with the preliminary results. In addition to checking more relevant genes and more precisely identifying and verifying the core genes of the two diseases, we chose the intersection of genes obtained by various analysis methods. These 126 genes were shown to be significantly enriched for the cell cycle, angiogenesis, and hormone anabolism pathways. We further checked into the co-expression of these genes and observed 4 pairs of genes out of a large number that were concurrently positive- or negative-regulated. *HIF-1A* activates the transcription of numerous genes, including those involved in energy metabolism, angiogenesis, apoptosis, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia, serving as a master regulator of cellular and systemic homeostatic response to hypoxia (29); *ATG5* encoded protein participates in several cellular functions, including the production of autophagic vesicles, mitochondrial quality control following oxidative damage, inhibition of the innate antiviral immune response, and proliferation and development of lymphocytes (30). We also observed that the preprohormone *ADM*, which is produced by this gene, can be broken down into two physiologically active peptides: adrenomedullin and pro-adrenomedullin N-terminal 20 peptide. Adrenomedullin is a 52 AA peptide having a variety of activities, such as vasodilation, hormone secretion regulation, angiogenesis stimulation, and antibacterial action. It also plays a significant role in oxidative stress (31); *CST3* inhibitors appear to have preventive properties in a variety of human fluids and secretions, but they also play a crucial regulatory role in the development of cancer and other diseases (32) (Figure 8B). These genes have a strong connection to the REDOX of the disease. Therefore, synergistic high expression in NAFLD and sarcopenia is significant.

However, there are fewer studies related to the direct occurrence of RNA splicing in NAFLD, but lipid accumulation, as well as obesity, are closely associated with the development of NAFLD. Which is the main cause of increased alternative RNA splicing in the liver. Gene expression data from the liver and muscle of Pihlajamaki et al. provided that obese patients found substantial downregulation of RNA splicing genes, suggesting that the expression of RNA splicing-related genes is negatively associated with liver lipids accumulation and hyperinsulinemia and that altered expression of RNA splicing factors may contribute to obesity-related phenotypes (33). Also, NAFLD, especially sarcopenia, as a disease of the elderly, is significantly associated with increased RNA splicing (34). For example, Li et al. published an article in Cell Metabolism demonstrating that death-associated protein kinase-related apoptosis-inducing kinase-2 (*DRAK2*) can inhibit the phosphorylation of *SRSF6* by the *SRSF* kinase *SRPK1*, and regulates selective splicing of mitochondrial function-related genes (35).

The activation of BMP signaling in skeletal muscle is significant in maintaining muscle mass as well as muscle-nerve interaction during cachexia and the aging process (36, 37). Restoring *BMP* activity ameliorates cancer-mediated muscle wasting and sarcopenia (36, 37). The activity of *BMP* receptors in muscles induced hypertrophy was dependent on Smad1/5-mediated activation of mTOR signaling (38). *TFDP-1* is a heterodimerization partner for members of the E2F family of transcription factors and up-regulates *E2F*-mediated transcriptional activation (39). *E2F/TFDP-1* regulates the expression of various cellular promoters, particularly gene products that are involved in the cell cycle (40). The combination of *TFDP1* with *E2F*s can promote liver regeneration by regulating *MYCN* transcription (41). Elevated expression of *TFDP1* was associated significantly with larger tumor size and down-regulation of *TFDP1* inhibited the growth of Hep3B cells. In conclusion, overexpression of *TFDP1* may contribute to the progression of some HCCs by promoting the growth of the tumor cells (40). Murine and human HCC data indicate significant correlations of *STMN1* expression with *E2F1/TFPD1* and with *KPNA2* expression and their association with poor prognosis in HCC patients (42). These four genes are negatively regulated and there are opposite regulatory patterns, and we checked their roles and found that the mechanisms are also different in the two diseases.

We also examined the TF regulatory network for these 8 genes, and we found that several of the transcription factors among these genes had strong connections to fibrosis, damage, and fat metabolism (Figure 8D). Resveratrol, which ranked top among such genes to predict small molecule medicines, was discovered to have a beneficial preventative impact on obesity-induced diet in NAFLD and NASH patients (43) (Table 1). It can also improve the validation status of skeletal muscles (44). Resveratrol is also a highly significant healthcare product in daily life, demonstrating the necessity of a daily supplement. In addition, the last few medicines are also widely used. This evidence can support the continued usage of previously prescribed medicines.

When compared to other research, our study still has several limitations. For example, disease development may be regulated at various histological levels, and we have only conducted a preliminary investigation of the co-regulatory mechanisms of NAFLD and sarcopenia at the transcriptome level. For instance, studies on DNA/RNA methylation have been applied to explain how so many diseases develop (39). Our analysis also revealed a strong correlation between both diseases and lipid metabolism as well as oxidative stress, demonstrating the importance of further metabolomic research (26, 45). What's more, the research should really be based on healthy samples to obtain differentially expressed genes and then compare them. However, since healthy human liver and muscle samples are not easy to obtain, we only collected partial liver control datasets, but considering that the liver's gene expression is affected by sex and age (46) (47), we were unable to find a dataset that could be matched exactly. The dataset was not available for muscle. Therefore, the study was mainly conducted on the expression profile of the disease. Therefore, it is necessary to update the data in healthy subjects if they are available subsequently.

In summary, our work demonstrates the potential transcriptome regulatory mechanisms of NAFLD and sarcopenia. Through a thorough mapping of the transcription pattern, the key genes, molecular processes, and potential therapeutic targets that cause NAFLD and sarcopenia were examined. It offers a new perspective and supporting evidence to decrease the high incidence of NAFLD in sarcopenia patients.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be listed below. Repository/Repositories Accession Number Gene Expression Omnibus GSE167523 Gene Expression Omnibus GSE167186.

Author contributions

JY and FY designed the study. ZX and ZY performed data analysis. ZX prepared the figures and tables. ZX, ZY, and SL wrote the manuscript and approved the final draft. ZX, ZY, and ZT participated in data interpretation and analysis. ZX, ZY, and SL were involved in proofreading and deep editing and approved the final manuscript. JY and FY devised the main conceptual idea, supervised the project, performed proofreading and deep editing of the manuscript, and approved the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1140804/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Differential gene expression in NAFLD and Sarcopenia. (A) The PCA gene expression profile in NAFLD and Sarcopenia patients; (B) The KEGG enrichment of the up-regulated pathway in sarcopenia; (C) The KEGG enrichment of the up-regulated pathway in NAFLD.

SUPPLEMENTARY FIGURE 2
Determination of soft-threshold power in the WGCNA. (A) Analysis of the scale-free index for various soft-threshold powers (β). (B) Analysis of the mean connectivity for various soft-threshold powers.

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Effect of sarcopenia, osteoporosis, and osteosarcopenia on spine fracture in American adults with prediabetes

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Objective: This study aimed to investigate the effect of sarcopenia, osteoporosis, and osteosarcopenia on spine fracture in patients with prediabetes.

Methods: We collected and analyzed the data from the U.S. National Health and Nutrition Examination Surveys during the period from 2009 to 2018. Bone mineral density and the skeletal muscle mass index (SMI) were measured with dual-energy X-ray absorptiometry (DXA). The diagnosis of spine fracture was based on DXA and history.

Results: People with prediabetes were more likely to develop sarcopenia than normal glucose tolerance subjects (OR 1.33, 95% CI 1.07–1.66), while there was no significant increase of osteoporosis in prediabetes (OR 0.91, 95% CI 0.78–1.05). The SMI was independently associated with osteoporosis in prediabetes adults (OR 0.65, 95% CI 0.50–0.85). Both sarcopenia and osteoporosis were positively associated with spine fracture in prediabetes (OR 4.44, 95% CI 1.76–11.21, and OR 2.90, 95% CI 1.85–4.56, respectively). The risk of spine fracture was substantially higher in the presence of osteosarcopenia (OR 6.63; 95% CI, 1.34–32.94) than in the presence of sarcopenia or osteoporosis alone in prediabetes.

Conclusion: In adults with prediabetes, both sarcopenia and osteoporosis are risk factors for spine fracture, and the combination of sarcopenia and osteoporosis further increases the prevalence of spine fracture.

KEYWORDS

prediabetes, sarcopenia, osteoporosis, spine fracture, osteosarcopenia

Introduction

Prediabetes refers to an intermediate metabolic state between normoglycemia and diabetes, and it includes impaired fasting plasma glucose, impaired glucose tolerance, and mildly raised hemoglobin A1c (HbA1c). Although there is no clinically confirmed hyperglycemia in prediabetes, a series of pathophysiological changes related to diabetes have occurred. Recent evidence has shown that the prevalence of diabetes-associated

complications in prediabetes starts to rise compared with those with normal glucose levels (1).

Osteoporosis describes a systemic bone disease that is prone to fractures due to a decrease in bone mass and the destruction of bone microstructures, resulting in increased bone fragility, whereas sarcopenia refers to decreased muscle mass, strength, and function. The incidence of both osteoporosis and sarcopenia increases as the aggravated population ages. Both osteoporosis and sarcopenia can lead to a greater risk of falls, fractures, hospitalization, and mortality. Because of the close relationship between the two conditions, the concept of osteosarcopenia has been established, which refers to the coexistence of osteoporosis and sarcopenia.

Previous studies have shown that people with diabetes are more likely to have sarcopenia (2, 3), and people with diabetes are at a higher risk of developing fractures (4). Therefore, sarcopenia and osteoporosis are increasingly recognized as chronic complications of diabetes. For people with prediabetes, the risk of sarcopenia, osteoporosis, and osteosarcopenia and their impact on fractures are still unclear.

In this study, we analyzed the data from the American NHANES from 2009 to 2018 to examine the association among sarcopenia, osteoporosis, and prediabetes and the effect of sarcopenia, osteoporosis, and osteosarcopenia on spine fracture in American adults with prediabetes.

Methods

Population

NHANES consists of a cross-sectional multistage, stratified, and clustered probability sample of the deinstitutionalized population in the United States. It was conducted by the National Center for Health Statistics and approved by the National Center for Health Statistics institutional review board. Written informed consent was received for all participants.

The data of participants in the American NHANES 2009–2018 survey were analyzed. NHANES 2009–2018 data are publicly available and can be accessed online (https://www.cdc.gov).

Participants with missing relevant data and the lack of relevant examinations were excluded from the analyses. The analyses of the present study were limited to individuals aged ≥18 years.

Measurements

Information was collected through family interviews and physical examinations in a mobile examination center. A standardized questionnaire was used to collect data on age, sex, race, education level, physical activity, and the history of fracture. Race was self-reported, and in the present study, it was categorized into white, black, Mexican, Asian, and other races. Current smoking was defined as having smoked 100 cigarettes or more in one's lifetime and currently smoking cigarettes. The education level was categorized as less than 9th grade, 9–11th grade, high school graduate, AA degree, and college or above. The BMI was calculated by dividing body weight (kg) by the square of height (m). Steroid use was defined as ever taken any prednisone or cortisone pills nearly every day for a month or longer. Information about physical activity was self-reported by participants using the Global Physical Activity Questionnaire since the 2007–2008 cycle. Based on the data from self-reported questionnaire, metabolic equivalents (METs) can be calculated, which were used to estimate the average weekly energy expenditure of participants (5).

BMD was evaluated by DXA. HbA1c levels were measured by testing whole blood samples using the method of high-performance liquid chromatography. The glucose tolerance test is to measure the plasma glucose value 2 h after the oral administration of 75 g glucose.

Definition of variables

Participants eligible for any of the following conditions were classified as diabetic patients in the present study: (1) a confirmed history of diabetes in questionnaire; (2) HbA1c level ≥ 6.5% (6); and (3) fasting glucose level ≥ 7.0 mmol/L (6). Participants who accord with all of the following conditions were defined as NGT: (1) a denied history of diabetes or prediabetes in the questionnaire; (2) HbA1c level <5.7% (6); and (3) fasting glucose level <5.6mmol/L. The remaining participants were defined as prediabetes.

T-scores were calculated as ($BMD_{respondent}$-mean $BMD_{reference\ group}$)/$SD_{reference\ group}$. In the formula above, SD stands for standard deviation. Osteoporosis was defined as a T-score<−2.5 in total lumbar spine (L1–L4) or femoral neck tested by DXA. As recommended by the World Health Organization (7), the diagnosis of osteoporosis should be based on ethnic and sex-specific reference values. Therefore, the race-specific reference value of BMD for the calculation of T-scores at the femoral neck and the lumbar spine was obtained from the Vital and Health Statistics from the Centers for Disease Control (CDC) (8).

The appendicular SMI was calculated by dividing the appendicular skeletal muscle mass (kg) by square of height (m). The SMI cutoff values for the diagnosis of low muscle mass were 7.0 kg/m^2 for men and 5.5kg/m^2 for women (9), according to the 2nd meeting of European Working Group on Sarcopenia in Older People.

The presence of either of the following conditions is defined as a spine fracture: previous spine fracture history in the questionnaire; the vertebral fracture status summary in DXA suggests a fracture (mild, moderate, or severe fracture at any level in T4–L4).

Statistical analysis

The Kolmogorov–Smirnov method was used to evaluate the data distribution. Continuous variables are represented as mean ± standard deviation for normally distributed data or medians and interquartile ranges in parentheses for abnormally distributed data. The chi-square test, Mann–Whitney U test, or independent t-test

was performed to compare the differences between two groups when appropriate. Categorical variables are represented as frequency (percentage), and between-group differences were evaluated by the chi-square test. Logistic regression was used to adjust for potential confounding variables when appropriate. *P*-values < 0.05 were considered indicative of statistical significance. All statistical analyses were performed using STATA 12.0.

Results

The baseline clinical characteristics of the participants enrolled in this study are shown in Tables 1 (all the subjects) and 2 (subjects with prediabetes). From 2009 to 2018, a total of 23,825 adults were included in the study, of whom 7,427 (31.2%) had prediabetes. As compared to normoglycemic people, subjects with prediabetes had a higher proportion of men, older age, a higher proportion of black race, a lower education level, less physical activity, a higher BMI, and higher waist circumference (WC), so did the subjects with diabetes. In terms of the HbA1c level, as expected, the diabetic group was higher than the prediabetic group, and the prediabetic group was higher than the NGT group. The trend of the insulin level among the three groups appeared the same with the HbA1c level. There was no significant difference among the three groups on Serum 25(OH)D. Interestingly, the lumbar and spinal bone mineral density of the prediabetic group was lower than that of the NGT group, while there was no significant difference between the diabetic group and the NGT group, which may be explained by the excessive

TABLE 1 Characteristics of U.S. adults with diabetes, with prediabetes and with NGT, 2009–2018.

	NGT (n = 11,896)	Prediabetes (n = 7,427)	Diabetes (n = 4,502)
Sex (male, %)	5,603 (47.1%)	3,654 (49.2%)**	2,314 (51.4%)***
Age (years)	41 ± 18	53 ± 17***	61 ± 14***
Race[a]			
White	4,607 (38.7%)	2,601 (35.0%)***	1,417 (31.5%)***
Black	2,445 (20.6%)	1,829 (24.7%)	1,143 (25.4%)
Hispanic	2,751 (23.1%)	1,806 (24.3%)	1,234 (27.4%)
Asian	1,607 (13.5%)	937 (12.6%)	564 (12.5%)
Other	486 (4.1%)	254 (3.4%)	144 (3.2%)
Educational level[a]			
<9th grade	1,001 (7.0%)	1,011 (11.3%)***	931 (17.0%)***
9–11th grade	1,785 (12.4%)	1,248 (13.9%)	859 (15.7%)
High school	3,172 (22.1%)	2,049 (22.9%)	1,238 (22.6%)
AA degree	4,512 (31.4%)	2,614 (29.2%)	1,513 (27.6%)
College or above	3,890 (27.1%)	2,026 (22.6%)	941 (17.2%)
MET (min/week)	5,040 (2,100, 1,1760)	4,200 (1,680, 10,080) ***	3,360 (1,260, 7,280) ***
BMI (kg/m^2)	27.4 ± 6.3	30.1 ± 7.2***	32.2 ± 7.6***
WC (cm)	93.6 ± 15.4	101.7 ± 15.9***	108.5 ± 16.2***
HbA1c (%)	5.2 ± 0.3	5.7 ± 0.3***	7.2 ± 1.7***
Insulin (μU/ml)	8.32 (5.58, 12.9)	11.49 (7.15, 18.42)***	13.58 (8.44, 22.62)***
Serum 25(OH)D (nmol/L)	63.7 ± 27.1	64.7 ± 28.0	63.7 ± 27.9
Lumbar spine BMD (g/cm^2)	1.05 ± 0.15	1.03 ± 0.15***	1.04 ± 0.16
Total spine BMD (g/cm^2)	1.03 ± 0.14	1.02 ± 0.16**	1.03 ± 0.17
Osteoporosis prevalence (%)	372 (6.39%)	416 (9.72%)***	278 (9.41%)***
SMI (kg/m^2)	7.7 ± 1.6	8.3 ± 1.8***	8.6 ± 1.8***
Sarcopenia prevalence (%)	824 (6.9%)	245 (3.3%)***	70 (1.6%)***
Spine fracture prevalence (%)	143 (1.2%)	134 (1.8%)***	204 (2.3%)***

**p < 0.01, ***p < 0.001 vs control.
[a]Data are proportions within group.
MET, metabolic equivalents; BMI, body mass index; WC, waist circumference; 25(OH)D, 25-hydroxyvitamin D.

weight of the diabetic group (10). In terms of prevalence of osteoporosis, the diabetic group was higher than the prediabetic group, and the prediabetic group was higher than the NGT group. The trend of spine fracture prevalence among three groups appeared the same as osteoporosis prevalence. In terms of the SMI, the diabetic group was higher than the prediabetic group, and the prediabetic group was higher than the NGT group, which may be explained by the excessive weight of prediabetic and diabetic groups.

After adjusting for age, sex, race, BMI, current smoking status, educational level, and physical activity (MET score), people with prediabetes were more likely to develop sarcopenia than NGT subjects (OR 1.33, 95% CI 1.07–1.66), while prediabetes was not an independent risk factor for osteoporosis (OR 0.91, 95% CI 0.78–1.05) (Table 2).

Furthermore, in order to explore the effects of osteoporosis and sarcopenia on spinal fractures in the population of prediabetes, we divided the prediabetes population into four groups: normal group (without sarcopenia or osteoporosis), sarcopenia group, osteoporosis group, and osteosarcopenia group (with both sarcopenia and osteoporosis). The subject characteristics of the four groups are shown in Table 3. Individuals in the osteosarcopenia group were significantly older and had a lower BMI, lower WC, and less physical activity than normal subjects. As expected, subjects in osteosarcopenia group had lower BMD, a lower SMI, and higher spine fracture prevalence than individuals in the normal group. After adjusting for confounders, the SMI was independently associated with osteoporosis in prediabetes adults (OR 0.65, 95% CI 0.50–0.85) (Table 4).

As shown in Figure 1, in the prediabetes population, sarcopenia was not an independent risk factor for spine fracture, while osteoporosis and osteosarcopenia were independent risk factors for spine fracture without adjustment for any confounding factors. In Table 5, after adjusting for age, sex, race, BMI, steroid use, current smoking status, educational level, and physical activity (MET score), both sarcopenia and osteoporosis were positively associated with spine fracture in the fully adjusted model (model 3, OR 4.44, 95% CI 1.76–11.21, and OR 2.90, 95% CI 1.85–4.56, respectively). Furthermore, the likelihood of spine fracture was substantially higher in the presence of osteosarcopenia (OR 6.63; 95% CI, 1.34–32.94). Unlike prediabetes, there was no significant association between sarcopenia and spine fracture in the NGT group, while sarcopenia and osteosarcopenia were still positively associated with spine fracture in the NGT group (model 3, OR 2.40, 95% CI 1.53–3.76, and OR 4.31, 95% CI 1.17–15.92, respectively).

Discussion

Prediabetes and osteoporosis

Recently, the correlation between diabetes and bone health is attracting increasing attention. It is well known that type 2 diabetes predisposes individuals to a higher risk of fractures; even type 2 diabetes is associated with an average or higher BMD (11). Nevertheless, there are few studies exploring the relation between prediabetes and skeletal health, and the results were conflicting (12–14). This study found an increased risk of spine fractures in prediabetes. In addition, in this study, although the risk of spine fracture increased in the prediabetes population compared with the NGT, the prevalence of osteoporosis was not significantly different from that in the NGT population. Previous studies have also found that the risks of hip fractures begun to increase in prediabetes (15). Thus, similar to the condition in diabetes, the bone in prediabetes appears to have relatively low strength for a given BMD. As a result, the BMD as a conventional tool appears to underestimate the risk of fracture in individuals with prediabetes, which is a challenge for clinicians.

Prediabetes and sarcopenia

A previous study has reported that muscle strength was lower in diabetes patients than individuals without diabetes (16), and type 2 diabetes is related to accelerated loss of leg muscle strength in elderly individuals (17). In fact, type 2 diabetes has already been identified as an independent risk factor for sarcopenia (18). In terms of sarcopenia, it has been revealed that strength of hand grip adjusted by the BMI (19) or body weight (20) is related to prediabetes. Kaga et al. recently reported that prediabetes is an independent risk factor for sarcopenia in older Japanese men but not in older Japanese women (21). In the present study, after adjusting for age, sex, race, BMI, current smoking status, educational level, and physical activity (MET score), prediabetes

TABLE 2 Association between prediabetes and the odds of sarcopenia and osteoporosis.

	Sarcopenia			Osteoporosis		
	NGT	Prediabetes		NGT	Prediabetes	
		OR (95%CI)	*P*		OR (95%CI)	*P*
Model 1	1.00 (Ref.)	0.57 (0.49–0.67)	<0.001	1.00 (Ref.)	1.79 (1.59–2.00)	<0.001
Model 2	1.00 (Ref.)	1.33 (1.08–1.64)	0.008	1.00 (Ref.)	0.93 (0.80–1.07)	0.306
Model 3	1.00 (Ref.)	1.33 (1.07–1.66)	0.011	1.00 (Ref.)	0.91 (0.78–1.05)	0.187

Data are summarized as OR (95% CI) unless otherwise indicated.
Model 1 was unadjusted.
Model 2 was adjusted for age, sex, race, and BMI.
Model 3 was adjusted for model 2 adjustments plus current smoking status, educational level and physical activity (MET score).

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TABLE 3 Characteristics of prediabetes adults with sarcopenia, with osteoporosis, and with osteosarcopenia.

	Sarcopenia (–) Osteoporosis (–)	Sarcopenia (+) Osteoporosis (–)	Sarcopenia (-) Osteoporosis (+)	Sarcopenia (+) Osteoporosis (+)	P-value
	n = 6,339	n = 224	n = 614	n = 21	
Sex (male, %)	3,379 (53.3%)	88 (39.3%)	140 (22.8%)	9 (42.9%)	<0.001
Age (years)	41.2 ± 11.6	43.2 ± 12.5	65.5 ± 12.9	51.4 ± 7.5	<0.001
Race[a]					<0.001
White	1,540 (32.3%)	71 (31.7%)	243 (49.6%)	5 (23.8%)	
Black	1,308 (27.4%)	20 (8.9%)	65 (13.3%)	3 (14.3%)	
Hispanic	1,168 (24.5%)	44 (19.6%)	106 (21.6%)	3 (14.3%)	
Asian	570 (11.9%)	83 (37.1%)	67 (13.7%)	9 (42.9%)	
Other	185 (3.9%)	6 (2.7%)	9 (1.8%)	1 (4.8%)	
Educational level[a]					<0.001
<9th grade	625 (10.1%)	9 (4.3%)	85 (14.0%)	0 (0%)	
9–11th grade	880 (14.2%)	22 (10.4%)	89 (14.6%)	5 (23.8%)	
High school	1,437 (23.2%)	47 (22.3%)	144 (23.7%)	7 (33.3%)	
AA degree	1.844 (29.7%)	64 (30.3%)	167 (27.5%)	3 (14.3%)	
College or above	1,415 (22.8%)	69 (32.7%)	123 (20.2%)	6 (28.6%)	
Steroid use (%)	184 (5.1%)	4 (5.4%)	62(11.8%)	1(6.3%)	<0.001
Current smoker (%)	2,841 (44.8%)	90 (40.2%)	267 (43.5%)	10 (47.6%)	0.513
MET (min/week)	5,880 (2,520, 13,440)	3,360 (1,680, 10,640)	2,520 (11,20, 6,720)	3,360 (1,680, 4,620)	<0.001
BMI (kg/m^2)	30.8 ± 6.7	21.4 ± 2.4	28.7 ± 6.5	20.4 ± 2.3	<0.001
WC (cm)	101.6 ± 15.3	82.3 ± 8.9	98.9 ± 14.5	82.2 ± 7.4	<0.001
Serum 25(OH)D (nmol/L)	62.0 ± 26.3	61.7 ± 24.8	78.5 ± 30.9	65.2 ± 34.8	<0.001
HbA1c (%)	5.65 ± 0.35	5.53 ± 0.39	5.76 ± 0.30	5.61 ± 0.33	<0.001
Insulin (μU/mL)	12.1 (7.6, 19.2)	6.2 (4.3, 9.9)	10.2 (6.4, 14.3)	5.94 (3.83, 11.86)	<0.001
Lumbar spine BMD(g/cm^2)	1.04 ± 0.14	0.98 ± 0.12	0.77 ± 0.12	0.78 ± 0.10	<0.001
Total spine BMD (g/cm^2)	1.06 ± 0.13	0.96 ± 0.11	0.84 ± 0.15	0.78 ± 0.11	<0.001
SMI (kg/m^2)	8.55 ± 1.65	5.69 ± 0.76	7.96 ± 1.48	5.62 ± 0.89	<0.001
Spine fracture prevalence (%)	108 (1.70%)	7 (3.13%)	47 (7.65%)	2 (9.52%)	<0.001

[a]Data are proportions within group.
MET, metabolic equivalents; BMI, body mass index; WC, waist circumference.

TABLE 4 Association between the SMI and osteoporosis in prediabetes adults.

	OR (95%CI)	*p*
Model 1	0.79(0.71–0.87)	<0.001
Model 2	0.64(0.49–0.82)	0.001
Model 3	0.65(0.50–0.85)	0.001

Data are summarized as OR (95% CI) unless otherwise indicated.
Model 1 was unadjusted.
Model 2 was adjusted for age, sex, race, and BMI.
Model 3 was adjusted for model 2 adjustments plus current smoking status, educational level and physical activity (MET score).

is an independent risk factor for sarcopenia in the multiracial group. Therefore, it is necessary for healthcare providers to pay more attention to the development of sarcopenia in prediabetes as well as diabetes.

Sarcopenia and osteoporosis

In the present study, osteoporosis is closely related to the SMI in subjects with prediabetes. To the best of our knowledge, our study is the first attempt to provide the association between the SMI and

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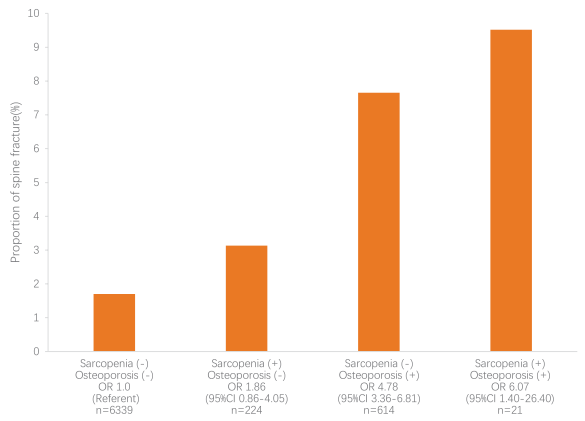

FIGURE 1
The relative risk for spine fracture according to sarcopenia and osteoporosis status. The relative risk for spine fracture was highest in subjects with sarcopenia and osteoporosis ($P<0.05$).
CI, confidence interval; OR, odds ratio.

osteoporosis in U.S. adults with prediabetes. Sharing the same mechanical and molecular mechanisms, muscle and skeleton function are closely linked (22). Both skeleton and muscle mass are intrinsically related to the declined physical performance with aging, while the bone–muscle crosstalk, which is the molecular mechanisms linking bone to muscle function, is less well defined. Hormones were identified as having an important role in the development of osteosarcopenia, including growth hormone (GH)/insulin-like growth factor-1 (IGF-1) and gonadal sex hormones (23).

Osteosarcopenia and fracture

Previous studies have shown that the coexistence of sarcopenia and osteoporosis was associated with some adverse outcomes, such as depression, malnutrition, peptic ulcer disease, inflammatory arthritis, and reduced mobility (24). Meanwhile, there are studies demonstrating that subjects with both osteoporosis and sarcopenia are at a higher risk of falls and frailty than those with osteoporosis or sarcopenia alone (24, 25). In a Korean study conducted in hip fracture patients, osteosarcopenia was associated with a higher 1-year mortality rate (15.1%) compared with subjects with osteoporosis (5.1%) or sarcopenia (10.3%) alone (26). In the present study, in patients with prediabetes, sarcopenia increases the risk of spinal fractures by 4.4 times, osteoporosis increases the risk of spinal fractures by 2.9 times, and sarcopenia combined with osteoporosis increases the risk of spinal fractures by 6.6 times. As for people with NGT, although sarcopenia does not significantly increase the risk of spinal fractures, its combination with osteoporosis further increases the prevalence of spinal fractures.

In conclusion, patients with prediabetes had an increased risk of sarcopenia compared with people with NGT. In adults with prediabetes, muscle weight loss is associated with osteoporosis; meanwhile, osteoporosis and sarcopenia both increase the risk of spinal fractures, while the combined presence of sarcopenia and osteoporosis further increases the prevalence of spinal fractures. For patients with prediabetes, in order to prevent spinal fracture, attention should be paid to the prevention and treatment of sarcopenia and osteoporosis, and special attention should be paid to the combination of sarcopenia and osteoporosis.

A key strength of this analysis is the source of the data. NHANES is a series of meticulously conducted surveys with continuous quality control, ensuring that the data are timely and of high quality. NHANES also uses population-based cluster random selection to identify a nationally representative sample that can be applied to the whole U.S. population. However, it has some limitations. First, the definition of osteoporosis, in addition to BMD < −2.5, also includes a history of fragility fractures, which were not included in the osteoporosis group because fragility fractures could not be defined. Second, the diagnosis of sarcopenia, in addition to decreased muscle quantity, also includes a decrease in muscle quality, which was not analyzed in this study due to the lack

TABLE 5 Incidence rate ratios (95% CI) for spine fracture according to categories based on sarcopenia and osteoporosis in NGT/prediabetes adults.

	Sarcopenia (–) Osteoporosis (–)	Sarcopenia (+) Osteoporosis (–)		Sarcopenia (–) Osteoporosis (+)		Sarcopenia (+) Osteoporosis (+)	
		OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
NGT							
Model 1	1.00 (Ref.)	0.47 (0.17–1.27)	0.135	8.87 (6.35–12.39)	<0.001	5.61 (1.72–18.25)	0.004
Model 2	1.00 (Ref.)	1.47 (0.50–4.30)	0.483	2.63 (1.66–4.16)	<0.001	7.87 (2.19–28.24)	0.002
Model 3	1.00 (Ref.)	1.32 (0.44–3.95)	0.620	2.40 (1.53–3.76)	<0.001	4.31 (1.17–15.92)	0.028
Prediabetes							
Model 1	1.00 (Ref.)	1.86 (0.86–4.05)	0.117	4.78 (3.36–6.81)	<0.001	6.07 (1.40–26.40)	0.016
Model 2	1.00 (Ref.)	4.82 (1.99–11.66)	<0.001	2.87 (1.82–4.50)	<0.001	13.00 (2.73–61.93)	0.001
Model 3	1.00 (Ref.)	4.44 (1.76–11.21)	0.002	2.90 (1.85–4.56)	<0.001	6.63 (1.34–32.94)	0.021

Data are summarized as OR (95% CI) unless otherwise indicated.
Model 1 was unadjusted.
Model 2 was adjusted for age, sex, race, and BMI.
Model 3 was adjusted for model 2 adjustments plus steroid use, current smoking status, educational level, and physical activity (MET score).

of relevant test results. Third, the reference standards for muscle mass are diverse, and this study uses the criteria of the second meeting of the European Sarcopenia Working Group, which does not necessarily apply to people of African, Asian, Hispanic, or other races. Fourth, because some of the respondents did not complete the full set of examinations, fewer people were diagnosed with osteosarcopenia. It is hoped that data with larger sample size will be available for future studies in this area.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL and SC conceived and designed the experiments. YL performed the data analysis. YL wrote the manuscript. XZ provided supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COVID-19 and sarcopenia-related traits: a bidirectional Mendelian randomization study

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Background: Emerging evidence suggested that coronavirus disease 2019 (COVID-19) patients were more prone to acute skeletal muscle loss and suffer sequelae, including weakness, arthromyalgia, depression and anxiety. Meanwhile, it was observed that sarcopenia (SP) was associated with susceptibility, hospitalization and severity of COVID-19. However, it is not known whether there is causal relationship between COVID-19 and SP-related traits. Mendelian randomization (MR) was a valid method for inferring causality.

Methods: Data was extracted from the COVID-19 Host Genetic Initiative and the UK Biobank without sample overlapping. The MR analysis was performed with inverse variance weighted, weighted median, MR-Egger, RAPS and CAUSE, MR-APSS. Sensitivity analysis was conducted with MR-Egger intercept test, Cochran's Q test, MR-PRESSO to eliminate pleiotropy.

Results: There was insufficient result in the MR-APSS method to support a direct causal relationship after the Bonferroni correction. Most other MR results were also nominally consistent with the MR-APSS result.

Conclusions: Our study first explored the causal relationship between COVID-19 and SP-related traits, but the result indicated that they may indirectly interact with each other. We highlighted that older people had better absorb enough nutrition and strengthen exercise to directly cope with SP during the COVID-19 pandemic.

KEYWORDS

COVID-19, sarcopenia, mendelian randomization, long COVID-19, aging

Introduction

The coronavirus disease 2019 (COVID-19) has evolved into an ongoing global pandemic affecting more than 600 million people, resulting in nearly 7 million deaths (1). Age, concurrent frailty and comorbidities were associated with higher risk of being positive for COVID-19, hospitalized and mortality (2). Meanwhile, accumulating evidence

suggests that COVID-19 survivors could experience various sequelae, mainly including weakness, arthromyalgia, depression, anxiety and memory loss (3). Due to the complicated pathogenesis of COVID-19, the extremely challenging pandemic has forced people to live with COVID-19, which means it is important to evaluate the relevance between COVID-19 and other comorbidities.

Sarcopenia (SP) is the loss of skeletal muscle mass associated with aging which causes an involution of muscle strength, and/or low physical performance (4). Skeletal muscle-related traits have been widely reported in both acute COVID-19 and post-acute sequelae of COVID-19 (5). Recent findings have shown that higher grip strength was associated with a lower risk of COVID-19 hospitalization and a better prognosis (6, 7). Another study reported that there was no significant difference in grip strength among COVID-19 patients with different severity after 12 weeks (8). A retrospective study showed that an acute skeletal muscle loss was evident in consecutive hospitalized patients with COVID-19 compared with those without COVID-19 and contributed to poor clinical outcomes (9). COVID-19 patients with SP had a higher number of persistent symptoms than patients without SP, but that was not statistically significant (10). These observational studies show that there appears to be a correlation between COVID-19 and SP, but it is inconsistent. These results also made it elusive to assess the causal relationship between COVID-19 and SP-related traits.

Mendelian randomization (MR) is a valid approach to infer possible causality between exposure and outcome, reducing bias from confounding factors and reverse causality in epidemiological studies (11). In the present study, we performed a two-sample MR to assess the potential causal effect between COVID-19 and SP-related traits using instrumental variables (IVs) from the summary genome-wide association study (GWAS) datasets. Overall, Results obtained in this study may help for identify the role of SP in the pandemic to reduce infection and attenuate clinical symptoms. It can also provide new insight into dealing with the post-acute sequelae of COVID-19 to treat or prevent the persistence of these long-lasting symptoms.

Materials and methods

Study design

The MR analysis was performed to explore the causality between COVID-19 and SP-related traits. In the forward MR analysis, COVID-19 was considered as the exposure and SP-related traits were considered as the outcome, whereas the reverse MR analysis investigated SP-related traits as the exposure and COVID-19 as the outcome. The following 3 main assumptions were satisfied (1): the IV is tightly associated to exposure; (2) the IV is not related to any confounder of the exposure-outcome connection; (3) the IV can only affect the outcome *via* the exposure (11).

Data source

In this MR study, GWAS summary statistics for COVID-19 phenotypes were extracted from the COVID-19 Host Genetic Initiative (HGI) (Round 5) (12). COVID-19 phenotypes included severity (4,792-1,054,664), hospitalization (8,316-1,549,095), susceptibility (3,2494-1,316,207). The COVID-19 cases were diagnosed by laboratory confirmation or by electrical health records (using physician notes or ICD), or self-reported COVID-19 infections from the patients. Severe COVID-19 cases were defined as patients who died or required respiratory support (including bilevel positive airway pressure, continuous positive airway pressure, intubation, or high-flow nasal cannula). The controls were defined as the individuals enrolled in the cohorts and not included as cases. The COVID-19 related data was retrieved from the European population except the UK Biobank participants. The data and more information can be found online.

All the GWAS summary statistics for SP-related traits were extracted from the UK Biobank. UK Biobank is a large-scale biomedical database and research resource, globally accessible to approved researchers undertaking vital research into the most common and life-threatening diseases, containing in-depth genetic and health information from 500 000 UK participants (13). Appendicular lean mass (ALM) has been proposed as a validated and reliable indicator of muscle mass in older adults (14). ALM was quantified by appendicular fat-free mass using the bioelectrical impedance analysis with 450,243 UK Biobank individuals and adjusted by appendicular fat mass and other covariates (15). Grip strength has been widely recognized as a significant indicator of SP (16). The hand grip strength was measured with a calibrated device in a simple and non-invasive way and adjusted for hand size (17). The UK Biobank grip strength data was adjusted for age, age^2, sex, sex × age, and sex × age^2 (13), including 461,089 individuals of European descent for right hand grip strength and 461,026 individuals for left hand grip strength (18). The summary-level statistics of walking pace were also obtained from the UK Biobank, including 459,915 individuals of European ancestry (18).

The genetic IVs of COVID-19 and SP-related traits were retrieved from publicly available database without sample overlapping. Ethical permission was not applicable to this study. More details for phenotype and previously ethical approval can be found in the original publications or GWAS (12, 15, 18).

MR analysis

Independent single nucleotide polymorphisms (SNPs) at the genome-wide significance level ($p < 5 \times 10^{-8}$) were selected as IVs for exposure (clumping $r^2 = 0.001$ and kb = 10,000) (19). Related data of IVs were also extracted from the outcome datasets without proxies. After harmonizing each pair of the exposure and outcome datasets, the inverse variance weighted (IVW) model were conducted to assess the causality. The IVW method can provide the most accurate and stable estimation of causal effects when all IVs were valid without directional pleiotropy (20). MR-Egger intercept test was employed to evaluate horizontal pleiotropy (21). MR pleiotropy residual sum and outlier (MR-PRESSO) was conducted to identify and obtain corrected results by removing pleiotropic IVs (22). After that, The IVW method was reperformed

to assess the robustness. Several sensitivity analyses were also performed, including weighted median estimation, MR-Egger regression, MR Robust Adjusted Profile Score (RAPS). The weighted median method could control the Type 1 error rates and provide consistent causal estimates when more than 50% IVs were valid and enrolled (23). MR-Egger regression could test IVs with considerable pleiotropy and heterogeneity, whereas this approach had poor statistical power and required larger sample size (21). RAPS could tackle the idiosyncratic pleiotropy even for up to hundreds of weak IVs (24). Heterogeneity across these selected IVs was assessed by Cochran's Q statistic. F statistic was calculated to test the strength of genetic IVs and genetic IV with F statistics > 10 was statistically considered as a strong instrument to minimize bias. The proportion of variance explained was also measured.

Actually, a small subset of SNPs were included as IVs for causal inference due to the strict inclusion and exclusion criteria, especially for COVID-19. MR Causal Analysis Using Summary Effect Estimates (CAUSE) and MR Accounting for Pleiotropy and Sample Structure simultaneously (MR-APSS) were employed to improve statistical power in the analysis, mainly by relaxing the threshold to utilize more IVs instead of only IVs at the genome-wide significance level (25, 26). Compared with other methods, the CAUSE method could avoid more false positives and calculate the shared (non-causal) effect, accounting for correlated pleiotropy induced by confounders or unmeasured shared factors. The q value was also calculated as an estimate of the proportion of pleiotropic variants (25). Default parameters were used in the CAUSE procedures ($p < 5 \times 10^{-3}$) (https://jean997.github.io/cause/ldl_cad.html). MR-APSS was a recently proposed method in 2022, accounting for sample structure as a major confounding factor including cryptic relatedness, population stratification, and sample overlap (26). We employed the same parameters as used in an originally example recommended by the authors ($p < 5 \times 10^{-5}$) (https://github.com/YangLabHKUST/MR-APSS/blob/master/MRAPSS_Rpackage_Tutorial.pdf).

Concerning multiple testing of COVID-19 and SP-related traits, we conservatively adjusted the p-values after the Bonferroni correction (p = 0.05/12 = 4.17E-03). The MR analyses were conducted with the R packages "MungeSumstats", "TwosampleMR", "CAUSE", "MRAPSS" in the R statistical software (Version 4.1.3).

Results

Stage 1: a bi-directional two-sample MR analysis

In the forward MR analysis, we analyzed the causal effect of COVID-19 on SP-related traits. The IVW results suggested that susceptibility, hospitalization and severity of COVID-19 had no causal effect on ALM, right hand grip strength, left hand grip strength and walking pace after the Bonferroni correction (Table 1; Figure 1). Consistently, the weighted median, the RAPS, the MR-Egger, the CAUSE, the MR-APSS methods further strengthened the hypothesis that COVID-19 was not a causal risk factor for SP-related traits (Table 2). Notably, several results indicated the nominal causality of COVID-19 on SP-related traits using the IVW and the RAPS methods, contradicting the results with the CAUSE, the MR-APSS methods. The median shared effect ranged from −0.04 to 0.03 in the CAUSE methods, suggesting rarely bias induced by horizontal pleiotropy. The low q indicated poor correlation between genetic effects of COVID-19 on SP-related traits.

In the reverse MR analysis, similar results were identified in the five MR tests, reflecting that SP-related traits had no causal effect on COVID-19 after the Bonferroni correction (Tables 3, 4). The median shared effect ranged from −3.02 to 0.36, meaning bias induced by pleiotropic variants.

Stage 2: sensitivity analysis

To evaluate the robustness of the above results, extensive sensitivity analyses were performed, including Cochran's Q test, MR-Egger intercept test, MR-PRESSO global test, and F statistics (Table 5). The Cochran's Q test identified 2 pair of the exposure and outcome datasets so that a random-effects model was applied for them. After removing outliers detected by MR-PRESSO (Supplementary Table 1), we only observed significantly horizontal pleiotropy of walking pace on hospitalization in MR-Egger intercept test. All the F statistics of selected IVs were above than 10, indicating that they were valid enough to minimize potential bias. The proportion of variance explained grew with the increasing IVs, especially in the MR-APSS, the CAUSE methods (Supplementary Table 2). Details of IVs were provided in Additional Tables.

Discussion

Based on the MR results in our analysis, we conservatively summarized that there was insufficient evidence to determine a causal link between COVID-19 and SP-related traits after the Bonferroni correction. Most MR results were also nominally consistent with the conclusion. We performed the first bi-directional two-sample MR analysis to evaluate causal relationship between COVID-19 and SP-related traits, using the MR-APSS method.

Actually, several studies with related themes were reported. Three MR studies indicated that genetic evidence did not support a significant causal effect between COVID-19 and telomere length (27–29), although the cohort study in UK Biobank showed that shorter telomere length was associated with higher risk of adverse COVID-19 outcomes (29). A MR study including 261,000 older participants estimated that telomere length would not affect grip strength, sarcopenia, or falls (30). Telomere length did not occupy a unique position in the causal relationship between COVID-19 and SP-related traits. Another three MR studies suggested that physical activity had no causal effect on COVID-19 outcomes after the Bonferroni correction, but the results nominally contradicted each other (31–33). Meanwhile, the observational study also reported a

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TABLE 1 Primary mendelian randomization estimates of COVID-19 on sarcopenia-related traits.

Exposures	Outcomes	IVW		Weighted median		MR-Egger		RAPS	
		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
susceptibility	ALM	-0.014(-0.041, 0.012)	0.287	-0.013(-0.043, 0.017)	0.381	-0.010(-0.079, 0.059)	0.821	-0.014(-0.043, 0.014)	0.314
susceptibility	grip strength (right)	0.026(-0.004, 0.057)	0.092	NA	NA	NA	NA	0.026(-0.007, 0.060)	0.123
susceptibility	grip strength (left)	-0.005(-0.035, 0.026)	0.772	NA	NA	NA	NA	-0.005(-0.037, 0.028)	0.787
susceptibility	walking pace	-0.020(-0.036, -0.004)	0.014	-0.010(-0.030, 0.010)	0.311	0.006(-0.064, 0.077)	0.877	-0.016(-0.036, 0.004)	0.110
hospitalization	ALM	-0.019(-0.036, -0.003)	0.024	NA	NA	NA	NA	-0.020(-0.038, -0.002)	0.032
hospitalization	grip strength (right)	0.009(0.002, 0.016)	0.015	0.008(-3.972e-4, 0.016)	0.062	0.003(-0.013, 0.019)	0.711	0.009(0.001, 0.016)	0.021
hospitalization	grip strength (left)	0.002(-0.005, 0.009)	0.540	4.071e-4(-0.008, 0.009)	0.925	-0.001(-0.018, 0.015)	0.888	0.002(-0.005, 0.009)	0.620
hospitalization	walking pace	-0.006(-0.012, 1.229e-4)	0.055	-0.003(-0.010, 0.004)	0.400	-2.331e-4(-0.014, 0.014)	0.976	-0.006(-0.012, 8.030e-4)	0.087
severity	ALM	-0.007(-0.015, 7.333e-4)	0.075	-0.005(-0.014, 0.005)	0.350	-0.002(-0.032, 0.028)	0.919	-0.007(-0.019, 0.005)	0.269
severity	grip strength (right)	0.006(0.001, 0.012)	0.016	0.007(6.797e-4, 0.013)	0.030	9.228e-4(-0.013, 0.015)	0.899	0.007(0.001, 0.012)	0.019
severity	grip strength (left)	0.002(-0.003, 0.007)	0.443	2.161e-4(-0.006, 0.007)	0.948	-0.002(-0.015, 0.012)	0.806	0.002(-0.004, 0.007)	0.515
severity	walking pace	-0.006(-0.013, 9.986e-4)	0.094	-0.003(-0.008, 0.003)	0.373	0.005(-0.012, 0.023)	0.594	-0.004(-0.011, 0.002)	0.151

NA occurred because only two valid instruments were included in the analysis.
Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.
COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score. NA, not applicable.

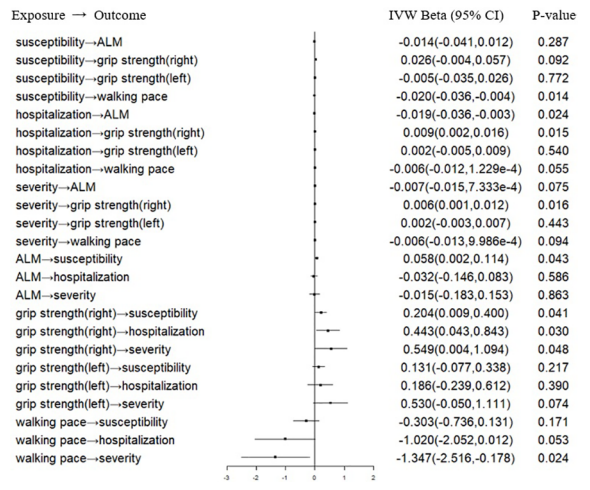

FIGURE 1
Forest plot of MR IVW analyses between COVID-19 and SP-related traits. IVW, inverse-variance weighted; CI, confidence interval; ALM, appendicular lean mass; COVID-19, coronavirus disease 2019. MR, mendelian randomization; SP, sarcopenia.

protective effect of objectively measured physical activity on COVID-19 outcomes (33). A meta-analysis of 7 randomized controlled trials showed that exercise could improve muscle mass, muscle strength, and walking speed in 3 months (34). A recent study including 435,504 UK Biobank participants observed a paradoxical result that lean mass index was not associated with COVID-19 phenotypes in a prospective cohort study while lean mass had a significant positive causal effect on COVID-19 outcomes in related MR analysis, which might require more robust MR Methods and better lean mass related data sources (35). Combined, due to ethical and practical constraints, cross-sectional designs and most low-quality randomized controlled trials could only provide correlation rather than causality. Meanwhile, although MR study could evaluate causality, it was also affected by quality of data sources and MR methods. Our MR results so far did not conflict with most findings of related MR studies or RCTs.

Undoubtedly, there were many clinical studies with high quality observed that COVID-19 was associated with acute SP in hospital and SP in long COVID-19 syndrome (9, 10). It was also observed that the presence of SP in the general population was positively correlated with the infection rate of COVID-19 (36), which contributed to poor clinical outcomes. Obviously, they appeared

TABLE 2 Mendelian randomization estimates of COVID-19 on sarcopenia-related traits using the CAUSE and MR-APSS methods.

Exposures	Outcomes	CAUSE			MR-APSS	
		Median causal effect (95% CI)	Median q (CI)	P causal vs sharing	Beta (95% CI)	p
susceptibility	ALM	0.03 (-0.53,0.48)	0.03 (0,0.22)	1	0.081 (-0.397,0.559)	0.740
susceptibility	grip strength (right)	0.01 (-0.16,0.18)	0.04 (0,0.24)	0.94	-0.295 (-0.993,0.404)	0.408
susceptibility	grip strength (left)	0.01 (-0.16,0.18)	0.04 (0,0.24)	0.99	-0.429 (-1.005,0.147)	0.144
susceptibility	walking pace	-0.01 (-0.16,0.13)	0.04 (0,0.23)	0.98	-0.124 (-0.702,0.455)	0.675
hospitalization	ALM	-0.04 (-0.2,0.09)	0.06 (0,0.24)	0.93	-0.069 (-0.735,0.598)	0.840
hospitalization	grip strength (right)	0 (-0.10,0.09)	0.03 (0,0.23)	0.55	-0.098 (-0.455,0.260)	0.593
hospitalization	grip strength (left)	0 (-0.10,0.10)	0.03 (0,0.22)	1.00	-0.257 (-0.592,0.077)	0.132
hospitalization	walking pace	0 (-0.06,0.05)	0.05 (0,0.25)	0.80	-0.045 (-0.306,0.216)	0.735
severity	ALM	0.02 (-0.15,0.07)	0.07 (0,0.26)	0.21	-0.011 (-0.465,0.443)	0.962
severity	grip strength (right)	-0.02 (-0.04,0.02)	0.08 (0.01,0.25)	0.37	-0.023 (-0.274,0.228)	0.858
severity	grip strength (left)	-0.02 (-0.05,0.03)	0.07 (0.01,0.25)	0.98	-0.150 (-0.386,0.097)	0.215
severity	walking pace	-0.01 (-0.04,0.04)	0.05 (0,0.25)	0.47	-0.118 (-0.269,0.034)	0.127

Sharing model better fit for the data in the CAUSE method.
Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.
COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; CAUSE, Causal Analysis Using Summary Effect Estimates; MR-APSS, MR Accounting for Pleiotropy and Sample Structure simultaneously.

TABLE 3 Primary mendelian randomization estimates of sarcopenia-related traits on COVID-19.

Exposures	Outcomes	IVW		Weighted median		MR-Egger		RAPS	
		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
ALM	susceptibility	0.058 (0.002, 0.114)	0.043	0.082 (-0.012, 0.176)	0.086	0.053 (-0.079, 0.186)	0.430	0.070 (0.009, 0.131)	0.024
ALM	hospitalization	-0.032 (-0.146, 0.083)	0.586	-0.080 (-0.268, 0.107)	0.402	-0.262 (-0.540, 0.016)	0.065	-0.017 (-0.146, 0.112)	0.800
ALM	severity	-0.015 (-0.183, 0.153)	0.863	-0.009 (-0.255, 0.238)	0.945	-0.299 (-0.692, 0.095)	0.138	-0.022 (-0.200, 0.157)	0.814
grip strength (right)	susceptibility	0.204 (0.009, 0.400)	0.041	0.124 (-0.172, 0.420)	0.411	0.342 (-0.406, 1.091)	0.372	0.142 (-0.070, 0.354)	0.191
grip strength (right)	hospitalization	0.443 (0.043, 0.843)	0.030	0.538 (-0.047, 1.123)	0.072	0.276 (-1.272, 1.824)	0.728	0.261 (-0.180, 0.701)	0.246
grip strength (right)	severity	0.549 (0.004, 1.094)	0.048	0.594 (-0.212, 1.400)	0.148	1.347 (-0.678, 3.373)	0.195	0.604 (0.035, 1.173)	0.038
grip strength (left)	susceptibility	0.131 (-0.077, 0.338)	0.217	0.024 (-0.286, 0.334)	0.880	0.288 (-0.586, 1.162)	0.520	0.060 (-0.187, 0.308)	0.632
grip strength (left)	hospitalization	0.186 (-0.239, 0.612)	0.390	0.378 (-0.284, 1.040)	0.263	0.067 (-1.768, 1.903)	0.943	0.186 (-0.282, 0.654)	0.436
grip strength (left)	severity	0.530 (-0.050, 1.111)	0.074	0.570 (-0.291, 1.432)	0.194	1.232 (-1.025, 3.489)	0.287	0.525 (-0.082, 1.133)	0.090
walking pace	susceptibility	-0.303 (-0.736, 0.131)	0.171	-0.238 (-0.881, 0.405)	0.469	1.441 (-0.751, 3.634)	0.205	-0.239 (-0.733, 0.256)	0.344
walking pace	hospitalization	-1.020 (-2.052, 0.012)	0.053	-1.022 (-2.273, 0.229)	0.109	4.373 (-0.413, 9.160)	0.081	-0.988 (-2.003, 0.026)	0.056
walking pace	severity	-1.347 (-2.516, -0.178)	0.024	-1.222 (-2.967, 0.524)	0.170	1.114 (-4.976, 7.204)	0.722	-1.405 (-2.690, -0.119)	0.032

Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.
COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score.

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TABLE 4 Mendelian randomization estimates of sarcopenia-related traits on COVID-19 using the CAUSE and MR-APSS methods.

Exposures	Outcomes	CAUSE			MR-APSS	
		Median causal effect (95% CI)	Median q (CI)	P causal vs sharing	Beta (95% CI)	p
ALM	susceptibility	0.26 (-0.25,0.94)	0.08 (0,0.28)	0.28	0.008 (0.002,0.015)	0.008
grip strength (right)	susceptibility	-0.7 (-6.8,1.99)	0.01 (0,0.18)	1	0.001 (-0.007,0.008)	0.836
grip strength (left)	susceptibility	-1.08 (-6.53,3.57)	0.01 (0,0.16)	0.97	-0.004 (-0.015,0.008)	0.506
walking pace	susceptibility	0.36 (-1.77,2.63)	0.04 (0,0.24)	0.57	0.019 (-0.005,0.043)	0.120
ALM	hospitalization	-0.42 (-7.28,4.85)	0.03 (0,0.2)	1	0.013 (-0.015,0.041)	0.348
grip strength (right)	hospitalization	-0.62 (-10.87,7.35)	0.02 (0,0.2)	1	0.016 (-0.021,0.052)	0.394
grip strength (left)	hospitalization	0.16 (-2.28,2.46)	0.03 (0,0.22)	0.90	0.019 (-0.008,0.046)	0.176
walking pace	hospitalization	-1.25 (-7.62,3.68)	0.03 (0,0.22)	0.75	-0.002 (-0.031,0.026)	0.887
ALM	severity	-1.18 (-11.66,6.27)	0.02 (0,0.2)	1	0.016 (-0.023,0.056)	0.416
grip strength (right)	severity	-0.4 (-4.38,3.2)	0.03 (0,0.22)	0.81	-0.037 (-0.089,0.016)	0.173
grip strength (left)	severity	-2.32 (-8.05,2.36)	0.08 (0,0.32)	0.25	-0.033 (-0.102,0.035)	0.343
walking pace	severity	-3.02 (-11.97,2.81)	0.09 (0,0.33)	0.18	-0.055 (-0.161,0.051)	0.307

Sharing model better fit for the data in the CAUSE method.
Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.
COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; CAUSE, Causal Analysis Using Summary Effect Estimates; MR-APSS, MR Accounting for Pleiotropy and Sample Structure simultaneously.

to form a dangerous vicious cycle. However, our MR results did not provide sufficient evidence to support a direct interaction between COVID-19 and SP, so that other factors may participate in this cycle to assist its formation. Malnutrition, reduced activity, distress and anxiety were likely to play indispensable roles in the cycle. Compared to discharged patients, patients with COVID-19 who died had higher nutritional and SP risk, lower albumin and total protein (37, 38). The muscle would atrophy significantly within two days after fixation and progress over the next 5 days (39). Patients with COVID-19 usually stay in hospital for more than 10 days (40, 41). During the acute period of COVID-19, common symptoms included depression mood (32.6%), anxiety (35.7%), insomnia (41.9%) (42). During the lockdown period, malnutrition, reduced activity, distress and anxiety were also prevalent (43–45), which was also positively correlated with susceptibility, hospitalization and severity of COVID-19 (46). These factors might act as competitive confounders in an observational study or mediating factors in a MR study. Cognitive impairment, frailty and other aging-associated diseases had the potential to serve as candidate factors (47, 48). On the basis of these observations and our MR results, we highlighted that older people should pay more attention to prevention, diagnosis, and treatment of SP instead of specific interactions between COVID-19 and SP, which would make it easier to break the dangerous vicious cycle and improve quality of life. In addition, targeting other mediating factors might also play a role. Nutritional supplementation and muscle training could provide significant improvement in muscle function and strength for COVID-19 survivors (49, 50).

In the COVID-19 pandemic, it has been reported that patients with more severe COVID-19 infection had a higher elevated serum creatine kinase level and more prone to rhabdomyolysis (51, 52), indicating that COVID-19 could cause damage to skeletal muscle. The mechanisms of individual organ damage might involve a systemic inflammatory response (53). In autopsy analysis, severe acute respiratory syndrome coronavirus 2(SARS-CoV2) virus particles were detected in organs including the heart, liver and kidney (54–56), while SARS-CoV virus particle could not be detected in skeletal muscle in SARS patients (57). Combined our MR results, we prefer that skeletal muscle injury is attributed to systemic inflammation instead of direct virus invasion. Nowadays, most countries and regions stopped requiring SARS-CoV-2 testing in public places, and mandatory quarantine (58). After vaccination, older people can adopt healthy lifestyles by increasing physical activity, improving glycemic control and body weight to reverse the situation in preparation for the next COVID-wave. Obviously, future studies across RCT or basic research from a variety of ethnic backgrounds are required to completely disentangle pathogenic mechanisms and develop effective interventions for attenuate clinical symptoms.

This study is the first bi-directional MR study to evaluate causal relationship between COVID-19 and SP-related traits, using the MR-APSS method. All parameters were set according to recommendations and thresholds were not relaxed. The COVID-19 related data was retrieved from the European population except the UK Biobank participants and the sarcopenia related data was extracted from the UK Biobank, which avoided sample overlapping and reduced bias. Extremely strict parameters and F statistic were used to ensure the validity of IV. CAUSE and MR-APSS were performed to include more IVs to improve statistical power, and consistent results were obtained. Nevertheless, there were several potential limitations in our MR analysis. First, all the data came from the European population therefore our result might only apply

TABLE 5 Sensitivity analysis of the primary causal association between COVID-19 and sarcopenia-related traits .

Exposures	Outcomes	Cochran's Q (P)	MR-Egger (P)	MR-PRESSO (P)	F
susceptibility	ALM	0.975	0.916	0.025	58.413
susceptibility	grip strength (right)	0.780	NA	<0.001	33.786
susceptibility	grip strength (left)	0.683	NA	0.019	33.786
susceptibility	walking pace	0.073	0.511	0.181	51.485
hospitalization	ALM	0.185	NA	<0.001	54.200
hospitalization	grip strength (right)	0.933	0.523	<0.001	88.914
hospitalization	grip strength (left)	0.480	0.680	<0.001	88.914
hospitalization	walking pace	0.476	0.444	0.022	87.276
severity	ALM	0.052	0.705	<0.001	68.426
severity	grip strength (right)	0.858	0.431	0.025	67.269
severity	grip strength (left)	0.697	0.576	0.040	67.269
severity	walking pace	0.028	0.247	0.007	69.587
ALM	susceptibility	0.123	0.945	0.095	101.024
ALM	hospitalization	0.064	0.073	0.022	101.717
ALM	severity	0.006	0.119	0.002	99.158
grip strength (right)	susceptibility	0.141	0.707	<0.001	47.652
grip strength (right)	hospitalization	0.141	0.826	0.019	47.716
grip strength (right)	severity	0.318	0.423	0.256	47.600
grip strength (left)	susceptibility	0.061	0.715	0.041	48.385
grip strength (left)	hospitalization	0.054	0.896	0.073	48.466
grip strength (left)	severity	0.752	0.530	0.764	48.466
walking pace	susceptibility	0.178	0.118	0.195	40.294
walking pace	hospitalization	0.038	0.030	0.039	40.294
walking pace	severity	0.289	0.423	0.321	40.294

NA occurred because only two valid instruments were included in the analysis.
COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score. NA, not applicable.

to Europeans. Second, it was difficult to completely remove mediation and pleiotropy so that we cannot rule out the possibility that mediating factors mediating the causality between COVID-19 and SP-related traits. Third, though the GWAS data was constantly being updated, better data sources were still required, especially for COVID-19.

Conclusion

The mechanisms between COVID-19 and SP have not yet been fully elucidated. Our MR results did not support a direct causal relationship after the Bonferroni correction, indicating that they may indirectly interact with each other through systemic inflammatory response and other diseases. Our new insights might inform better practices to recognize, evaluate and both prevent and treat SP in the COVID-19 pandemic. We highlighted that older people should absorb adequate nutrition and strengthen exercise to cope with SP and break the dangerous vicious cycle.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

CL had the idea and drafted the final manuscript, NL performed data analysis, YZ and BX created the tables. Other authors gave constructive suggestions during the process. TX and HL drafted the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1162936/full#supplementary-material

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Sarcopenia and osteosarcopenia among patients undergoing hemodialysis

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Background: Sarcopenia and osteoporosis are closely interconnected and associated with adverse health outcomes. Osteosarcopenia is the concurrent presence of the two conditions and has rarely been reported in hemodialysis patients. Whether hemodialysis patients with osteosarcopenia are at greater risk of mortality than those with either condition alone remains unknown. The aim of this study was to explore the prevalence of sarcopenia and its association with osteoporosis and to determine its impact on survival risk in hemodialysis patients.

Methods: A total of 209 adults undergoing hemodialysis were enrolled from the dialysis center in the West China Hospital of Sichuan University, and our study was registered at the Chinese Clinical Trial Register (number: ChiCTR2100043932). Muscle mass, handgrip strength, bone mineral density (BMD), and biochemical parameters were assessed. All deaths were recorded during a follow-up of 35.15 ± 15.37 months.

Results: Seventy-eight patients were diagnosed with sarcopenia, with a prevalence of 37.3%. After adjustment for potential confounders, age (OR=1.094, P <0.001), female sex (OR= 3.44, P =0.005), diabetes (OR=3.756, P =0.008), CRP (OR=1.09, P =0.015), serum magnesium (OR=0.755, p=0.042) and BMI (OR=0.701, P <0.001) were independently associated with sarcopenia. Among the 209 patients, 103 patients completed the BMD assessment. The prevalence of osteosarcopenia was 22.3%, while 20.4% of participants had sarcopenia alone and 12.6% had osteoporosis alone. The proportions of patients who died were 13.0% for nonsarcopenia&nonosteoporosis, 15.4% for osteoporosis alone, 47.6% for sarcopenia alone, and 52.2% for osteosarcopenia. Cox regression analysis showed that osteosarcopenia was independently associated with all-cause mortality (HR=3.74, 95% CI: 1.172-11.938), while osteoporosis alone and sarcopenia alone were not.

Conclusion: Patients undergoing hemodialysis had a high incidence of sarcopenia and osteosarcopenia, muscle mass and strength showed a significant association with BMD, and osteosarcopenia might have a powerful impact on mortality in those patients.

Clinical trial registration: http://www.chictr.org.cn/, identifier ChiCTR2100043932.

KEYWORDS

osteosarcopenia, Sarcopenia, osteoporosis, mortality, hemodialysis

Introduction

Sarcopenia (SP) refers to the gradual decline in both skeletal muscle function and mass and was first proposed in the 1980s (1). It is a progressive and systemic skeletal muscle disorder and has been reported to be associated with adverse clinical outcomes such as physical disability, falls,and all-cause mortality (2–5). Ageing, low nutrient intake, low activity and sedentary lifestyle are underlying causes of sarcopenia (6). There are multiple definitions of sarcopenia, including the European Working Group on Sarcopenia in Older People (EWGSOP), International Working Group on Sarcopenia (IWGS) and Asian Working Group for Sarcopenia (AWGS). All definitions are based on muscle mass, muscle strength, and physical performance but different cut-off points, so there is a lack of standard definitions in clinical practice (7). Sarcopenia occurs commonly in older people and is defined as an age-related disease. While it has also been found in other diseases, such as some cancers, endocrine diseases and metabolic disorders, disease-related sarcopenia is currently included in many research studies (8, 9). End-stage renal disease (ESRD) is a global health concern that has attracted increasing attention. Dialysis, as the main renal replacement therapy, accounts for 62.7% of ESRD patients, and the related complications are also gradually increasing (10). The accelerated process of protein wasting, multiple metabolic derangements, and nutrient deficiency may induce accelerated degradation of muscle mass and lead to sarcopenia in ESRD patients undergoing maintenance hemodialysis (MHD) (11, 12). Studies have reported that more than 20% of ESRD patients have sarcopenia, which is significantly higher than the prevalence in the general population (13, 14).

Muscle synthesis and bone metabolism seem to be interconnected. Skeletal muscle can secrete factors to regulate bone metabolism, such as myostatin, IGF-1, and FGF-2. Bone also functions as an endocrine organ to produce cytokines that act on muscle, including FGF23, sclerostin, and osteocalcin (15). Osteoporosis (OP) is a disease characterized by decreased bone mineral density (BMD) and damaged bone structure, leading to a risk of fractures (16). Skeletal muscle loss often coincides with low bone density, and the prevalence of osteoporosis among patients with sarcopenia is higher than that among those without sarcopenia. Osteoporosis is also an independent predictor of sarcopenia (17).

Osteosarcopenia (OS) is defined by the concurrent presence of osteoporosis and sarcopenia, a new concept proposed in 2009 by Duque and colleagues (18). It is worth noting that osteosarcopenia is a unique disease that involves the combination of low bone density and muscle mass, strength, and/or function. Currently, the criteria for osteosarcopenia are inconsistent, with some studies referring to osteopenia and sarcopenia, while others are defined as osteoporosis and sarcopenia (19). It has been reported that osteoporosis and sarcopenia share common risk factors, so osteosarcopenia is associated with aging, low nutritional status, low physical function and some chronic diseases (20). The coexistence of low bone mass and the low muscle mass, strength and function will contribute to a worse outcome than each one alone (21). The concurrent presence of osteoporosis and sarcopenia can affect each other and lead to a worsening of outcomes, such as higher risk of falls, fractures, and mortality (22, 23). Inoue et al. reported that the incidence of social frailty was 8.0% in robust patients, 11.8% in osteoporosis alone, 17.9% in sarcopenia alone, and 29.1% in osteosarcopenia (24). In addition, a study reported that the fracture risk is 3.5-fold higher than that in sarcopenia and osteoporosis alone (25).

The prevalence of bone metabolism disorders and aggravated muscle wasting in ESRD patients leads to a high incidence of osteosarcopenia. However, few studies have evaluated the association between sarcopenia and osteoporosis in MHD patients. And osteosarcopenia as a new concept, there are lacking of studies to explore its effect on clinical outcomes. Early detection of osteosarcopenia in MHD patients may improve prognosis and reduce mortality. Our study aimed to investigate the actual situation of sarcopenia and the relationship between sarcopenia and osteoporosis in MHD patients.

Materials and methods

Subjects

This prospective study was conducted in MHD patients from the dialysis center in the West China Hospital of Sichuan University between July 2018 and March 2020 (shown in Figure 1). The inclusion criteria were as follows (1): being under MHD for more than 3 months (2); at least 18 years of age; and (3) consent to participate in this study. The exclusion criteria were as follows (1): accepted anti-osteoporosis treatment in the past 6 months, such as bisphosphonates (2); patients for which BIA could not be performed (such as in patients who underwent pacemaker installation and amputation surgery); and (3) had other diseases affecting bone metabolism.

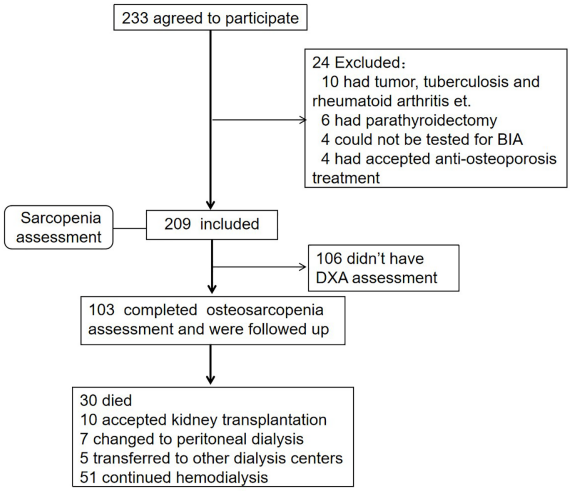

FIGURE 1
Flow diagram. A total of 209 participants had accepted sarcopenia assessment, and 103 completed the DXA test concurrently and were followed up for 35.15 ± 15.37 months.

Baseline data were collected between July 2018 and March 2020. The follow-up deadline was October 1, 2022. The endpoint was overall mortality, and censored events included transfer to another dialysis center, kidney transplantation, conversion to peritoneal dialysis, and survival at the deadline. Our study was registered at the Chinese Clinical Trial Register (http://www.chictr.org.cn/; ChiCTR2100043932), and was approved by the Ethics Committee of West China Hospital of Sichuan University (2020-446).

General data collection

General information was collected by medical records or questionnaires as follows: age, body mass index (BMI), dialysis vintage, previous osteoporosis fracture and other underlying conditions.

Laboratory biochemical index

Avoiding the influence of dialysate on results, blood samples were obtained before performing hemodialysis, and laboratory indicators included albumin, calcium, magnesium, phosphorus, parathyroid hormone (PTH), alkaline phosphatase (ALP), 25-hydroxyvitamin D [25(OH)D], and C-reactive protein (CRP). Serum calcium was adjusted by the equation: measured calcium (mmol/l) + 0.02x [40-serum albumin (g/dL)].

Anthropometric measurements

Body composition was estimated by the BIA method (InbodyS720, Biospace, Seoul, South Korea). The appendicular skeletal muscle mass index (ASMI) was calculated using the following formula: muscle mass of the four limbs (kg)/height^2 (m^2). Handgrip strength (HGS) was assessed on the non-fistula side using a digital grip strength dynamometer (CAMRY, EH101), three measurements were averaged and used in the analyses. Total hip, femoral neck, and lumbar spine BMD (g/cm2) measurements were performed using dual-energy X-ray absorptiometry (DXA) (GE Lunar, ME + 212243, USA).

Diagnosis of sarcopenia, osteoporosis and osteosarcopenia

Sarcopenia was defined as the loss of skeletal muscle mass and strength according to the AWGS criteria. The cut-off points of the ASMI were 7.0kg/m^2 for males and 5.4 kg/m^2 for females, and 26 kg for males and 18 kg for females for handgrip strength. Osteoporosis was diagnosed as T≤-2.5 measured by DXA, according to the World Health Organization (WHO) criteria. Osteosarcopenia is defined as the presence of sarcopenia combined with osteoporosis.

Statistical analyses

Continuous variables were presented as the mean ± SD or median and interquartile interval according to the distribution and percentages for categorical variables. The comparison of quantitative variables was performed using the T test or Mann–Whitney U test (two groups) and one-way ANOVA or Kruskal–Wallis test (three or more groups). Chi-square tests were used for qualitative variables. Logistic regression (Forwards: LR) was used to explore the independent factors associated with sarcopenia. Pearson's linear analysis was used to test the correlation between ASMI, HGS and BMD. Cox regression proportional hazards models were used to estimate the adjusted risk of mortality, after adjustment for age, sex, dialysis vintage, diabetes, cardiovascular disease, and fracture history et. $P < 0.05$ was considered statistically significant. Analyses were performed by SPSS Statistics 23 (IBM, Armonk, NY).

Result

Patient demographics

The studied sample comprised 209 patients (47.4% male), with a mean age of 58.45 ± 15.31 years (range, 21–88). In all, 78 (37.3%) participants presented sarcopenia. The characteristics of the patients are described in Table 1. Sarcopenia patients, in this study, were more likely to be female (p=0.01) and older (P <0.001), and had a lower BMI (P =0.006) than nonsarcopenia patients. Regarding the biochemical parameters, the sarcopenia group had higher CRP levels (P <0.001) and lower serum phosphorus (P =0.033), serum magnesium (P=0.004), and albumin (P=0.002) levels. The prevalence rates of fracture history (P =0.002) and diabetes (P =0.006) were higher in the sarcopenia group than that in the nonsarcopenia group.

Factors associated with sarcopenia

The above variables with P<0.1 were included in the multivariate logistical regression analysis. Age (OR=1.094, P <0.001), female sex (OR= 3.44, P =0.005), diabetes (OR=3.756, P =0.008), and CRP (OR=1.09, P =0.015) were independent risk factors for sarcopenia, and serum magnesium (OR=0.755, p=0.042) and BMI (OR=0.701, P <0.001) were protective factors for sarcopenia in our study, as shown in Table 2.

The prevalence of osteosarcopenia

Among the 209 patients, 103 patients completed the BMD assessment. According to the results, patients were divided into nonsarcopenia&nonosteoporosis (44.7%), osteoporosis alone (12.6%), sarcopenia alone (20.4%), and osteosarcopenia (22.3%). The characteristics of patients according to osteosarcopenia

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TABLE 1 Demographic and clinical characteristics of participants.

	sarcopenia (n=78)	nonsarcopenia (n=131)	p
Age(years)	66.92 ± 13.64	53.42 ± 14.01	<0.001*
Female, n (%)	50(64.1%)	60(45.8%)	0.01 *
Dialysis vintage(years)	5(3,10)	5(2, 8)	0.059
ASMI (kg/m^2)	5.39 ± 0.91	6.84 ± 1.19	<0.001*
HGS (kg)	13.4 ± 5.14	24.17 ± 8.89	<0.001*
BMI (kg/m^2)	21.26 ± 2.82	22.79 ± 3.35	<0.001*
Calcium(mmol/L)	2.32 ± 0.27	2.28 ± 0.23	0.203
Phosphorus(mmol/L)	1.76 ± 0.55	1.91 ± 0.46	0.033 *
PTH (pmol/L)	31.78 (13.56, 55.99)	33.68 (19.56, 52.56)	0.329
Magnesium (mmol/L)	1.03 ± 0.14	1.1 ± 0.19	0.004*
ALP (IU/L)	100.5(73,135.25)	82(65,101)	0.21
25(OH)D (nmol/L)	50.3 ± 22.23	53.39 ± 22.74	0.357
CRP(mg/L)	5.22(2.85,8.93)	3.22(1.97,5.65)	<0.001*
Albumin (g/L)	40.41 ± 4.58	42.29 ± 4.01	0.002*
Fracture history, n (%)	16(20.5%)	8(6.1%)	0.002*
Diabetes, n (%)	29(37.2%)	26(19.5%)	0.006*
Coronary artery disease, n (%)	19(24.4%)	20(15.3%)	0.103

ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase; 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein *p<0.05

categories are described in Table 3. Osteosarcopenia patients had significantly higher rates of fracture history and mortality and a lower albumin level. Sarcopenia alone patients were older and had higher CRP levels and rates of diabetes. The 25(OH)D levels were significantly lower in osteoporosis alone patients.

Correlation between sarcopenia and osteoporosi

As described above, 63.9% (23/36) of patients with osteoporosis had sarcopenia in this cohort, and the risk of sarcopenia was 3.875-

TABLE 2 Factors associated with sarcopenia.

	Logistic regression		
	OR	95%CI P	
Age (per one year increase)	1.094	1.061-1.127	<0.001*
Female	3.44	1.438-8.227	0.005*
BMI (per one kg/m^2 increase)	0.701	0.596-0.823	<0.001*
CRP (per one mg/L increase)	1.09	1.017-1.169	0.015*
Magnesium (per 0.1 mmol/L increase)	0.755	0.725-0.989	0.042*
Phosphorus (per one mmol/L increase)	–	–	0.656
Albumin (per one g/L increase)	–	–	0.987
Fracture history	–	–	0.251
Diabetes	3.756	1.416-9.963	0.008*
Dialysis vintage (per one year increase)	–	–	0.5

BMI, Body mass index; CRP, C-reactive protein.
*p<0.05.

TABLE 3 Prevalence of patient classification based on osteosarcopenia.

	NONS n=46	OP alone n=13	SP alone n=21	OS n=23
Age (year)	52.04 ± 15.24	60.7 ± 17.76	68.2 ± 14.59*	66.82 ± 10.64
Female, n (%)	24 (52.2%)	12 (92.3%)‡	9 (42.9%)†§	19 (82.6%)‡
Dialysis vintage (years)	5 (3,6)	5 (2.5,8.5)	8 (4.2,10)	4 (3,8)
BMD (g/cm^2)				
lumbar spine	1.07 ± 0.17†§	0.81 ± 0.15*‡	1.14 ± 0.3†§	0.84 ± 0.14*‡
femoral neck	0.83 ± 0.12†§	0.61 ± 0.07*‡	0.78 ± 0.11†§	0.64 ± 0.1*‡
total hip	0.88 ± 0.13†§	0.64 ± 0.08 *‡	0.85 ± 0.13†§	0.68 ± 0.11*‡
BMI (kg/m^2)	22.85 ± 3.23	23.65 ± 4.41§	22.6 ± 3.34	21.25 ± 2.67†
ASMI (kg/m^2)	6.77 ± 1.21‡	6.15 ± 0.76§	5.71 ± 0.85*	5.08 ± 0.92*†
HGS (kg)	22.91 ± 8.77‡	19.14 ± 5.73§	15.07 ± 5.04*	12.34 ± 4.97*†
Calcium (mmol/L)	2.45 ± 0.25	2.34 ± 0.25	2.36 ± 0.21	2.35 ± 0.22
Magnesium (mmol/L)	1.07 ± 0.15	1.12 ± 0.14	1.01 ± 0.15	1.05 ± 0.14
Phosphorus (mmol/L)	1.82 ± 0.39	1.93 ± 0.46‡	1.79 ± 0.59†	1.87 ± 0.52
25 (OH)D (nmol/L)	53.79 ± 20.49†	37.85 ± 9.81*	49.16 ± 18.72	49.57 ± 20.6
PTH (pmol/L)	28.89 (15.19,56.76)	18.36 (13.62,37.3)	27.07 (7.95,59.41)	22.56 (11.42,43.29)
ALP (IU/L)	79 (58.5,95.5)	77 (63,108.5)	99 (75,133.5)	77 (62,115)
CRP (mg/L)	4.79 (2.48,7.28)	3.18‡ (1.37,6.84)	5.71†§ (4.18,18.55)	3.13‡ (2.21,6.23)
Albumin (g/L)	42.51 ± 4.46§	41.89 ± 3.91	40.82 ± 6.32	40.93 ± 3.51*
Diabetes, n (%)	11 (24.4%)	1 (7.7%)‡	11 (52.4%)†	8 (34.8%)
Cardiovascular disease, n (%)	6 (13.1%)	2 (15.4%)	8 (38.1%)	3 (13%)
Fracture history, n (%)	2 (4.3%)†§	4 (30.8%) *	5 (23.8%)	9 (39.1%) *
Mortality, n (%)	6 (13.0%)‡§	2 (15.4%)	10 (47.6%) *	12 (52.2%) *

*, significant difference from normal; †, significant difference from osteoporosis only; ‡, significant difference from sarcopenia only; §, significant difference from osteosarcopenia.
NONS, nonosteoporosis&nonsarcopenia; OP, osteoporosis; SP, sarcopenia; OS, osteosarcopenia; BMD, bone mineral density; ASMI, appendicular skeletal muscle mass index; HGS, handgrip strength; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase; 25 (OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein.

fold higher in patients with osteoporosis than in those without osteoporosis. There was a significant, positive correlation between ASMI and BMD of the lumbar spine (r = 0.346), femoral neck (r = 0.407), and total hip (r = 0.468) (P < 0.001 for all). Handgrip strength was significantly correlated with the BMD of the femoral neck (r = 0.296, P = 0.002) and total hip (r = 0.253, P = 0.011) but not with the BMD of the lumbar spine, as shown in Figure 2.

Postoperative survival analysis

The respective proportions of patients in this study who died over a mean follow-up period of 35.15 ± 15.37 months were 13.0% for nonsarcopenia&nonosteoporosis, 15.4% for osteoporosis alone, 47.6% for sarcopenia alone, and 52.2% for osteosarcopenia. Cox proportional regression analysis showed that osteosarcopenia and sarcopenia alone had an increased hazard for mortality in unadjusted models. After adjustment for age and sex, the increase hazard was disappeared in sarcopenia alone, while remained significant for osteosarcopenia patients (HR=3.74, 95% CI: 1.172-11.938), even further adjusted dialysis vintage, diabetes, cardiovascular disease, and fracture history et. (shown in Table 4)

Discussion

The occurrence of sarcopenia in ESRD have attracted the worldwide attention nowadays (26, 27). Due to the different diagnostic criteria, there was great variability in the prevalence of sarcopenia in hemodialysis patients, approximately 13.7%-73.5% (28). A standardized diagnostic method for sarcopenia is important for clinical diagnosis and research in the future. According to the AWGS criteria, sarcopenia was diagnosed in 37.3% of the patients in our study, and 28% for male 50% for female respectively. Sex hormones on muscle function have been studied, different effects of androgens and estrogens lead to differences in skeletal muscle

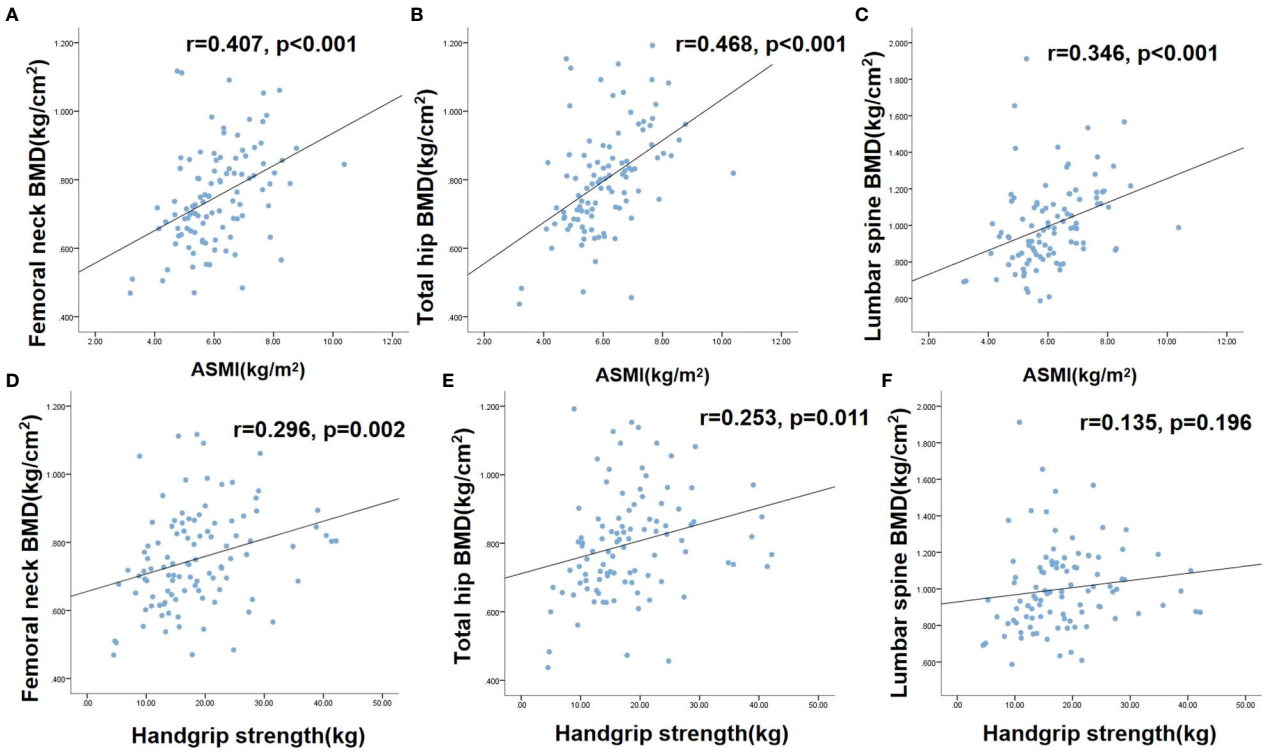

FIGURE 2
The correlations between sarcopenia and osteoporosis Figure 1. **(A)** correlation between femoral neck BMD and ASMI; **(B)** correlation between total hip BMD and ASMI; **(C)** correlation between lumbar spine BMD and ASMI; **(D)** correlation between femoral neck BMD and handgrip strength; **(E)** correlation between total hip BMD and handgrip strength. **(F)** correlation between lumbar spine BMD and handgrip strength. BMD, Bone mineral density; ASMI, Appendicular skeletal muscle mass index.

morphology and function. Testosterone is widely believed to affect muscle protein synthesis and muscular regeneration to increase muscle mass and strength (29, 30). The effect of estrogens on muscle is still in the exploratory phase, and the evidence that estrogen has a significant effect on muscle mass is lacking (31). Study have reported that estrogens have anti-catabolic effect on skeletal muscle, and hormone replacement therapy can preserve muscle mass (32). However, the effect of estrogen on skeletal muscle is not as well recognized as that of testosterone. HbA1c levels were found to be related to skeletal mass and to be an independent factor of

TABLE 4 Cox regression models for mortality according to osteosarcopenia.

Model		COX regression analysis	
		HR	P
1	OP alone	1.12 (0.225-5.576)	0.890
	SP alone	3.146 (1.132-8.742)	0.028*
	OS	4.345 (1.626-11.609)	0.003*
2	OP alone	0.911 (0.162-5.131)	0.916
	SP alone	1.987 (0.618-6.394)	0.249
	OS	3.63 (1.256-10.486)	0.017*
3	OP alone	0.841 (0.135-5.233)	0.853
	SP alone	0.356 (0.527-5.951)	0.356
	OS	3.74 (1.172-11.938)	0.026*

Model 1, unadjusted.
Model 2, adjusted for age, sex.
Model 3, adjusted Model 2+ dialysis vintage, diabetes, cardiovascular disease, fracture history.
OP, osteoporosis; SP, sarcopenia; OS, osteosarcopenia.
*p<0.05

sarcopenia in a multicenter cross-sectional study (33). Consistent with this study, the incidence of sarcopenia was higher in patients with diabetes, and diabetes was an independent contributor to sarcopenia in hemodialysis patients (34). However, the reason for the high incidence of sarcopenia in diabetic patients is not clear. One of the explanations is that insulin resistance is involved in skeletal muscle protein breakdown, and impaired insulin/IGF-I signaling could lead to a drop in phosphorylated Akt and muscle loss (35–37). Some studies reported that the level of insulin was inversely related to handgrip strength, and patients with insulin resistance had lower handgrip strength (38, 39). In addition to insulin, glucose may also be closely related to skeletal muscle maintenance, and hyperglycemia could inhibit muscle regeneration and accelerate sarcopenia (40). Serum magnesium was observed to be a protective factor against sarcopenia in our study. Magnesium is involved in the synthesis of protein and ATP and plays a key role in muscle metabolism and function (41, 42). A cross-sectional study including 396,283 participants also reported that higher serum magnesium was associated with lower odds of sarcopenia (43). Scott et al. investigated that magnesium supplementation was a positive predictor of change in muscle mass ($\beta = 0.07$, P=0.02), and it can ameliorate the progression of sarcopenia in older individuals (44). An observational study involving 156,575 patients and a cross-sectional study of 2570 women also showed that dietary magnesium is positively associated with skeletal muscle mass and grip strength (45, 46). Only one RCT including 139 healthy older women reported that 300 mg magnesium supplementation for 3 months would improve muscle mass (47). In the light of these studies, we expect more RCTs in the coming years to elucidate the effect of magnesium intake on sarcopenia.

It has been widely assumed that bone and skeletal muscle are interrelated tissues with shared mechanical and molecular mechanisms and are regulated by many common factors. Bone and muscle communicate in the "bone-muscle unit" through paracrine and endocrine signals to coordinate their development (48, 49). Bone metabolism disorder also accelerates the progression of sarcopenia in patients on MHD. The loss of muscle mass and function can also promote osteoporosis in reverse. In our study, skeletal muscle mass and strength were positively associated with BMD, while a correlation was not found between lumbar spine BMD and grip strength. This may be because aortic calcification is common in dialysis patients, which affects the measurement of lumbar spine BMD. Therefore, the lumbar spine is not a good site for bone density measurement in dialysis patients, especially those with aortic calcification. Our study showed that the rate of sarcopenia in patients with osteoporosis was 3.875 times than in those without osteoporosis. Yoshimura et al. found that patients with osteoporosis were 2.99 times more likely to develop sarcopenia than people without osteoporosis in four years (17). A systematic analysis of 38 studies including 224,321 participants suggested that sarcopenia increased the risk of osteoporosis by 3.06 times. In addition, this systematic analysis also included 7 trials involving 171,514 participants revealed that each standard deviation (SD) increase in relative appendicular skeletal muscle mass (RASM) was associated with a significant 35% reduction in osteoporosis risk (50). Ahn et al. reported that left hand grip strength was significantly associated with osteoporosis in female aged 60–69 years, while not found in aged 70 years and in the right hand (51).

Reduced muscle mass and strength, and low bone density are significantly associated with falls, fractures and mortality, which would contribute to a decline in the quality of life and an increase in the economic burden. Osteosarcopenia was proposed as a new concept to strengthen the awareness of healthy bone and muscle. At present, there are few studies on the epidemiology of osteosarcopenia, especially in hemodialysis patients. In our study, 22.3% of the patients presented with osteosarcopenia, higher than 5.8% in the general population and 17.2% in patients with kidney transplantation (52, 53). The age difference between osteosarcopenia and sarcopenia was smaller than that between osteoporosis patients, indicating that the progression from sarcopenia to osteosarcopenia is faster than that from osteoporosis. Muscle wasting could accelerate the loss of BMD; in terms of the pathological mechanism, mechanical contraction of muscles stimulates bone formation and prevents bone mineral loss (54, 55). Osteosarcopenia is a strong predictor of morbidity and mortality, as it could lead to lower quality of life and increased falls and fractures. A meta-analysis suggested that osteosarcopenia was significantly associated with the risk of mortality (OR 1.66, 95% CI 1.23–2.26), fracture (OR 2.46, 95% CI 1.83–3.30), and falls (OR 1.62, 95% CI 1.28–2.04) compared with nonosteosarcopenia (56). After adjusting for age, sex, diabetes, cardiovascular disease, and fracture history, osteosarcopenia remained an independent risk factor for all-cause mortality, while it disappeared in sarcopenia alone. Our study suggested that the coexistence of sarcopenia and osteoporosis increased the risk of all-cause death, meaning both bone and muscle are equally important. We expect more trials with large sample sizes to explore the prevalence of osteosarcopenia and its impact on fracture and death in hemodialysis patients.

Currently, scholars have a deep understanding of osteoporosis in dialysis patients, while the understanding and attention of sarcopenia, especially osteosarcopenia, are still insufficient. As a result, sarcopenia and osteoporosis tend to occur simultaneously for one person, and both are strongly associated with poor health outcomes. Therefore, attention should be given to muscle health as well as bone problems. Exercise and nutrition are critical to osteosarcopenia. The majority of studies have found that exercise may exert a beneficial effect on osteosarcopenia by improving muscle mass, strength and function, especially resistance training, which can increase the cross-sectional area and size of muscle fibers (57–59). A healthy diet plays an essential role in muscle and bone maintenance and preventing the progression of osteosarcopenia. It has been observed that proteins rich in leucine are more important in protein synthesis, and leucine supplementation increases anabolism and lean body mass (60, 61). For patients with dialysis, an increased amount of protein (1.0-1.2g/kg/day) is recommended (62). Vitamin D supplementation for sarcopenia remains controversial. Study has reported that 1,25-dihydroxyvitamin D can bind to vitamin D receptors on skeletal muscle to regulate the number and volume of type II muscle fibers and improve skeletal muscle strength and mass (63). A meta-analysis of 30 RCTs involving 5615 individuals showed that vitamin D

supplementation had a small positive effect on muscle strength, but not found on muscle mass. And for people who presented low 25-hydroxyvitamin D level and aged 65 years or older, the effect on muscle strength was even more pronounced (64). While, a recent meta-analysis of 10 RCTs reported that vitamin D monotherapy did not improve any sarcopenia in ages >50 years old (65). We expect additional studies to explore it. Additionally, improving clinicians' awareness of osteosarcopenia and testing muscle mass and grip strength along with bone mineral density examination will contribute to determining the presence of osteosarcopenia, taking effective intervention measures to prevent disease progression, and reducing the occurrence of poor outcomes.

Our study also had some limitations. First, our study was a single-center study with a small sample size; therefore, the study subjects cannot be generalized to all hemodialysis patients. Second, the results of the BIA test were affected by body water, and although the BIA test was performed after dialysis, it may still affect the measurement.

Conclusion

Sarcopenia is highly present in MHD patients and is also consistently positively associated with osteoporosis. Osteosarcopenia is not rare and has a greater risk of mortality than either sarcopenia alone or osteoporosis alone. Early comprehensive evaluation and treatment of bone disorders and muscle mass and function loss is necessary. In addition, more clinical trials on the influence of osteosarcopenia and therapeutic interventions for muscle anabolism and bone disorders in dialysis patients are needed in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of West China Hospital of Sichuan University, approval number (2020-446). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ conceived and designed the study. TX completed the literature searches and data analysis. TX drafted the manuscript. LZ and PF revised the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The effects of exercise training on body composition in postmenopausal women: a systematic review and meta-analysis

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Introduction: We conducted a systematic review and meta-analysis to investigate the effect of exercise training on body composition outcomes in postmenopausal women.

Methods: PubMed, Web of Science, CINAHL, and Medline were searched to identify the randomized controlled trials which evaluated effect of exercise training versus control in postmenopausal women. Standardized mean differences (SMD), weighted mean differences (WMD) and 95% confidence intervals (95% CIs) were calculated using random effects model.

Results: One hundred and one studies involving 5,697 postmenopausal women were included in the meta-analysis. Results indicated that exercise training effectively increased muscle mass/ volume, muscle and fiber cross-sectional area and fat-free mass, and decreased fat mass, body fat percentage, waist circumference and visceral fat. Furthermore, subgroup analyses results revealed that aerobic and combined training had greater beneficial effects on fat mass outcomes, whereas resistance and combined training had greater beneficial effects on muscle mass outcomes.

Discussion: Overall, our results revealed that exercise training is effective for improving body composition in postmenopausal women. To be specific, aerobic training is effective on fat loss, whereas resistance training is effective on muscle gain. However, combination of aerobic and resistance trainings may be considered a viable strategy to improve body composition in postmenopausal women.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42021283425.

KEYWORDS

exercise training, body composition, fat mass, muscle mass, menopause

Introduction

The postmenopausal phase in women is a critical stage of aging represented by unavoidable changes in the production of endogenous sex hormones, and results hormonal imbalance (1–3). These hormonal changes are associated with increased risks for developing obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases (CVD) (4–6). During the postmenopausal stage, women may experience a series of physiological changes in several cardiometabolic health outcomes (7, 8). Some of the common changes include increased body weight and fat mass, especially redistribution of body fat toward abdominal areas, which contributes to the development of negative cardiometabolic outcomes (9–11). In this regard, menopausal age in women may be associated with increased prevalence of obesity and obesity-related disorders, including metabolic syndrome (12). In the United States, the prevalence of obesity is approximately 65% among women aged 40 to 65 years (13).

Insufficient physical activity is associated with poor menopausal outcomes and increased health risk during the postmenopausal stage of life (14), while lifestyle interventions with either type of exercise is appropriate and effective in promoting the physiological or psychological outcomes in postmenopausal women (15). As a non-pharmacological strategy, exercise training has been shown to be effective, safe, and important to attenuate the age-induced health adversities, and may attribute to improve cardiometabolic outcomes (16, 17). The beneficial effects of exercise intervention are mainly relied on the type of exercise. Resistance training (RT) is known for improving the muscle strength and mass, as well as benefitting the sarcopenia-related phenotypes (18–21). Aerobic training (AT) is known for improving pulmonary function and decreasing fat mass, especially visceral fat in older adults (22–24). However, it is claimed that AT also improves muscle function and lead to skeletal muscle hypertrophy. Therefore, AT also considered as a viable training method to combat sarcopenia in the elderly population (25–27). Besides, previous meta-analyses have confirmed the beneficial effects of RT on muscle mass (28, 29) and AT on fat mass (22) in older adults.

Although several meta-analyses have explored the effects of exercise training in older adults, yet no meta-analysis focused on postmenopausal women and their physical fitness status. Given that this population is affected by hormonal imbalance during aging, such hormonal changes are associated with poor outcomes in health and fitness related variables. The aim of this systematic review and meta-analysis was to elucidate the effects of exercise training on body composition, including muscle mass, fat-free mass (FFM), fat mass, body fat percentage, waist circumference, and visceral fat in postmenopausal women. Subgroup analyses were conducted for the variables, including age of participants, and duration and type of exercise training (aerobic, resistance, and combined) to identify the influential variable and to emphasize the practical and clinical importance of exercise.

Methods

This systematic review and meta-analysis was conducted in accordance with the latest guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (30), and the Cochrane Handbook of Systematic Reviews of Interventions (31). This study was registered with PROSPERO International prospective register of systematic reviews (ID: CRD42021283425).

Systematic search strategy

A systematic search was conducted in electronic databases, including PubMed, Web of Science, CINAHL, and Medline for research published from inception to October 2021 to identify original articles using the following search strategy: ("menopausal" or "post menopause" or "post-menopause" or "menopause" or "elderly women" or "older women") AND ("exercise" or "exercise training" or "physical activity"). The search strategy was adapted for each database and was conducted using "AND" and "OR" Boolean operators. When available in the respective databases, limitations were applied for English language,

human participants, article/document type, and randomized controlled trials. In addition, reference lists of all retrieved records and previous meta-analyses (32, 33) were screened for relevant articles. After removing duplicate publications, the titles, abstracts, and keywords of the remaining studies were screened to assess the study eligibility for full-text review against inclusion and exclusion criteria. Then, the full-texts of the studies that met criteria were further screened. The search strategy and screening processes were conducted independently by two authors (AM and MS), and any disagreements were resolved through discussion with another author (MKh).

Inclusion and exclusion criteria

According to the PRISMA latest guidelines (30) and our study purpose, we have followed these criteria to include or exclude the articles. Inclusion criteria were as follows: (a) English language, peer-reviewed articles; (b) randomized controlled trials that included exercise training versus non-exercise (control) groups; (c) studies on postmenopausal women; (d) studies measured the main outcomes at baseline and post-intervention; and (e) intervention durations ≥ 4 weeks. In order to maximize generalizability, participants included middle-aged to older women who were postmenopausal, ranging from healthy (absence of disease diagnosis) to frail with chronic diseases. Exercise training modalities included any mode of exercise training, such as aerobic training, resistance training, combined training, functional training, yoga, high-intensity interval training (HIIT) and Tai chi. For the main outcomes, studies were included that measured at least one of the following body composition item: muscle mass and volume, muscle and fiber cross-sectional area (CSA), fat-free mass (FFM) (or lean mass if FFM was not available), fat mass, body fat percentage, waist circumference, and visceral fat. Body composition outcomes were measured by magnetic resonance imaging (MRI), computerized tomography (CT), ultrasound, densitometry, dual energy X-ray absorptiometry (DXA), hydro-densitometry, or In-body and/or whole-body air plethysmography (BodPod) (34). Waist circumference was measured by tape and recorded in cm or inches. Exclusion criteria include non-English, non-full text articles (conference abstracts), intervention with a duration of less than 4 weeks, and non-original studies.

Data extraction and synthesis

Two reviewers (A H M and M H S) independently extracted the following data from each included study: 1) study characteristics, including study design and year of publication; 2) participant characteristics, including sample size, biological sex, health status, age, and body mass index (BMI); 3) intervention characteristic, including training type, intensity, frequency, duration; and supervision of exercise sessions; 4) outcome variables and assessment methodologies; 5) pre- and post-intervention means and standard deviations (SD), or mean changes and their SD values for outcomes. When required, the means and SDs were calculated from the reported standard errors, medians, ranges and/or interquartile ranges as described previously (31, 35, 36). In addition, when required, Getdata Graph Digitizer software was used for extracting data from figures (37). For studies with multiple intervention arms, all comparisons were included and subsequently the sample size of the repeated intervention was divided by the number of comparisons to avoid double counting. Furthermore, for studies that did not provide sufficient information, we have contacted the corresponding author of the relevant articles.

Quality assessment and sensitivity analysis

The methodological quality for each included study was assessed by two independent reviewers (AM and MS) using the Physiotherapy Evidence Database (PEDro) tool (38), and any disagreements were resolved through discussion with another author (MKh). This tool examined the following domains: eligibility criteria, random allocation of participants, allocation concealment, group similarity at baseline, blinding of participants, blinding of intervention providers, assessors blinded, outcome measures assessed in 85% of participants, intention-to-treat analysis, reporting of between groups statistical comparisons and point measures, and measures of variability reported for main effects. However, we excluded 2 items including blinding of participants and intervention providers because these could not feasibly be blinded with regard to assigned exercise conditions during studies, and this may not influence the quality of studies (39). Therefore, study quality was assessed based on the remaining 9 items. Each source of bias was judged as low, high, or unclear (due to insufficient detail) (Supplementary Table 2). In addition, sensitivity analyses were performed by omitting each study individually to determine whether results changed significantly.

Statistical analysis

Meta-analysis was conducted using random effects models using the DerSimonian and Laird approach (39) to calculate standardized mean differences (SMD) or weighted mean differences (WMD) and 95% confidence intervals (CIs) for comparing the effects of exercise training versus control on muscle mass and volume, muscle and fiber CSA, FFM, fat mass, body fat percentage, visceral fat mass, and waist circumference. In addition, several sub-group analyses were performed based on age (middle-aged: <65yrs and older adults: ≥65yrs), type of training (aerobic, resistance, combined) and intervention duration (medium-term: ≤16 weeks, long-term: >16 weeks). Subgroup analyses were performed when there were more than 3 interventions for each subgroup. Interpretation of effect sizes was conducted using Cochrane guidelines as follows: 0.20–0.49 indicating small effect size, 0.5–0.79 indicating medium effect size, and >0.8 indicating large effect size (40). Statistical heterogeneity was evaluated using Cochran Q tests and I^2 statistics as follows: 25% indicating low heterogeneity, 50% indicating moderate heterogeneity, and 70% indicating high heterogeneity (41). Publication bias was assessed with visual interpretation of funnel plots and Egger's tests as secondary

determinants of bias at a cut-point of p<0.10 (42). In addition, trim and fill correction was used to address the potential effects of publication bias where relevant (43).

Results

Included study characteristics

The search strategy retrieved 990 records from PubMed, 1,290 records from Web of Science, 942 records from CINAHL, and 1,292 records from MEDLINE. After examination for duplicates, 1,998 articles were excluded, and then 2,223 articles were excluded after reviewing the titles and abstracts. A total of 294 articles were identified for full-text assessment based on inclusion and exclusion criteria. An additional 196 articles were excluded due to the reasons presented in Figure 1. Finally, 101 articles of randomized controlled trials with parallel arm-trials were included in the meta-analysis (Figure 1).

Participant characteristics

A total of 5,697 postmenopausal women were included in the meta-analysis. The mean age of participants was ranged from 51 to ~89 yrs., and the mean BMI was ranged from 21 to 34 kg.m^2. Sample size of individual studies was ranged from 14 to 320 participants. To increase the generalizability of our meta-analysis results, postmenopausal women regardless of their health status, comprised a wide range of health (absence of disease) and chronic disease characteristics (metabolic diseases, cardiovascular diseases, cancer, and osteoporosis) were included. Full details of participant characteristics are summarized in Supplementary Table 1.

Intervention characteristics

Exercise training characteristics are summarized in Supplementary Table 1. All included studies compared the effects of exercise training versus a control group using random allocation. Intervention durations of included studies was ranged from 4 weeks to 18 months, while frequency of exercise sessions was ranged from 1 to 7 per week, with three sessions being the most common. For type of exercise training, most of the included studies conducted aerobic, resistance, or combined training, and others used water-based exercise, yoga, Tai chi, Pilates, yoga and Korean dance, and functional training. Exercise training was supervised in several studies, while other studies followed both supervised and unsupervised exercise training during the intervention period. However, supervision details were not clearly reported in few studies.

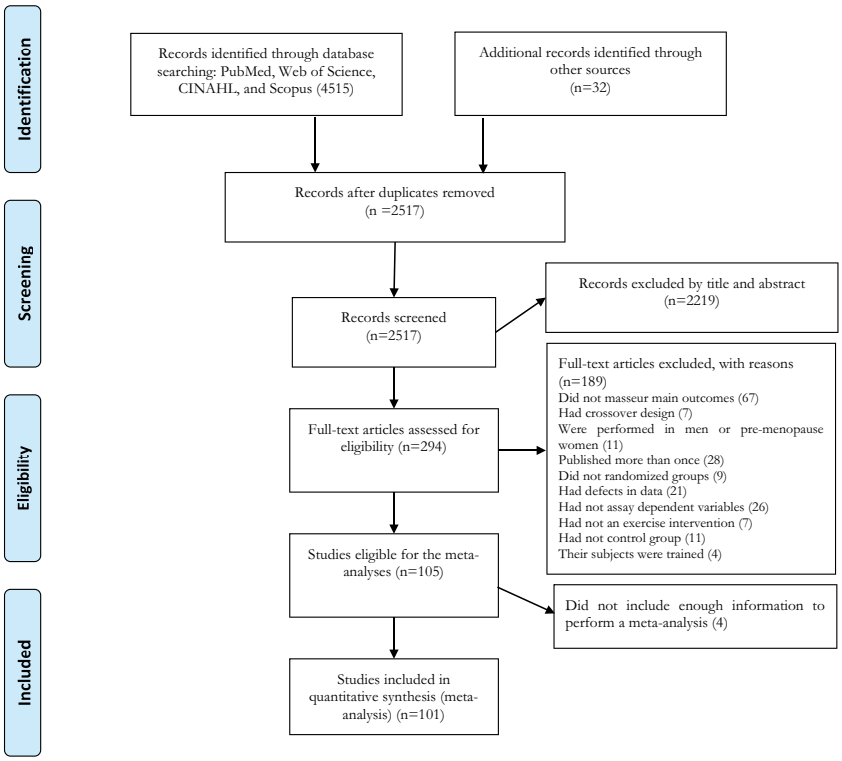

FIGURE 1
Flow diagram of systematic literature search.

Meta-analysis

Body composition

Muscle mass

Based on 26 intervention arms, exercise training increased muscle mass/volume (SMD: 0.26; 95% CI: 0.13, 0.39; P=0.001) (Figure 2). There was no significant heterogeneity amongst the included studies (I^2 = 0.00%; p=0.99). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicate bias was present (p=0.35). After accounting missing studies (5 studies) with the trim and fill method, the overall change was 0.20 (95% CI: 0.08, 0.32). In addition, sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant increase in muscle mass in middle-aged (SMD: 0.26, p=0.01) and older adults (SMD: 0.26, p=0.001), with resistance training (SMD: 0.27, p=0.001), combined training (SMD: 0.26, p=0.02), in medium-term interventions (SMD: 0.26, p=0.002) and long-term interventions (SMD: 0.26, p=0.008) (Supplementary Table 3).

Muscle and fiber CSA

Based on 15 intervention arms, exercise training increased muscle and fiber CSA (SMD: 0.50; 95% CI: 0.25, 0.75; P=0.001) (Figure 3). There was no significant heterogeneity amongst included studies (I^2 = 0.00%; p=0.49). Visual interpretation of funnel plots did not suggest publication bias, but the Egger's test did indicate that bias was likely (p=0.002). In addition, sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant increase in muscle mass in older adults (SMD: 0.59, p=0.001), with resistance training (SMD: 0.57, p=0.001), in medium-term interventions (SMD: 0.64, p=0.02) and long-term interventions (SMD: 0.44, p=0.005) (Supplementary Table 3).

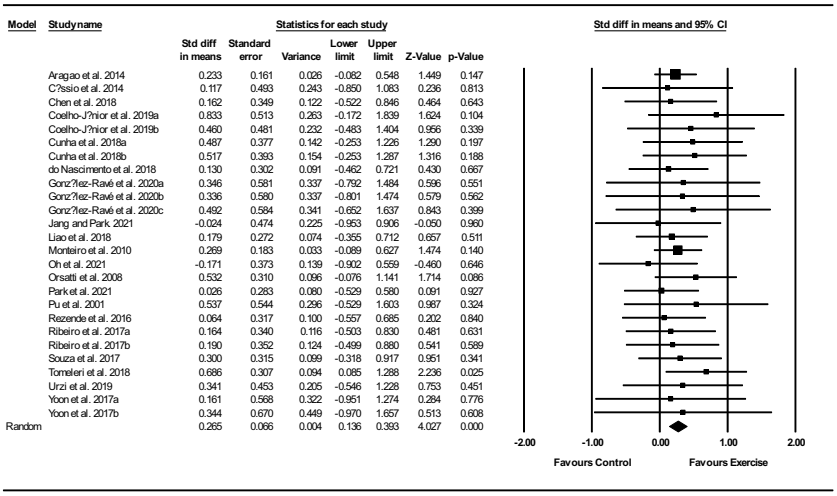

FIGURE 2
Forest plot of the effects of exercise training versus control on muscle mass. Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

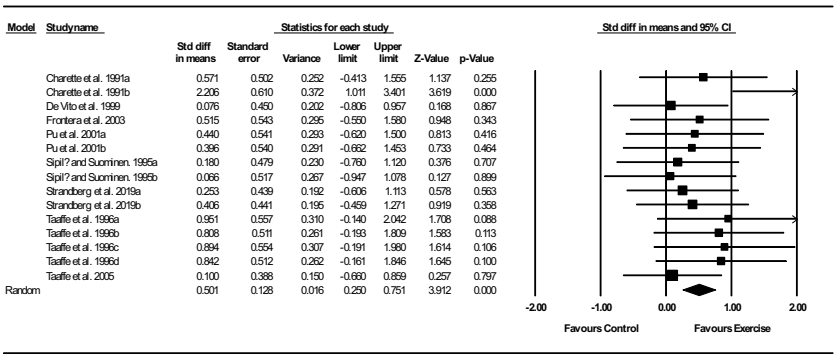

FIGURE 3
Forest plot of the effects of exercise training versus control on muscle and fiber CSA. Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

FFM

Based on 56 intervention arms, exercise training increased FFM (WMD: 0.66 kg; 95% CI: 0.50, 0.81; P=0.001) (Figure 4). There was no significant heterogeneity amongst included studies (I^2 = 0.00%; p=0.62). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicate bias was present (p=0.18). After accounting missing studies (6 studies) with the trim and fill method, the overall change was 0.66 kg (95% CI: 0.45, 0.87). In addition, sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant increase in FFM mass in middle-aged (WMD: 0.71 kg, p=0.001) and older adults (WMD: 0.86 kg, p=0.001), with resistance training (WMD: 0.90 kg, p=0.001), combined training (WMD: 0.68 kg, p=0.001), water-based training (WMD: 2.49 kg, p=0.005), in medium-term interventions (WMD: 0.83 kg, p=0.001) and long-term interventions (WMD: 0.79 kg, p=0.001) (Supplementary Table 3).

Fat mass

Based on 43 intervention arms, exercise training decreased fat mass (WMD: -1.27 kg; 95% CI: -1.93, -0.62; P=0.001) (Figure 5). There was significant heterogeneity amongst included studies (I^2 = 56.46%; p=0.001). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicate bias was present (p=0.54). After accounting missing studies (16 studies) with the trim and fill method, the overall change was -2.63 kg (95% CI: -2.63, -1.38). Sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant decrease in fat mass in middle-aged adults (WMD: -1.15, p=0.001), with aerobic training (WMD: -1.94, p=0.001), in medium-term interventions (WMD: -1.17, p=0.002), and long-term interventions (WMD: -1.24, p=0.02) (Supplementary Table 3).

Body fat percentage

Based on 85 intervention arms, exercise training decreased body fat percentage (WMD: -1.86%; 95% CI: -2.42, -1.29; P=0.001) (Figure 6). There was significant heterogeneity amongst included studies (I^2 = 77.20%; p=0.001). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicate bias was present (p=0.59). After accounting missing studies (28 studies) with the trim and fill method, the overall change was -2.59% (95% CI: -3.11, -2.06). In addition, sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant decrease in fat percentage in middle-aged adults (WMD: -1.92%, p=0.001) and older adults (WMD: -1.76%, p=0.001), with resistance training (WMD: -1.20%, p=0.001), aerobic training (WMD: -1.68%, p=0.001), combined training (WMD: -2.24%, p=0.001), in medium-term interventions

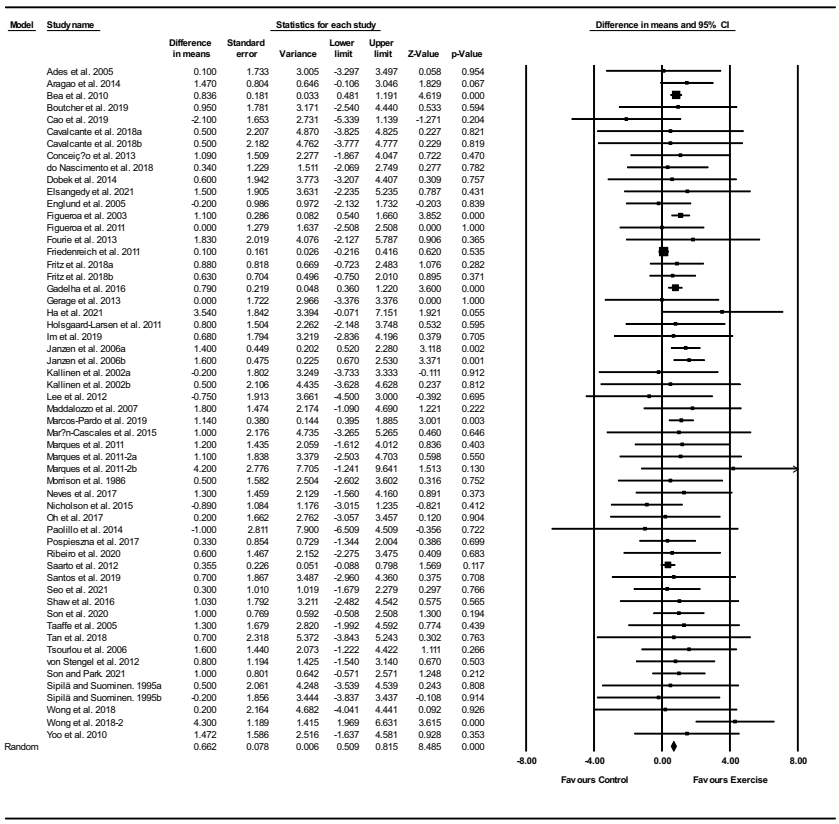

FIGURE 4
Forest plot of the effects of exercise training versus control on FFM. Data are reported as WMD (95% confidence limits). WMD, weighted mean difference.

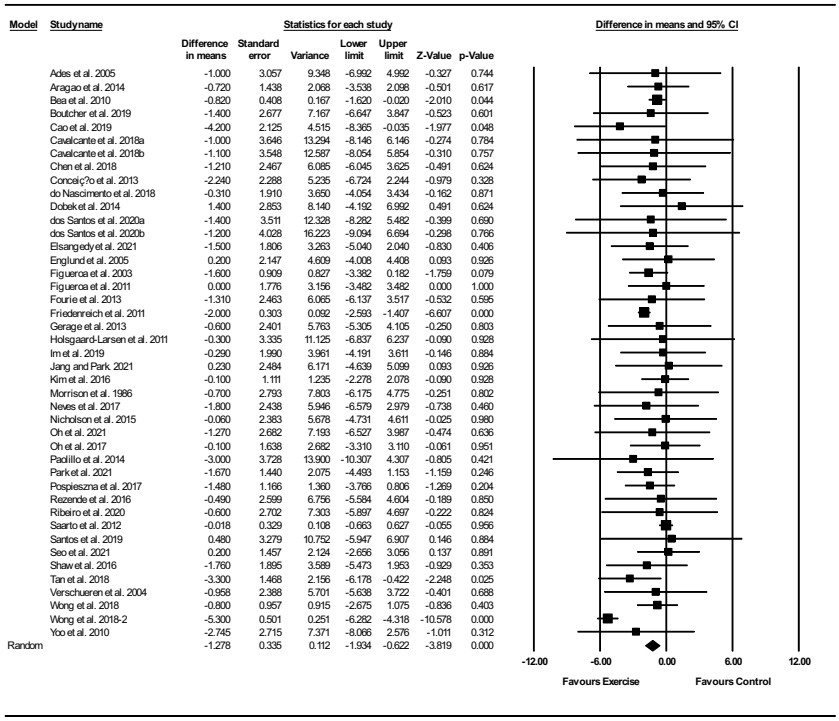

FIGURE 5
Forest plot of the effects of exercise training versus control on fat mass. Data are reported as WMD (95% confidence limits). WMD, weighted mean difference.

(WMD: -1.79%, p=0.001) and long-term interventions (WMD: -1.82%, p=0.001) (Supplementary Table 3).

Waist circumference

Based on 26 intervention arms, exercise training decreased waist circumference (WMD: -1.45 cm; 95% CI: -2.05, -0.83; P=0.001) (Figure 7). There was no significant heterogeneity amongst included studies (I^2 = 0.00%; p=0.79). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicated that bias was present (p=0.63). After accounting missing studies (3 studies) with the trim and fill method, the overall change was -1.35 cm (95% CI: -1.96, -0.74). In addition, sensitivity analysis by omitting individual studies showed that significance did not change. Subgroup analyses revealed a significant decrease in waist circumference in middle-aged (WMD: -1.42 cm, p=0.001), older adults (WMD: -1.50 cm, p=0.04), with aerobic training (WMD: -2.30 cm, p=0.001), combined training (WMD: -1.66 cm, p=0.03), in medium-term interventions (WMD: -2.69 cm, p=0.001) and long-term interventions (WMD: -1.18 cm, p=0.002) (Supplementary Table 3).

Visceral fat

Based on 11 intervention arms, exercise training decreased visceral fat (SMD: -0.38; 95% CI: -0.62, -0.14; P=0.002) (Figure 8). There was significant heterogeneity amongst included studies (I^2 = 53.64%; p=0.01). Visual interpretation of funnel plots suggested publication bias, but the Egger's test did not indicate bias was present (p=0.61). After accounting missing studies (1 studies) with the trim and fill method, the overall change was -0.34 (95% CI: -0.59, -0.10). In addition, sensitivity analysis by omitting individual studies showed that significance did not change.

Discussion

In this meta-analysis with a large sample size, we have assessed the effects of exercise training on body composition, including muscle mass, muscle and fiber CSA, lean mass or fat-free mass, fat mass, body fat percentage, waist circumference, and visceral fat in postmenopausal women. Our main findings revealed that exercise training positively influenced the body composition components, including muscle mass, muscle fiber CSA, FFM, fat mass, body fat percentage, waist circumference, and visceral fat in postmenopausal women. Greater beneficial effects on fat mass outcomes were evidenced with aerobic training, whereas greater beneficial effects on muscle mass outcomes were reported with resistance training. In addition, a majority of these beneficial effects appears to be occurred with medium- and long-term interventions and also in middle-aged and older postmenopausal women.

Muscle mass outcomes

The loss of muscle mass is considered to be an important contributor of strength loss in older adults with advancing age (44). Menopausal period is associated with loss of muscle mass and muscle strength, which may progress to sarcopenia over a period of

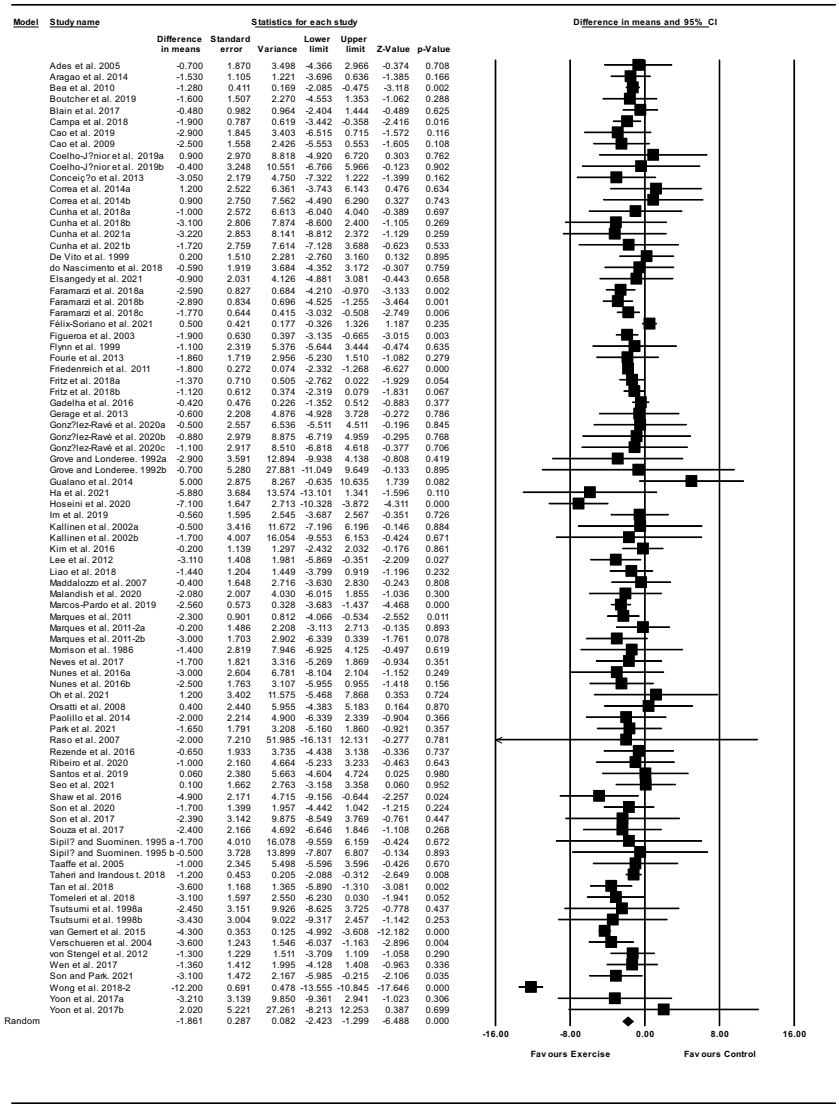

FIGURE 6
Forest plot of the effects of exercise training versus control on body fat percentage. Data are reported as WMD (95% confidence limits). WMD, weighted mean difference.

time (45), and this phenomenon is primarily linked with natural decrease of estrogen in postmenopausal women (46–48). Natural decline in estrogen was reported to cause endocrine dysfunction, metabolic syndrome, decreased bone mass density, muscle mass and strength, and increased visceral fat mass (45, 48). Nevertheless, loss of muscle mass due to age cannot be ruled-out as older men also represented with higher prevalence of sarcopenia. Previous studies have shown sex-specific absolute loss of muscle loss, where elderly men are likely to have more muscle mass than elderly women, but tend to lose muscle mass faster (49–51). Although men experienced greater loss of absolute muscle mass, women experienced greater decrements in muscle quality (52). In this context, either type of exercise training is a practical strategy to prevent or delay the age-induced loss of muscle mass in men and women.

Previous reviews and meta-analyses have determined the effectiveness of exercise training and indicated that exercise is a one of the best approach to prevent and treat the muscle weakness in older adults (53–56), however less is known about such benefits among postmenopausal women specifically. Of particular importance for postmenopausal women with a high risk for sarcopenia, our results confirmed the positive effects of exercise training on muscle mass. Although aerobic training may also have minimal effects on muscle size (57), our results suggested that resistance training is important for increasing muscle mass, and did not indicate significant increases for aerobic training interventions. Nevertheless, combined training was similarly effective as compared with resistance training. These results are consistent with previous meta-analyses indicating that resistance training increased muscle mass in older adults and even very old adults (28, 56). Although

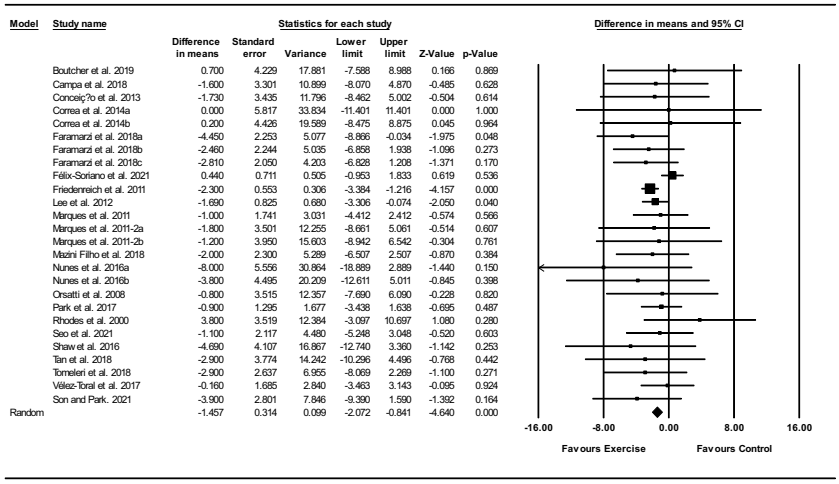

FIGURE 7
Forest plot of the effects of exercise training versus control on waist circumference. Data are reported as WMD (95% confidence limits). WMD, weighted mean difference.

older men may gain more absolute muscle size in response to resistance exercise training, there are no biological sex differences in relative muscle strength gains (54). The similar adaptations may be due to the fact that neither protein synthesis nor mTOR signaling differ between the biological sexes following resistance training (54). Our results indicate that combined training is also effective for increasing muscle mass and FFM, suggesting that in postmenopausal women, muscle mass development can also be improved by combining resistance training with aerobic training. In addition, our results suggested that muscle mass and FFM were increased irrespective of age groups in postmenopausal women. These adaptions are consistent with previous reviews suggesting the positive effects of resistance training in middle-aged, older, and very old adults (28, 56, 58). In addition, subgroup analysis based on intervention duration (medium-term: <16 weeks and long-term: ≥16 weeks), increased muscle mass and FFM occurred regardless of intervention duration. This results shows that exercise training with duration <16 weeks can be also important for improving muscle. However, it should be noted that muscle fiber CSA results should be interpreted with caution due to the small number of studies in some subgroups.

Fat mass outcomes

Despite the fact that exercise training is effective in reducing the fat mass, evidence regarding the types of exercise training in postmenopausal women is scarce. Although exercise training combined with diet has been shown to be an effective strategy for weight loss and fat mass reduction, regardless of exercise type, some

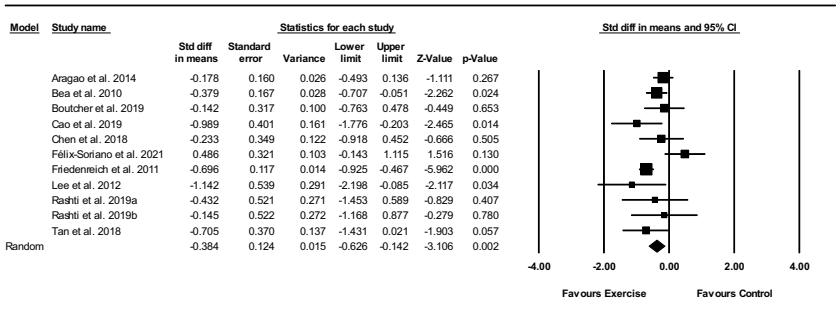

FIGURE 8
Forest plot of the effects of exercise training versus control on visceral fat. Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

systematic reviews and meta-analyses concluded that exercise interventions effectively reduced fat mass (59–63). In general, our results suggested that exercise training is effective for reducing the adiposity markers including fat mass, body fat percentage, visceral fat, and waist circumference. The potential mechanism for reductions in adiposity are related to altered energy balance where energy is expended during exercise as well as shortly after exercise as the body recovers, and increases in resting metabolic rate that follow increased lean body mass (64). However, it is important to note that the type of exercise is important as a moderator of the effectiveness of exercise training on fat mass. In this regard, previous systematic reviews have shown that aerobic training is more effective in reducing body weight, fat mass, and waist circumference when compared to resistance training in individuals with BMIs ≥ 25 kg/m^2 (65). In line with a systematic review conducted by Schwingshackl and colleagues (65), our results confirmed that aerobic training was effective in reducing fat mass, with small effects for resistance training (-0.45 kg) and not reaching statistical significance (p=0.06). Reductions in fat mass and related indicators following aerobic training interventions may be due to energy expenditure during the exercise bouts, which is likely to be higher as compared with resistance training (65, 66). In addition, we found that both aerobic and resistance trainings are effective in reducing body fat percentage. However, it should be noted that body fat percentage, particularly following resistance training interventions may include reduced fat mass as well as increased FFM, and our results also showed a significant increase in FFM with resistance training. Furthermore, we found that aerobic training is effective in reducing waist circumference and visceral fat, which was not the case for resistance training with regard to waist circumference. Visceral fat is known to be an important risk factor for many chronic diseases such as type 2 diabetes and cardiovascular diseases (60). In addition, waist circumference is considered as a surrogate clinical measure for visceral (abdominal) fat mass (67). In our study, there were a small number of studies that determined visceral fat, and therefore we could not perform subgroup analysis. But subgroup analysis based on exercise type, revealed significant reductions in waist circumference (-2.30 cm) occurred with aerobic training. The results for aerobic training were obtained from 3 studies, whereas there were 16 studies included for resistance exercise, which should be considered when interpreting the results. Furthermore, our results indicated that combined training is effective for decreasing body fat percentage and waist circumference, suggesting that this type of training may be a suitable strategy for optimization of the combination of both fat loss and muscle gain in postmenopausal women. For better understanding the role of participants' age and intervention duration on exercise-induced fat loss, subgroup analyses were conducted, and found that fat loss adaptations following training occurred regardless of age and intervention duration. These results are important, especially regarding age factor, indicating the effectiveness of exercise training for postmenopausal women at any age. Exercise training is also considered to be effective intervention for improving musculoskeletal health by a positive effect on bone mineral density (68, 69). Given that the increase in fat mass and the loss LBM affects on bone mineral density in postmenopausal women (70), exercise training may have a positive effect on bone mineral density by improving body composition.

Limitations

Our study has limitations that should be considered when interpreting the results. For outcome assessments, included studies measured body composition using different methods, which may lead to differences in reported results. There were significant heterogeneities among included studies with respect to some outcomes that may be due to differences in exercise interventions, participant characteristics, and the quality of the included studies. We did not include any limitations regarding the health of participants, and non-communicable chronic diseases such as obesity and type 2 diabetes may influence exercise training adaptations. In addition, we did not include any limitations on the age of participants. However, we performed subgroup analysis on middle-aged and older adults, showing positive effects of exercise regardless of age. Finally, we did not include bone mineral density as a outcomes

Conclusions

The current systematic review and meta-analysis demonstrated that exercise training is effective in improving the body composition in postmenopausal women, represented by increased muscle mass and decreased fat mass, regardless of age and intervention duration. In addition, our results confirmed that aerobic exercise is more beneficial on fat loss, while resistance exercise is more beneficial on muscle gain. Since body composition includes both lean and fat tissue, a combination of aerobic and resistance exercise may be beneficial to promote overall health among older women. Additional studies on the effectiveness of combined training in postmenopausal women depends on their physical fitness may be necessary before recommendations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

MKh, AM, MS, MP, SR, MKo and YL conceived and designed the study. MKh, AM, MS, HB and ME extracted the data. MKh, AM, MS, MKo and YL analyzed the data and completed the initial draft of the results. MKh, MKo and YL drafted the initial manuscript. And SR, MP, MKo and YL revised the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1183765/full#supplementary-material

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Sarcopenia prevalence and association with nutritional status in cohort of elderly patients affected by musculoskeletal concerns: a real-life analysis

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Introduction: The progressive loss of skeletal muscle mass, strength, and function that frequently occurs as people get older is referred to as sarcopenia. Elderly musculoskeletal aging, sarcopenia, and obesity are all intimately connected. Our study's aim is to investigate the prevalence of sarcopenia in a real cohort of patients over 65 with musculoskeletal conditions referring to a Rehabilitation Unit. The secondary aim of our study is to investigate associations between sarcopenia and alterations in nutritional status and Body Mass Index (BMI). Finally, quality of life and global health has been investigated in our population.

Materials and methods: From January 2019 to January 2021, 247 patients over 65 years old with musculoskeletal concerns were enrolled and participated in an observational study. As outcome measures, the Mini Nutritional Assessment (MNA), the 12-Item Short Form Health Survey (SF-12), and the Cumulative Illness Rating Scale Severity Index (CIRS-SI) were used. Additionally, measurements of total skeletal muscle mass (SMM) and appendicular muscle mass (ASMM) using bioelectrical impedance analysis, as well as a hand grip strength test of the non-dominant hand were taken. The Mid Upper Arm Circumference (MUAC) and the Calf Circumference (CC) were measured and recorded as further indications of possible sarcopenia.

Results: A percentage of 46.1% of subjects with overt sarcopenia was found and 10.1% showed a severe sarcopenia. Patients with severe sarcopenia showed significantly lower values of BMI and MNA. Additionally, sarcopenic patients showed significantly lower values in MNA when compared to non-sarcopenic patients. Considering SF-12, only the physical score revealed slight significant differences. In particular, patients affected by probable or severe sarcopenia

presented a lower value than non-sarcopenic patients. Concerning MUAC and CC, severe sarcopenic patients showed significant lower values for both the body parts.

Conclusion: Our study considers a cohort of real-life elderly subjects with musculoskeletal concerns and shows that these subjects are highly susceptible to sarcopenia. Therefore, rehabilitation for elderly patients with musculoskeletal concerns requires to be customized and multidisciplinary. Future research should further investigate these aspects in order to enable the early identification of sarcopenia and the formulation of customized rehabilitative programs.

KEYWORDS

early diagnosis, frailty, sarcopenic obesity, rehabilitation, frailty prevention, adult, aged

Introduction

According to the current definition, sarcopenia refers to the progressive loss of skeletal muscle mass, strength and performance that increases risk of physical disability and hospitalization (1). Sarcopenia is believed to be a condition typical of advanced age, even if muscle mass loss begins around the age of 40 (1, 2). Nevertheless, while muscle mass represents the 42% of global body mass in adults, it drops to about 27% in the elderly (3). Sarcopenia's negative effects can affect older subjects with a prevalence varying from 10% to 27% (4), increasing the risk of adverse consequences such as falls, fractures, depression, physical impairment, quality of life worsening, and increased mortality (5–8).

Sarcopenia pathophysiology is complex, with aging, sociodemographic factors, lifestyle choices, and a number of medical conditions being all factors that contribute (2). In particular, musculoskeletal aging and sarcopenia in the elderly have been demonstrated to be closely linked, since numerous studies have shown that cellular, mitochondrial and nervous impairment underlying ageing dysfunctions can also lead to the appearance of sarcopenia (9, 10). On the other hand, the adipose tissue redistribution represents another important age-related effect. In fact, as people age, subcutaneous adipose tissue declines gradually, visceral obesity increases, and adipocytes and lipids accumulate in the bone marrow, liver, and skeletal muscle (myosteatosis). In particular, total body fat increases with age until it reaches a plateau, and then it gradually begins to decline. Obesity and excessive caloric consumption can both contribute to the development of sarcopenia (11–13). Sarcopenia obesity supervenes when a decrease of lean body mass accompanied by an excessive accumulation of adipose tissue, particularly visceral fat, occurs (3, 14).

Even if musculoskeletal concerns are among the most common causes for older people to be admitted to a rehabilitation unit, to date, there are no studies that have investigated in real life the incidence of sarcopenia among elderly patients with musculoskeletal disorders. Therefore, our study aims to investigate the prevalence of sarcopenia (diagnosed through the algorithm proposed by the European Working Group on Sarcopenia in Older People-2 or EWGSOP-2) in a real-life cohort of patients over the age of 65 with musculoskeletal conditions referred to a Rehabilitation Unit on an outpatient basis. Given the association between sarcopenia and obesity, secondary aim of our study is to search for real-life associations between sarcopenia and changes in nutritional status and Body Mass Index (BMI) among a population of elderly subjects suffering from musculoskeletal concerns. Finally, quality of life and global health has been investigated in our population.

Materials and methods

Study design

An observational, prospective study was conducted involving a cohort of 247 patients with musculoskeletal disorders, enrolled from January 2019 to January 2021 at the Rehabilitation Unit of Padua University – General Hospital, Padua, Italy.

Participants

Subjects of both sexes over the age of 65 who had a diagnosis of musculoskeletal disorders were included in the study. The population under study included only community-dwelling subjects. Patients involved in the study presented a diagnosis of a musculoskeletal disorder, e.g., osteoarthritis, shoulder tendonitis, and chronic back pain. For the diagnosis of osteoarthritis, the

diagnostic criteria were based on the Kellgren-Lawrence grading system for radiographic assessment, while patients with post-bone fracture outcomes and chronic back pain had a well-established diagnosis made by a physician (medical history, clinical examination, imaging studies and surgical reports.). Enrolled subjects must be able to provide informed consent. In addition, enrolled patients had to complete the Short Portable Mental Status Questionnaire (SPMSQ), reporting a score ≥ 5, be able to walk without aids, and not present any conditions that would prevent them from perform bioelectrical impedance analysis (BIA).

People less than 65 years of age, non-community dwelling (nursing home, institutional setting, etc.) were excluded. Heart failure, respiratory failure, impaired cognitive functions (mini mental status examination<24), multiple musculoskeletal conditions, oncological or psychiatric comorbidities, and inability to properly comprehend and sign informed consent represented the exclusion criteria. Moreover, as an exclusion criterion, participants with specific diagnoses (such as spinal fractures, tumors, bone infections) that could potentially confound the study outcomes were excluded.

Outcome measures

Three different evaluation scales in the Italian validated version were employed:

- The Cumulative Illness Rating Scale Severity Index (CIRS-SI): a standardized instrument used in the geriatric field to measure the health of the elderly as objectively as possible. It requires the physician to assess and measure the clinical and functional severity of 14 disease categories. For each of these categories, a severity value must be defined, based on clinical history, objective examination and patient-reported symptoms. The scale provides a cumulative score, which can range from 0 to 56 (15).
- The Mini Nutritional Assessment (MNA): a screening tool that contribute to identify elderly patients who are malnourished or at risk of malnutrition. Thanks to 18 questions grouped in 4 sections (anthropometry, general state, eating habits and self-perceived health and nutrition states), the MNA provides a multidimensional assessment of the patient nutritional condition. The final score can reach a maximum of 30 points and allows the nutritional status to be classified: patients are considered well-fed when they reach a score ≥24 points, while they are at risk of malnutrition with a score between 23.5 and 17 (16).
- The 12-Item Short Form Health Survey (SF-12): a questionnaire readjusted from a larger version, the 36-Item Short Form Health Survey (SF-36), used to investigate the perception of personal psychophysical conditions, frequently employed in the rehabilitation field. The SF- 12 results, dual and expressed by the acronyms PCS (Physical Component Summary) and MCS (Mental Component Summary), can adequately summarize the size of the patient's impairment both from a physical and mental point of view (17).

Instrumental evaluations were also carried out, including:

- Hand grip strength evaluation of the non-dominant hand measured with a handheld dynamometer.
- Total Skeletal Muscular Mass (SMM) and Appendicular Skeletal Muscle Mass (ASMM) measurement through a bioelectrical impedance analysis employed to assess body composition (Biody Xpert, Interfit technology) (18).

The estimation of muscular masses, using the bioelectrical impedance analysis is well accepted. They are based on equation that combine height, sex, age and the parameters calculated by the proper instrument:

$$SMM\ (kg) = \{(Height^{2}/\mathrm{R} \cdot 0.401) + (\mathrm{sex} \cdot 3.825) + [\mathrm{age} \cdot (-0.071)]\} + 5.102$$

$$ASMM\ (kg) = -3.964 + (0.227 \cdot RI) + (0.095 \cdot Weight) + (1.384 \cdot sex) + (0.064 \cdot Xc)$$

where height is in cm, R is the resistance in Ohms, RI the resistance normalized for the height, the sex is 0 for biological females and 1 for biological males, age is in years and the Xc is the reactance measured in Ohms (19, 20).

Sarcopenia was considered probable when low muscle strength was detected. Sarcopenia diagnosis was confirmed if also low muscle quantity or quality was recorded. When low muscle strength, low muscle quantity/quality and low physical performance were all detected, sarcopenia was considered severe. In particular, according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the following values were used to define sarcopenia cut-off (21):

- Hand Grip Strength< 27 kg for male subjects and< 16 kg for female subjects;
- ASMM< 20 kg for male subjects and< 15 kg for female subjects;
- ASMM/height^2< 7.0 kg/m^2 for male subjects and< 6.0 kg/m^2 for female subjects.

According to the EWGSOP2, severe sarcopenia was defined testing gait speed through the 4 meters walking test: a gait speed ≤0.8 m/s both for males and females allowed to define a severe form of sarcopenia. The Calf Circumference (CC) and the Mid Upper Arm Circumference (MUAC) were measured and collected as further indications of possible sarcopenia, according to Hu et al. for MUAC (22) and Kawakami et al. for CC (23).

Statistical analysis

For the statistical analysis, we divided the whole sample of patients into four groups, according to the sarcopenia level measured by the association of strength, speed and ASMM/height^2 (levels: 0, normal; 1, probable sarcopenia, only reduced muscle strength; 2, sarcopenia, reduced strength and muscle mass; 3, severe sarcopenia, reduced strength, muscle mass and performance). To show the distribution of the sex and the CIRS-SI in relation to the sarcopenia level, we used a contingency table.

In order to evaluate the difference in BMI, MNA, SF-12 and arm and calf circumference among the four groups, we used the Kruskal-Wallis test, applying the Bonferroni correction for the repetitive measures. This test was used for the comparison of independent variables of multiple groups. Finally, Spearman correlation was employed to evaluate the association of the arm and calf circumference with other variables. We decided to use non-parametric tests because of the features of the data.

Quantitative data were shown as median values. The analyses were performed using the IBM SPSS Statistics Software version 26 and the significance was set as $p< 0.05$.

Results

A total of 247 patients were enrolled in our study, with a median age of 73 years (range 61 – 95 years). Among them, 98 men and 149 women were studied (Table 1). A percentage of 46.1% of subjects with overt sarcopenia was found and 10.1% showed a severe sarcopenia. The majority of the subjects presented a sarcopenia level 2 and low levels of global health, as assessed by the CIRS-SI (Table 2).

Considering the different sarcopenia levels, the most severe level group (level 3) showed significantly lower values of BMI and MNA in comparison with all the other groups. Additionally, level 2 showed significant lower values in MNA, exclusively in comparison with level 0. Considering SF-12, only the physical composite score revealed slight significant differences. In particular, group 3 and group 1 presented lower values than group 0 (Figure 1).

Concerning the arm and calf circumference, group 3 showed significant lower values for both the body parts in comparison with groups 0 and 1. Sarcopenia level 2 showed lower values than group 0 in CC (Figure 2). Significant direct correlations were found between BMI and MUAC and BMI and CC ($p< 0.01$, $r = 0.70$ and $r = 0.52$ respectively). A minimal direct correlation was found between MNA and CC (Figure 3).

Discussion

In our study, elderly patients with musculoskeletal disorders who accessed the outpatient clinics of the University of Padua Rehabilitation Unit were shown to frequently present sarcopenia and low levels of global health, as assessed by the CIRS-SI score. In particular, the sarcopenia prevalence in our study reconfirmed data already present in the literature (24). In our work, we decided to apply ASMM because it is reliable and shows a relative cost-effectiveness. The application of the parameters calculated by the bioelectrical impedance and the use of SMM and ASMM allowed us a clear identification of the four groups, with different level of sarcopenia. The groups showed some peculiar differences and let us speculate about patients' conditions and the different approaches to management.

Interestingly, when measuring BMI in patients referred to our center, we found that patients with severe sarcopenia had a sharp decline in BMI, whereas patients with probable sarcopenia and moderate sarcopenia had higher BMI scores that reached overweight levels. This agrees with the increasing evidence of an association between sarcopenia and obesity, while at extreme levels

TABLE 1 Data of age, BMI and anthropometric measures related to sex.

Sex	Number of patients	Age	BMI	MUAC	CC
Female	98	72.8	26.3	28.5	36.8
Male	149	73.4	26.7	28.2	35.8
Total	247	73.1	26.5	28.3	36.2

BMI, Body Mass Index; MUAC, Mid Upper Arm Circumference; CC, Calf Circumference.

TABLE 2 Data of MNA and SF-12 related to sarcopenia level.

Sarcopenia level	Number of patients	Percentage	MNA	SF-12 (PCS)	SF-12 (MCS)
0	64	25.9%	26.8	13.9	18.2
1	69	27.9%	25.7	12.7	17.5
2	89	36.1%	25.4	13.2	17.9
3	25	10.1%	23.2	11.7	17.3
Total	247	100.00%	25.6	13.1	17.8

Level 0, no sarcopenia; level 1, probable sarcopenia; level 2, sarcopenia; level 3, severe sarcopenia; MNA, Mini Nutritional Assessment; SF-12 (PCS), 12-Item Short Form Health Survey Physical Component Summary; SF-12 (MCS), 12-Item Short Form Health Survey Mental Component Summary.

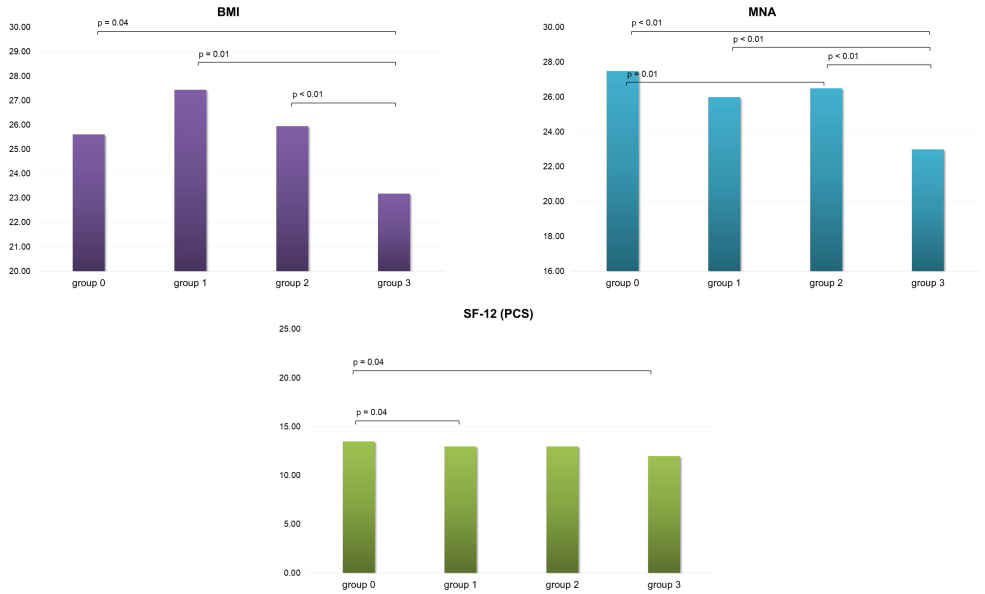

FIGURE 1
BMI, MNA and SF-12 (PCS) scores variation in the four group of patients evaluated.BMI, Body Mass Index; MNA, Mini Nutritional Assessment; SF-12 (PCS), 12-Item Short Form Health Survey Physical Component Summary; group 0, no sarcopenia; group 1, probable sarcopenia; group 2, sarcopenia; group 3, severe sarcopenia.

of sarcopenia not only muscle mass but also fat mass seem to be reduced.

Furthermore, our study showed that elderly subjects with musculoskeletal disorders are also prone to malnutrition and sarcopenia and malnutrition in this population seemed to be related. In literature, it has been demonstrated that specific foods and dietary habits can help prevent the loss of strength and function that comes with age (25, 26). Several randomized controlled trials seem to indicate that dietary protein consumption is essential for avoiding sarcopenia and muscle loss (26). Both selenium and magnesium have been investigated as dietary supplements, and they seem to have a possible relationship with physical activity and muscular function in older people (26). Improving diet and nutrition may be useful for both the prevention and treatment of sarcopenia as low nutritional status is widespread in the elderly, especially in frail subjects (12). Therefore, a proper rehabilitation program for elderly subjects with both sarcopenia and musculoskeletal concerns should include not only motor and strengthening exercises, but also educational initiatives to promote an adequate nutritional status. Progressive elastic band resistance exercises have been demonstrated to reduce fat mass and to increase physical function in patients with sarcopenic obesity and sarcopenia (27–30). Both water- and land-based activities have been shown to be beneficial in maintaining strength and in improving lower-body flexibility, with aquatic exercise appearing a better activity to improve dynamic balance and to manage comorbidities (31–35). Nutritional interventions should also be involved in the rehabilitative protocols suggested to these patients. Therefore, the rehabilitation team should include a nutrition expert, in order to help the patients receive the appropriate amount of protein as principal anabolic stimuli for muscle protein synthesis (1.0–1.2 g/kg body weight per day) and all the supplements that support the musculoskeletal health, such as vitamin D, antioxidant nutrients and long-chain polyunsaturated fatty acids (25, 36).

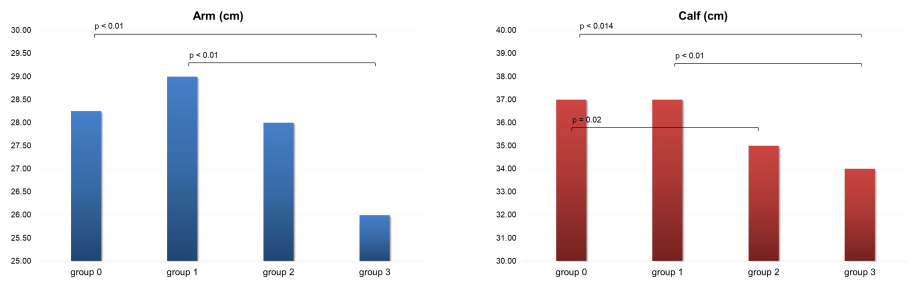

FIGURE 2
Arm and calf circumference in the four group of patients evaluated. Group 0, no sarcopenia; group 1, probable sarcopenia; group 2, sarcopenia; group 3, severe sarcopenia.

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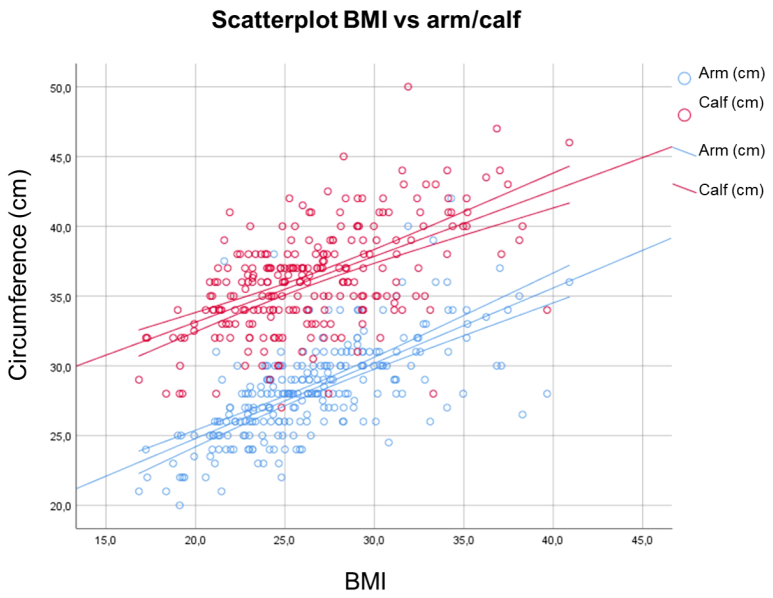

FIGURE 3
Correlations between BMI and MUAC and BMI and CC. BMI, Body Mass Index; MUAC, Mid Upper Arm Circumference; CC, Calf Circumference.

In our study, arm and calf circumference were shown to be reduced especially in patients with severe sarcopenia. Therefore, this study supports the use of these measurements for aiding in sarcopenia detection, reconfirming Hu et al. and Kawakami et al. findings (22, 23). They could therefore represent rapid indicators for the assessment of patients at increased risk of developing sarcopenia and thus be employed in clinical practice. A significant direct correlation between BMI and MUAC and CC circumferences was also obtained in our study, in accordance with previous results (37). Additionally, a slender direct association between MNA and CC was found. As a result, CC could be employed as a rapid outpatient tool for the assessment of the elderly patient nutritional status.

Our results showed also a moderate but significant reduction in the physical status category of quality of life in subjects with probable sarcopenia and severe sarcopenia when compared with the group of patients who did not present sarcopenia. This agrees with previous literature in which an association between quality of life and nutritional condition was found (38, 39). It is well-known that sarcopenia increases the risk of physical limitation and disability, lowering patients' quality of life.

According to our data, patients with both sarcopenia and worse nutritional status reported reduced quality of life. By reducing malnutrition and encouraging optimal functioning, good nutrition can enhance the health-related quality of life (38). Since low physical capacity and quality of life influence personal and social costs (40), it can be hypothesized that the development of programs aimed at preventing nutritional deficiencies in patients with musculoskeletal disorders could contribute not only to ameliorate quality of life but also to economic and social benefits.

From the findings of our study, we can conclude that evaluations of sarcopenia, quality of life, and nutritional status should become part of the rehabilitative outclinics protocol for elderly patients accessing the Rehabilitation Unit for musculoskeletal concerns. The management of elderly patients with sarcopenia or pre-sarcopenia conditions associated to musculoskeletal disorders should start with the early detection of different concerns. An early assessment resulting in the identification of otherwise neglected needs may contribute to the development of primary and secondary prevention strategies, avoiding the progression into real pathological conditions (i.e., probable sarcopenia into sarcopenia, nutritional deficiencies into malnutrition) (41). Subsequently, a multimodal and multidisciplinary rehabilitation program, including prevention strategies, motor activity, strengthening exercise, nutrition and educative interventions (42, 43), should be proposed.

The study has several limitations that should be taken into consideration when interpreting the results. Firstly, there is a potential for selection bias as the participant selection process may not accurately represent the broader population of elderly individuals with musculoskeletal disease. Secondly, the generalizability of the findings may be limited due to the nature of observational studies. The specific inclusion and exclusion criteria, as well as the characteristics of the participants, may restrict the ability to extend the results to broader populations or different settings. Thirdly, despite attempts to control for confounding through statistical analysis or study design, there may be unmeasured or unknown factors that influence the relationship between the variables under investigation.

Conclusion

Real-life elderly subjects with musculoskeletal concerns are highly susceptible to sarcopenia. Therefore, rehabilitation for elderly patients with musculoskeletal concerns requires

to be customized and multidisciplinary, addressing both the musculoskeletal condition and the needs associated to sarcopenia, including nutritional supplementation. To identify those who are more likely to develop sarcopenia, it is advisable to draw a user-friendly screening tool, e.g., using MUAC and CC. Nutritional assessment should be part of the screening process since early detection of a malnourished state may result in interventions to improve nutritional status and, as a result, quality of life. Future research should further investigate these aspects in order to enable the early identification of sarcopenia among elderly patients affected by musculoskeletal concerns and the formulation of customized multidisciplinary rehabilitative programs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and methodology, MM, DC, AF, YD and SM. Data collection, AB and MV. Data curation, MM, DC, AF, AB and NS. Data analysis, DC, AF and NS. Investigation, MM, DC, AB and MV. Writing—original draft preparation, MM and DC. Writing—review and editing, MM, DC, YD and SM. Supervision, SM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Predicted lean body mass in relation to cognitive function in the older adults

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Background: Previous findings about lean body mass (LBM) and cognitive function remain unclear. We aimed to examine this association by using data from the National Health and Nutrition Examination Survey (NHANES).

Methods: Using data from the NHANES 2011-2014, we conducted logistic regression models to investigate the relation between the predicted LBM and domain-specific cognitive function assessed by Digit Symbol Substitution Test (DSST), Consortium to Establish a Registry for Alzheimer's Disease Word Learning test (CERAD-WL) and Delayed Recall test (CERAD-DR), and Animal Fluency (AF) for information processing speed, memory, and executive function, respectively. Cognitive impairment was defined as the lowest quartile of each cognitive test in the total population. Sex-stratified analysis was further made.

Results: A total of 2955 participants aged 60 and above (mean [SD] age, 69.17 [0.20] years; 1511 female [51.13%]) were included in the study. After being adjusted for social economic factors, anthropometric parameters, and diseases, we found a positive association between predicted LBM and information processing speed (Odds ratio of DSST impairment= 0.95, 95%CI= 0.91 to 0.99) regardless of body mass index and sex. Compared with patients in the first quartile of predicted LBM, those in the fourth quartile had an odds ratio of 0.355 (95% confidence interval 0.153-0.822) for DSST impairment. No significant relation in other cognitive tests and predicted LBM was found whether stratified by sex or not.

Conclusion: Our findings point to the association between predicted lean body mass and cognitive dysfunction in information processing speed, which could be used for early detection and prevention of deterioration of cognitive function among older adults.

KEYWORDS

predicted lean mass, cognitive function, older adults, cross-sectional study, information processing speed

Introduction

Mild cognitive impairment (MCI), characterized by subtle changes in memory and thinking, is thought to be a reversible stage between being cognitively unimpaired and dementia (1). Approximately 12% to 18% of people aged 60 or older have MCI (1), of which 10% to 15% will progress to dementia each year (2–4), causing an enormous economic burden. In 2022, estimated total payments for all individuals with Alzheimer's or other dementias reach $321 billion (1). Because there are no disease-modifying methods (5), reducing the more modifiable risk of developing cognitive impairment or dementia is of high priority, especially in our rapidly aging population (6).

Some studies have linked body mass index (BMI) with a change in cognitive function (7–9). Higher BMI is thought to be a risk factor in middle age (10, 11). And due to lifestyle changes associated with incipient cognitive impairment, a more steep decline may be seen in BMI with a high (vs low) burden of AD or cerebral vascular disease (12). However, as a combination of fat mass and lean body mass (LBM), BMI may not adequately capture the differences in body composition. Older adults tend to have more fat mass and less muscle mass (lean body mass) with BMI unchanged (13, 14). Therefore, BMI may not be able to discriminate individuals at risk of cognitive dysfunction correctly. Fat mass was found higher in cognitively intact people compared with those not with covered mechanisms (15). However, the reported results about the association between body composition with overall cognitive function are controversial (16–18), and there is a paucity of data examining the relationship between LBM with specific cognitive domains (19), which is important to understand the relation between body composition and cognition.

Therefore, exploring the independent role of predicted LBM related to specific cognitive function in adults aged 60 or above may improve our knowledge of body composition and cognitive function and help to find the people with a high possibility of worse cognitive function.

Methods

Study population

The National Health and Nutrition Examination Survey (nhanes) is a series of continuous, ongoing cross-sectional surveys (20). Representative samples of the civilian noninstitutionalized household population of the United States were selected by a complex, multistage probability sampling design (20). Data were collected by personal interview, mobile physical examination, and laboratory tests and were released after every 2-year cycle. In this study, we incorporated data from two cycles of the NHANES (2011–2014) phases during which cognitive function tests were conducted.

Exposure measurements

Instead of direct methods of detecting lean body mass, we use validated anthropometric prediction equations to calculate predicted lean mass developed based on the populations of the NHANES 1999–2006 because of the cost of money and time (21). A total of 7531 men and 6534 women who underwent dual-energy X-ray absorptiometry (DXA) examination were included in this database, which is complex multistage probability sampled (21). Briefly, sex-separated analyses were conducted. DXA-measured lean body mass was predicted as a dependent variable about different combinations of anthropometric measures including age, ethnicity, height (cm), weight (kg), BMI (kg/m^2), waist circumference (cm), other circumference measures (i.e. arm, calf, and thigh (cm)) and skinfold measures (i.e. triceps and subscapular (mm)). The most accurate model used for prediction was determined in the prediction group and further validated predicted values in an independent group. By comparing predicted scores with the DXA-measured values and their correlation with obesity-related biomarkers, the predicted equation proved a high predictive ability for LBM (men: R^2 = 0.91; women: R^2 = 0.85). We calculated the predicted value of lean body mass according to the equation in the former study (21, 22).

Outcomes

Cognitive function was examined by a series of cognitive function tests conducted on all respondents aged 60 years and older in a mobile examination center (23), including the Digit Symbol Substitution Test (DSST), Consortium to Establish a Registry for Alzheimer's Disease Word Learning test (CERAD-WL) and Delayed Recall test (CERAD-DR), and Animal Fluency (AF). These tests evaluated domains of information processing speed (DSST), memory (CERAD), and executive function (AF).

In the DSST, participants are asked to fill 133 boxes according to symbols that were paired to nine numbers within 2 minutes (24). The score is the total number of correct matches. In the NHANES, participants were shown how to perform the task and then filled several practice boxes before the test.

The CERAD Word Learning subtest includes immediate and delayed learning parts, using a word list of 10 unrelated words (25). In the NHANES, participants were requested to read each word in the list aloud and recall as many as possible immediately. This process was repeated three times with the order of words changed (CERAD-WL -score1, CERAD-WL -score2, CERAD-WL-score3) and the total score for the learning task was 30. The delayed recall trial was conducted after approximately 8-10 minutes, where participants were requested to recall the words used in the CERAD-WL trial without review of the word list. CERAD-WL refers to the sum of the four scores, and CERAD-DR refers to the last score.

In the AF test, participants are asked to name as many animals as possible in one minute. The score is the sum of the number of correct answers. In NHANES, participants first were asked to name three items of clothing, another verbal fluency category, as a practice test.

Because there is no gold standard regarding the threshold score for which the cognitive tests indicate cognitive impairment, we selected the lowest quartile in the study group (DSST ≤ 34 points, CERAD-DR ≤ 4 points, CAEDR-WL ≤ 20 points, AF ≤ 13 points) to indicate poor cognitive performance, or impairment, consistent with methods previously published in the literature (23, 26).

Statistical analysis

Demographic variables were presented as means as the mean (standard deviation (SD)) for continuous variables or as the number of participants (percentage) for categorical variables according to the LBM. One-way analysis of variance (ANOVA) and X^2 test were performed for the comparison of characteristics according to quintiles of predicted lean mass for continuous variables and categorical variables respectively. Logistic regression models were used to calculate ORs and 95% confidence intervals (CIs) for the associations between predicted LBM and cognitive impairment. LBM was first considered as a continuous variable and then categorized into quartiles. We adjusted for age, sex, race/ethnicity (Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, other race-including multi-Racial), education (college and above, middle and high school, primary school and less), annual-household-income in model 1. We further adjusted for potential mediators, including drinking status (never, former, and current drinker), BMI, hypertension, smoking status (never, former, and current smoker), cardiovascular disease, diabetes, and chronic kidney disease in model 2. We conducted stratified analyses of the association of predicted LBM with cognitive function according to gender. All analyses were performed using R version 4.2.1(http://www.r-project.org). The statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Our analysis was restricted to persons who were ≥ 60 years (n = 3632). We excluded 436 missing information on cognitive tests and additionally 241 missing information on LBM. Therefore, a total of 2955 participants were enrolled in our present analysis (Figure 1). Table 1 depicts the characteristics of participants according to predicted LBM quartiles. The mean age of the study population was 69.17 (SD: 0.20) years. Participants with higher levels of predicted LBM tended to be younger, have higher BMI, higher annual household income, better education, and a higher prevalence of diabetes, and CVD, and were more likely to be male, alcohol consumer, and Non-Hispanic White.

When analyzed as a continuous variable, higher LBM was associated with a lower risk of DSST impairment (OR= 0.97, 95% CI= 0.94 to 1.00) (Table 2), while aging was associated with higher risk (OR= 1.11, 95%CI= 1.08 to 1.14). Compared to Mexican American, Non-Hispanic White has a lower risk of DSST impairment, while Non-Hispanic Black has a higher risk. Participants with higher education, and higher annual household income is less likely to develop DSST impairment. When adjusting for BMI, hypertension, smoke, alcohol, CVD, DM, and CKD, the association of LBM with DSST strengthened (OR= 0.95, 95%CI= 0.91 to 0.99). However, lean mass was not associated with CERAD-WL (OR=0.97, 95%CI= 0.94 to 1.01), CERAD -DR (OR= 0.98, 95%CI= 0.95 to 1.01), and AF (OR= 0.99, 95%CI= 0.96 to 1.02) impairment after adjusting for confounders (Supplementary Table 1).

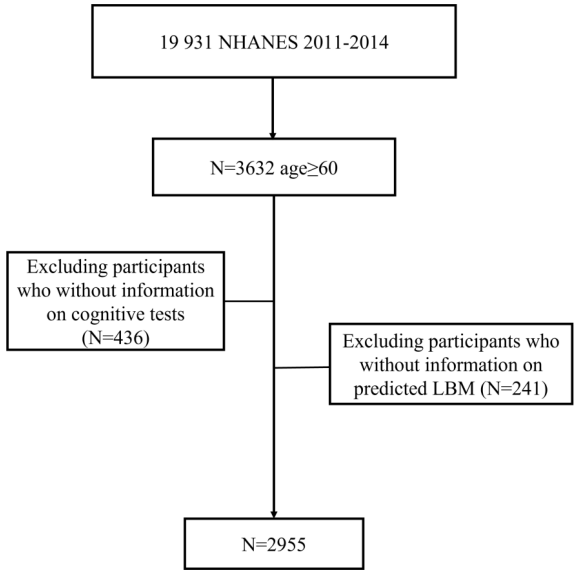

FIGURE 1
Flow chart of inclusion and exclusion of study participants.

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TABLE 1 Characteristics of study participants according to quintiles of predicted lean body mass [a].

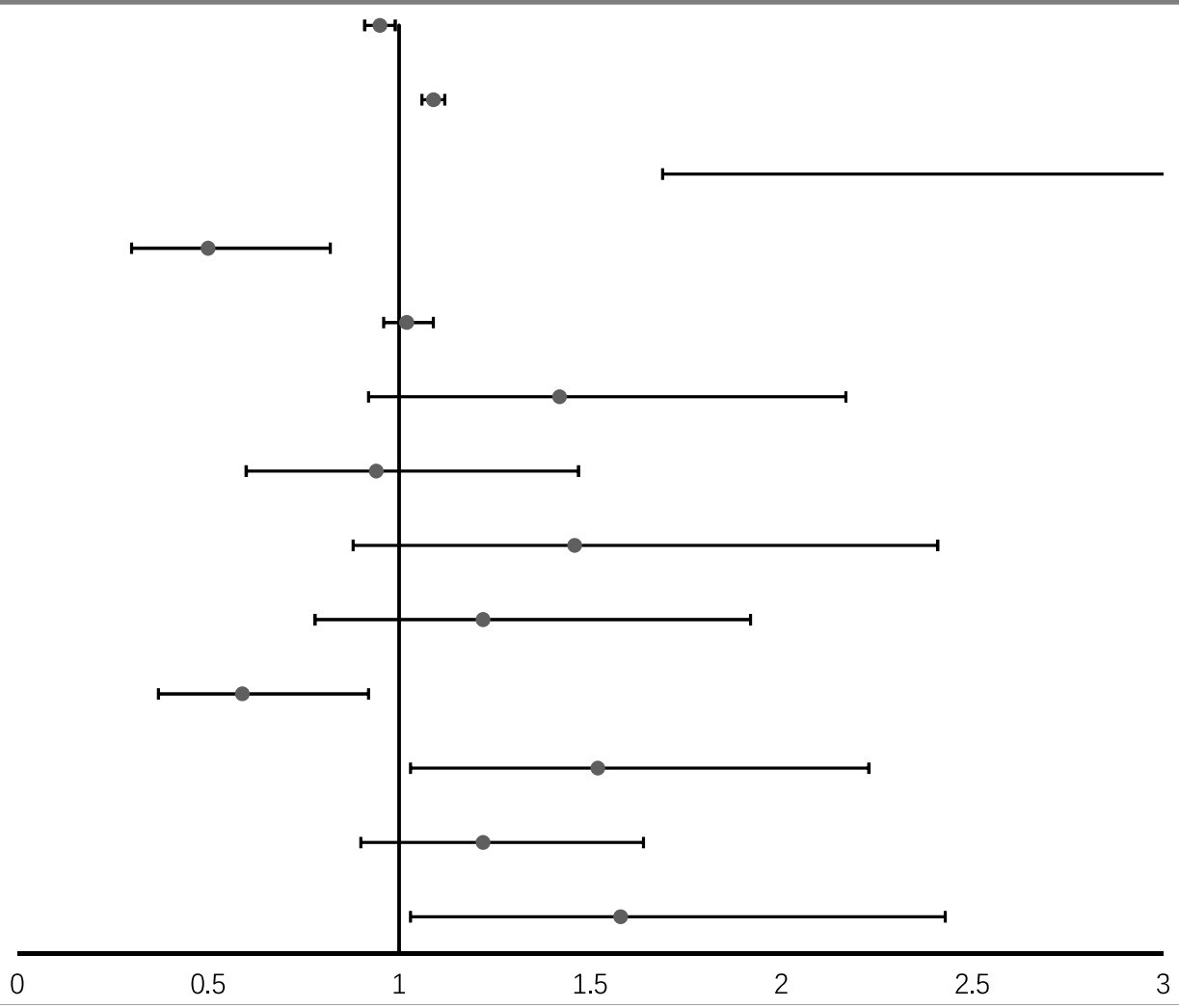
variable	total	Q1	Q2	Q3	Q4	P trend
Age, mean (SD), years	69.17 (0.20)	71.25 (0.35)	69.13 (0.29)	68.84 (0.32)	67.53 (0.28)	<0.0001
Sex, No. (%)						<0.0001
Female	1511 (51.13)	721 (98.60)	539 (83.44)	205 (31.22)	46 (5.78)	
Male	1444 (48.87)	18 (1.40)	199 (16.56)	534 (68.78)	693 (94.22)	
Ethnicity, No. (%)						<0.0001
Mexican American	274 (9.27)	76 (4.20)	64 (3.52)	77 (4.24)	57 (2.75)	
Non-Hispanic Black	717 (24.26)	68 (4.13)	182 (10.32)	210 (11.28)	257 (9.69)	
Non-Hispanic White	1345 (45.52)	356 (76.64)	320 (75.57)	306 (75.79)	363 (83.86)	
Other Hispanic	315 (10.66)	96 (5.37)	95 (4.88)	81 (4.07)	43 (1.82)	
Other Race-Including Multi-Racial	304 (10.29)	143 (9.67)	77 (5.71)	65 (4.63)	19 (1.88)	
Annual household income, No. (%)						<0.0001
<$65,000	2088 (74.07)	553 (71.85)	536 (67.23)	515 (61.02)	484 (55.13)	
≥$65,000	731 (25.93)	151 (28.15)	164 (32.77)	186 (38.98)	230 (44.87)	
Education, No. (%)						0.03
College and above	1475 (49.97)	363 (56.18)	361 (59.61)	358 (62.73)	393 (65.74)	
Middle and high school	1105 (37.43)	262 (35.28)	290 (34.62)	276 (30.21)	277 (30.02)	
Primary school and less	372 (12.6)	114 (8.54)	85 (5.76)	105 (7.06)	68 (4.24)	
DM, No. (%)	991 (33.54)	176 (18.80)	255 (28.05)	260 (28.61)	300 (33.05)	<0.001
CKD, No. (%)	985 (34.93)	242 (33.81)	253 (30.78)	244 (32.26)	246 (30.17)	0.62
CVD, No. (%)	641 (21.7)	128 (17.09)	156 (18.81)	178 (23.54)	179 (26.59)	0.01
Hypertension, No. (%)	2103 (71.17)	511 (66.52)	535 (67.10)	511 (64.16)	546 (69.92)	0.38
Smoke, No. (%)						<0.0001
former	1106 (37.45)	165 (28.99)	236 (31.88)	324 (44.78)	381 (51.92)	
never	1468 (49.71)	495 (60.53)	385 (54.00)	313 (44.99)	275 (38.76)	
now	379 (12.83)	78 (10.48)	117 (14.12)	101 (10.23)	83 (9.31)	
Alcohol, No. (%)						<0.0001
former	803 (27.61)	161 (21.66)	202 (23.30)	201 (23.43)	239 (24.58)	
never	492 (16.92)	214 (21.48)	130 (15.09)	89 (9.08)	59 (7.58)	
now	1613 (55.47)	349 (56.86)	392 (61.60)	441 (67.49)	431 (67.84)	
BMI, mean (SD), kg/m^2	28.97 (0.20)	24.61 (0.17)	29.24 (0.19)	29.34 (0.40)	32.51 (0.47)	<0.0001
WC, mean (SD), cm	102.38 (0.49)	89.20 (0.53)	101.13 (0.42)	104.10 (0.75)	114.50 (0.90)	<0.0001
Lean body mass, mean (SD), kg/m^2	48.65 (0.35)	34.80 (0.15)	42.83 (0.11)	51.40 (0.12)	64.69 (0.54)	<0.0001
CERAD-WL score, mean (SD), score	25.90 (0.31)	26.04 (0.37)	26.19 (0.43)	25.72 (0.32)	25.64 (0.46)	0.63
CERAD-DR score, mean (SD), score	6.23 (0.09)	6.30 (0.11)	6.27 (0.14)	6.21 (0.11)	6.16 (0.16)	0.77
AF score, mean (SD), score	18.14 (0.18)	17.17 (0.27)	17.96 (0.33)	18.41 (0.37)	18.97 (0.35)	<0.0001
DSST score, mean (SD), score	52.60 (0.57)	51.63 (0.92)	54.24 (0.91)	51.30 (0.88)	53.10 (0.72)	0.05

AF, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall test; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning test; DSST, Digit Symbol Substitution Test; BMI, body mass index; CI, confidence interval; Ref, reference; Edu, education; Eth, Ethnicity; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.

[a]All estimates accounted for sample weights and complex survey designs, and means and percentages were adjusted for survey weights of NHANES.

TABLE 2 Odds ratio (95%CI) for the associations between lean body mass and DSST impairment (results of model 2) [ac] .

Characteristic	Forest pot	OR (95% CI)
Lean body mass, kg/m^2		0.95 (0.91, 0.99) *
Age, years		1.09 (1.06, 1.12) *
Sex, male vs female		3.71 (1.69, 8.12) *
Annual household income ≥$65,000 vs <$65,000		0.50 (0.30, 0.82) *
BMI, kg/m^2		1.02 (0.96, 1.09)
Hypertension		1.42 (0.92, 2.17)
Former smoker vs never		0.94 (0.60, 1.47)
Now smoker vs never		1.46 (0.88, 2.41)
Former drinker vs never		1.22 (0.78, 1.92)
Now drinker vs never		0.59 (0.37, 0.92) *
CVD		1.52 (1.03, 2.23) *
DM		1.22 (0.90, 1.64)
CKD		1.58 (1.03, 2.43)



AF, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall test; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning test; DSST, Digit Symbol Substitution Test; BMI, body mass index; CI, confidence interval; Ref, reference; Edu, education; Eth, Ethnicity; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.

[a]All estimates accounted for sample weights and complex survey designs, and means and percentages were adjusted for survey weights of NHANES.

[C] Model 2 was adjusted for age, sex, race/ethnicity (Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, other race-including multi-Racial), education (college and above, middle and high school, primary school and less), annual-household-income, drinking status (never, former, and current drinker), BMI, hypertension, smoking status (never, former, and current smoker), cardiovascular disease, diabetes, and chronic kidney disease.

* $p<0.05$.

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When the predicted LBM was considered as a categorical variable, people with higher predicted LBM were more likely to have a lower risk of DSST impairment. (p for trend =0.018) and the highest predicted LBM quartile was associated with a 65.5% decrease in risk of DSST impairment (OR=0.355, 95%CI= 0.153 to 0.822) (Table 3). While the risk of CERAD-WL, CERAD-DR, and AF impairment was not associated with the category of predicted LBM (Supplementary Table 2).

When we examined the association between LBM and cognitive function stratified by sex, predicted LBM was associated with a lower risk of DSST impairment only in females (OR=0.9, 95%CI= 0.84 to 0.96) (Table 4). While taken as a categorical variable, higher predicted LBM was negatively associated with DSST impairment in both genders (female: OR=0.193, 95%CI= 0.043 to 0.876; male: OR=0.239, 95%CI= 0.043 to 0.863) (Supplementary Table 4).

Discussion

Our analysis of 2 cycles of the NHANES study showed that those with higher predicted LBM were associated with a lower risk of DSST impairment, where no association was found between BMI and DSST impairment. Although there was a trend showing that higher lean body mass was associated with a lower risk of cognitive impairment in other tests, we did not find statistical significance between groups.

Few investigators have studied the relationship between body composition and specific cognitive functions in normal people. A recent study reported uncorrelated associations between LBM with psychomotor function, attention, visual learning, and working memory (19). Skeletal muscle mass of the four limbs was associated only with delayed memory in Serena Low's study, while lower LESM (calculated as added left and right lower limbs divided by square of height) was independently associated with reduced cognitive function globally and specifically in domains of immediate memory, delayed memory and visuospatial/ constructional ability (27). To date, some studies have examined the relationship between lean mass loss and overall cognition, with inconsistent conclusions. Our findings are consistent with previous cohort studies that have reported a positive association between LBM and cognitive function (17, 28, 29). In a study of US elders using a standardized psychometric battery, accelerated loss of LBM was associated with worse cognitive performance and structure change of the brain (17). However, in a prospective study to assess various sarcopenia markers in conjunction with cognitive decline, muscle mass was not associated with the progression of cognitive impairment (30). Hye-Mi Noh et al. found that not the group with the highest total LBM but the second in females was associated with a lower risk for cognitive impairment. Discrepant findings may be due to the differences in the tools to screen for cognitive impairment, part of which is the low sensitivity of cognitive impairment; race/ethnicity, or residual confounding. Compared with these studies, NHANES is well designed with higher representativity and less sampling error; and this study included more participants and further stratified with sex and different cognitive tests. In our cohort, the 4th quartile of LBM was associated with higher BMI. However, the association between DSST and LBM remained significant after adjusting for BMI.

The positive association may result from shared mechanisms: lifestyle risk factors and poor nutrition (31). Aging is in conjunction with a sequence of exercise-related changes. Less physical activity can directly attribute to the decline of lean mass: age-related reductions in physical activity is the most important external cause of sarcopenia in normal aging (32). Physical activity can slow down the decline of cognitive function and protect the brain structure (33–36). On the other hand, the decrease in physical activity can also be the result of cognitive impairment, like AD, Parkinson, etc. Studies had found that low DSST was significantly associated with gait speed (37, 38). So, it might be a vicious circle in which physical activity and cognitive dysfunction favor each other. However, considering that dementia is a slowly progressive illness for which clinical symptoms may appear 20 years or more after pathophysiological changes in the brain, the relation between physical activity and cognitive dysfunction needs further explore.

Although this association was only found in the DSST test, the meaning cannot be ignored. DSST is a sensitive test to identify cognitive dysfunction, especially in impairments in processing speed, executive functioning, and working memory (39). The prevalence of low DSST was high (11%) even in the population of well-functioning older adults and related to a higher risk for mortality and disability (26). Participants with low DSST

TABLE 3 Odds ratio (95%CI) for the associations between lean body mass and DSST impairment [b], by predicted lean body mass index quartiles [a].

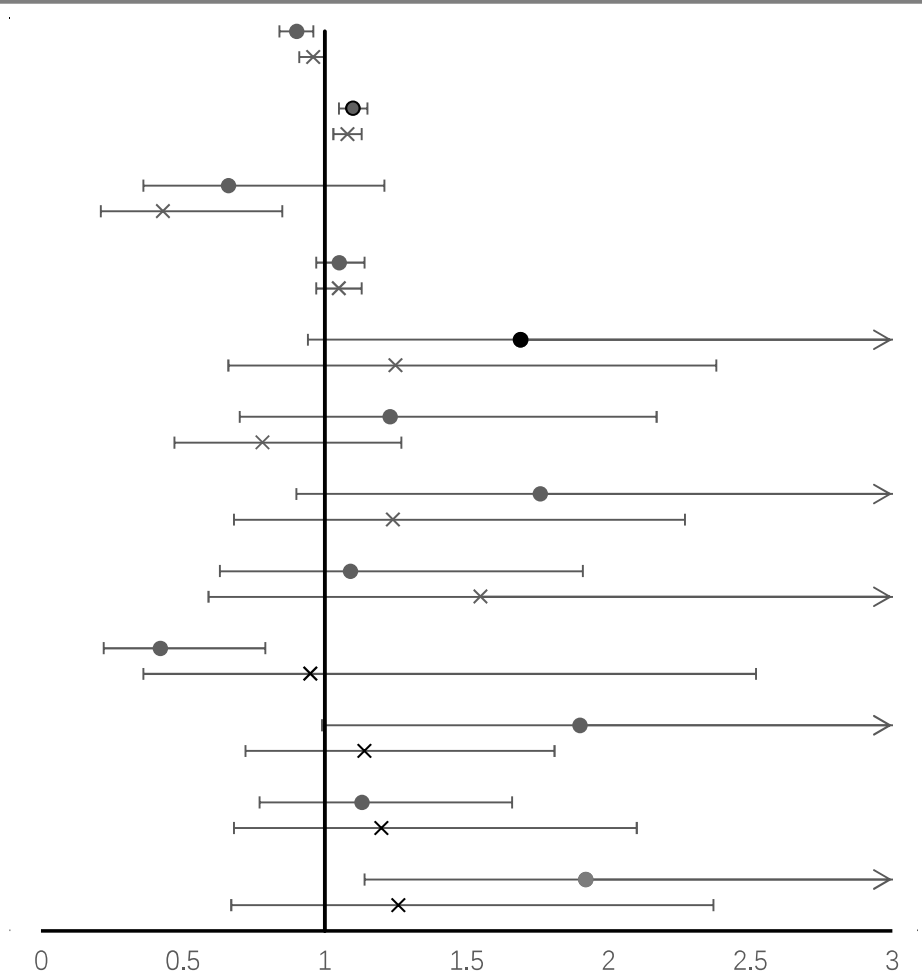
DSST impairment	Lean body mass							
	Q1	Q2	P	Q3	P	Q4	P	p for trend
Crude model	ref	0.74 (0.56,0.97)	0.04	0.82 (0.61,1.11)	0.19	0.57 (0.40,0.80)	0.00	0.01
Model 1	ref	0.63 (0.37, 1.08)	0.09	0.47 (0.22, 1.03)	0.06	0.37 (0.15, 0.90)	0.03	0.03
Model 2	ref	0.64 (0.38, 1.07)	0.08	0.47 (0.21, 1.02)	0.06	0.3 6(0.15, 0.82)	0.02	0.02

AF, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall test; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning test; DSST, Digit Symbol Substitution Test; BMI, body mass index; CI, confidence interval; Ref, reference; Edu, education; Eth, Ethnicity; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.

[a]All estimates accounted for sample weights and complex survey designs, and means and percentages were adjusted for survey weights of NHANES.

[b]DSST impairment was defined as a socre ≤ 34 points.

TABLE 4 Odds ratio (95%CI) for the associations between lean body mass and DSST impairment, stratified by sex (results of model 2) [ac].

Character	Forest plot	OR (95% CI)	
		Female	Male
Lean body mass, kg/m^2		0.90 (0.84, 0.96) *	0.96 (0.91, 1.00)
Age, years		1.10 (1.05, 1.15) *	1.08 (1.03, 1.13) *
Annual household income ≥$65,000 vs <$65,000		0.66 (0.36, 1.21)	0.43 (0.21, 0.85) *
BMI, kg/m^2		1.05 (0.97, 1.14)	1.05 (0.97, 1.13)
Hypertension		1.69 (0.94, 3.04)	1.25 (0.66, 2.38)
Former smoker vs never		1.23 (0.70, 2.17)	0.78 (0.47, 1.27)
Now smoker vs never		1.76 (0.90, 3.47)	1.24 (0.68, 2.27)
Former drinker vs never		1.09 (0.63, 1.91)	1.55 (0.59, 4.11)
Now drinker vs never		0.42 (0.22, 0.79) *	0.95 (0.36,2.52)
CVD		1.90 (0.99, 3.65)	1.14 (0.72, 1.81)
DM		1.13 (0.77, 1.66)	1.20 (0.68, 2.10)
CKD		1.92 (1.14, 3.23) *	1.26 (0.67, 2.37)

AF, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall test; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning test; DSST, Digit Symbol Substitution Test; BMI, body mass index; CI, confidence interval; Ref, reference; Edu, education; Eth, Ethnicity; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.

[a]All estimates accounted for sample weights and complex survey designs, and means and percentages were adjusted for survey weights of NHANES.

[C] Model 2 was adjusted for age, sex, race/ethnicity (Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, other race-including multi-Racial), education (college and above, middle and high school, primary school and less), annual household income, drinking status (never, former, and current drinker), BMI, hypertension, smoking status (never, former, and current smoker), cardiovascular disease, diabetes, and chronic kidney disease.

* $p<0.05$.

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performance had an increased risk of incident all-type dementia (40). And probable pathology basis was declaimed recently that declining processing speeds (tested by DSST) were associated with emerging PET-detected AD pathology in clinically normal older adults (41). In Caterina et al' work about cognitive-health people, lower DSST was associated with nearly twice the odds of developing 1+ clinical or subclinical disorders of cognition, mobility, and mood (42). Except for cognitive disorders, higher DSST was associated with a 28%-34% lower mortality risk in elders with white matter hyperintensities (43). In this context, this study has its merit in detecting people at high risk of low cognitive function and accepting early multi-domain preventive interventions, thereby interrupting the vicious circles and preventing or delaying dementia onset.

The current study has several limitations to be considered. First, it's a cross-sectional study, which prevents concluding on the causality between body composition and cognitive function. Second, our study was based on predicted body composition, which is a compromise of accuracy and cost and will inevitably cause measurement errors. However, the predictive ability of anthropometric equations was proved to be high (men: $R^2 = 0.91$; women: $R^2 = 0.85$) in an independent large validation study (21). Third, we didn't discriminate against the lean mass of different regions. Fourth, although we controlled the results for several potential confounders, some variables like APOE level, physical activity, the severity of different diseases, medicine or information on insulin-dependent (or not) were not included, which may have affected the association between LBM and cognitive impairment.

Conclusion

Our study provides new insights into the body composition and cognition function that predicted LBM was associated with lower DSST regardless of BMI. These findings highlight the importance of monitoring predicted LBM regularly among older adults through simple equations, which may help to identify populations at high risk of cognitive dysfunction for in-time intervention to improve prognosis. Although the mechanisms under this association are not figured out, maintaining relatively higher levels of LBM is importance for older adults. Further research is required to examine the causality and mechanisms between LBM and cognitive function.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

H-JG and XT contributed equally as co-first (or last) authors. J-BZ is corresponding author. H-JG, XT, Y-HC, Y-SQ, HX, IP, J-YZ have full access to all the data in this study and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis. H-JG and XT contributed to studies selection, data extraction, data analyses, and manuscript drafting. XT, Y-HC, Y-SQ, HX, IP, J-YZ contributed to data analyses, data interpretation, and manuscript drafting. J-BZ, H-JG, XT contributed to study design, data interpretation, and final approval of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1172233/full#supplementary-material

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Development and validation of a Sarcopenia Geriatric Scale (SARCO-GS): a new short scale for the screening of sarcopenia

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Introduction: Sarcopenia is a highly prevalent disease associated with adverse outcomes such as falls, disability, and death. The current international consensuses agree that muscle strength, muscle mass, and gait speed must be included in the definition. However, these proposed criteria require objective measurements that are not available for most populations. Since the timely identification of sarcopenia is a priority, several subjective screening scales have been developed; however, they have some limitations due to their low sensitivity. The objective of this work was to develop and validate SARCO-GS, a new short scale to screen sarcopenia that is affordable, easy, and accessible for all clinical care settings.

Methods and materials: The development of the SARCO-GS included four stages: (1) Review and analysis of documentary sources, (2) Contextualization of the theoretical model of sarcopenia, (3) Scale conformation, and (4) Reliability and validity analyses. SARCO-GS was validated in the FraDySMex study, which is a longitudinal cohort of community-dwelling adults.

Results: In the studied population (n=852), the average age was 68.9 years (SD 10.21) and 80.1% of the participants were women. SARCO-GS is a seven-item scale with an innovative structure that included five subjective questions (gait speed, muscular strength, muscle mass) and two measurements of muscular strength and muscle mass (Chair stand test and calf circumference). The results regarding criterion validity showed that the cut-off point ≥ 3 had good sensitivity (77.68%) versus the EWGSOP2 consensus, with an adequate Area Under the Receiver Operating Characteristic (AUC) (0.73), in addition to showing higher values of sensitivity and AUC than SARC-F and SARC-CalF using as reference the same consensus. Furthermore, SARCO-GS presented good predictive validity for functional dependence (HR=2.22, p=0.046) and acceptable correlation with other related measurements (construct validity). Regarding reliability, the scale showed acceptable internal reliability (correlation between items and total score: 0.50 to 0.70). After the validation analysis, the scale was adapted to English.

Conclusions: The SARCO-GS is a novel scale to screen sarcopenia with high sensitivity, good construct, predictive validity, and internal reliability that may be useful for health professionals in different clinical settings and for clinical research.

KEYWORDS

sarcopenia, scale, validation, screening, SARCO-GS, validity

1 Introduction

Sarcopenia is associated with age, and it is a common condition among older adults; however, most cases of sarcopenia are undiagnosed (1). A recent meta-analysis (2) estimated that the global prevalence of sarcopenia in older adults (≥60 years) ranged from 10% to 27% depending on the diagnostic criteria used for the evaluation. The main factors related to sarcopenia development are aging, low physical activity, some diseases (i.e., bone and joint diseases, and endocrine and neurological diseases), as well as nutritional factors such as an inadequate intake of energy, macronutrients, and micronutrients. These factors cause a set of alterations in skeletal muscle homeostasis, including mitochondrial dysfunction, neural plaque changes, motor neuron loss, oxidative stress, inflammation, and changes in hormones and growth factors, which are responsible for the loss of muscle mass and muscular strength (1). Several studies have identified that sarcopenia increases the risk of mortality (3), cognitive impairment (4), cardiovascular diseases (5), and functional disability (6), among other adverse health outcomes (6). There is no consensus about the clinical definition of sarcopenia (1, 7, 8). However, the existing definitions agree that it is a skeletal muscle disorder characterized by a loss of quantity and quality of muscle and low muscular strength (1, 7–10). In addition, the European Working Group on Sarcopenia in Older People (EWGSOP2) (10) and the Asian Working Group for Sarcopenia (AWGS) (9) included the presence of low physical performance (gait speed or chair stand). The EWGSOP2 (10), the AWGS (9), and the Foundation for the National Institutes of Health (FNIH) (11) have developed consensuses to diagnose sarcopenia based on objective measurements. These consensuses consider cut-off points for muscular mass, measured by dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA), and muscular strength measured by a manual dynamometer to establish the diagnosis of sarcopenia. The main limitation of these criteria is that they require expensive equipment to perform the measurements, making them unaffordable in clinical settings and communities. Besides, the different criteria for diagnosis reflect a need for more consensus regarding the cut-off points. However, there is a general agreement on the urgency of the call for action regarding early identification through screening scales and tests and the treatment of sarcopenia (8, 10, 11).

Given all the above, validated subjective screening scales have been developed comprising the self-report of factors related to muscle mass and muscle strength (12). The most used scale is the SARC-F (13), which has shown excellent predictive validity for adverse outcomes but low sensitivity (from 28.9 to 55.3% versus EWGSOP2); this is reported in several studies and summarized in a systematic review and meta-analysis which concluded that this scale is not optimal for sarcopenia screening (14). Subsequently, the SARC-CalF scale (15) was developed with the aim of improving sensitivity by including the measurement of calf circumference; this adjustment has shown to have a better sensitivity (from 33% to 66%) (15). However, another limitation of SARC-F and SARC-CalF is the inclusion of the number of falls within the factors evaluated to perform the diagnosis. Falls are a medium- and long-term adverse consequence of sarcopenia; therefore, this affects the early identification of individuals at risk to present adverse outcomes. Although other scales like the Mini Sarcopenia Risk Assessment (MSRA) questionnaire (16) and SarSA-Mod (17) present good or excellent sensitivity, they are focused on evaluating characteristics related to the risk of sarcopenia and not specifically to its presence.

Considering the above, our objective was to develop and validate SARCO-GS, a new short scale for the screening of sarcopenia that is affordable and easy to use, with good sensitivity, and accessible for all clinical care settings.

2 Methods and materials

2.1 Study design and population

The present study includes a longitudinal and cross-sectional data analysis on individuals aged 50 years or older participating in the FraDySMex study (Frailty, Dynapenia, and Sarcopenia in Mexican Adults). The details of the FraDySMex study (design and selection of participants) are available in other publications (18). In brief, it is a cohort study (panel study) of community-dwelling adults, mainly from three municipalities in the southeast of Mexico City. The inclusion criteria for the present study were (1): individuals who were able to move with or without assistive devices, (2) individuals who were able to answer the study questionnaire for themselves or with the help of a caregiver, (3) individuals who scored 10 points or fewer in the Mini-Mental State Examination (MMSE), and (4) individuals whose objective and subjective measurements were completed. The exclusion criteria were: (1) individuals who were institutionalized; (2) individuals with

decreased alertness; and (3) the presence of any acute or chronic condition that, according to the opinion of the medical staff, could affect the individual's ability to answer the proposed questionnaire and complete the objective evaluation. The study had a three-round design: the first round was carried out in 2014 (n=282), the second round in 2015 (n=457), and the third round in 2019 (n=852). In all rounds, the individuals underwent a series of objective and subjective evaluations by a multidisciplinary team at the Geriatric Assessment Center at the Ibero-American University and the Functional Evaluation Research Laboratory at the National Geriatric Institute in Mexico City. This study was approved by the Ethics Committee of the Angeles Mocel General Hospital and registered by the National Institute of Geriatrics (DI-PI-002/2014) and by the National Bioethics Commission (CONBIOETICA-09-cei-013- 20170517/2019). The informed written consent of all individuals was obtained.

2.2 Measurements

2.2.1 Sarcopenia

The diagnosis of sarcopenia was made using the EWGSOP2, FNIH, and AWGS consensuses, and the following measurements were considered:

1. Muscle mass: The body composition was measured by dual-energy x-ray absorptiometry (DXA) (Hologic Discovery-WI; Hologic, Bedford, MA). For the EWGSOP2 (10), the appendicular skeletal muscle mass (ASM) was calculated as the sum of the appendicular lean mass minus the bone mineral content of both arms and legs; the cut-off point for this measurement was <20 kg for men and <15 kg for women. For the FNIH consensus (11), the ASM/Body mass index (BMI) was used (cut-off points: <0.798 for men and <0.512 for women). Whereas for the AWGS (9), the skeletal muscle mass index (SMI) was obtained by dividing the ASM by the squared height (cut-off points: <7.00 kg/m^2 for men and <5.40 kg/m^2 for women).

2. Muscle strength: Grip strength was measured with a hydraulic hand dynamometer (Jamar, Duluth, MN). Three measurements were taken from each hand, and the highest result for the dominant hand was considered the final value. The cut-off points for the EWGSOP2 (10) were <27 kg for men and <16 kg for women; for the FNIH (11), they were <26 kg for men and <16 kg for women, while for the AWGS (9) they were <28 kg for men and <18 kg for women.

2.2.2 Other variables

- Data on age (50-69, 70 years and older), sex (male, female), and marital status (married/consensual union, single/divorced, widow/widower) were obtained from the questionnaires applied in each evaluation round.

- Anthropometric measurements. Weight was measured with a Body Composition Analyzer (Seca MBCA514), height was measured with a stadiometer (Seca 264), and the Body Mass Index (BMI) was estimated by dividing the weight by the squared height. The calf circumference was measured three times with an anthropometric tape (Seca 201). The first measurement was considered for the analysis since there were no significant differences between the three measurements. The cut-off point to screen low muscle mass was the one proposed in the SARC-CalF (≤33 cm for women and ≤34 cm for men) (15).

- Chair stand test. This test consisted of sit-to-stand repetitions (five times) while measuring the time it took the individual to execute the action; we considered this as an indicator of muscular strength. The considered cut-off point was the one proposed by the EWGSOP2 (>15 seconds).

- Quality of life. This was assessed by employing the visual analog scale from the EuroQol (EQ-VAS) (from 0 to 100 total score) (19).

- Functional dependence. This was evaluated by observing the ability to perform instrumental activities of daily living (IADL) with the Lawton Instrumental Activities of Daily Living Scale (Functional disability ≤7 points) (20), while the basic activities of daily living (ADL) were assessed with the Barthel Index (from 0 to 100 total score) (21).

- Comorbidity. This was measured with the Charlson comorbidity index (22) (low comorbidity: 0-2 points, high comorbidity ≥3 points).

- Nutritional status. This factor was evaluated with the Mini Nutritional Assessment (MNA) (from 0 to 21 total score) (23).

- Gait speed. This was measured with the GAITRite G walk System (m/seg).

- Physical performance. This was evaluated by employing the Short Physical Performance Battery (SPPB) (from 0 to 12 total score) (24).

- Phase angle. This was evaluated with a bioelectrical impedance tetrapolar, brand SECA-mBCA 514, at a frequency of 50Hz (from 0 to ∞ total score in grades).

- Cognitive impairment. This was assessed by the MMSE (score ≤23 in the case when the years of study were ≥5; score ≤19 if the years of study were between 1 and 4; score ≤ 16 if the years of study were <1) (25).

- Depression symptoms. They were evaluated with the seven-item Center for Epidemiologic Studies depression scale short form (CESD-7) (≥5 points) (26).

2.3 Development of SARCO-GS

The development of the SARCO-GS included three stages (1): a literature review about scales and consensuses to evaluate sarcopenia in older adults, (2) contextualization of the theoretical model, and (3) conformation of the scale.

2.3.1 First stage: review and analysis of documentary sources

This stage included a review of the scientific literature in the PubMed electronic database. The search strategy was carried out using the following Medical Subject Heading (MESH) terms: "Sarcopenia" AND "Diagnosis" AND "Aging" AND "Consensus" OR "Validation Study". In addition, the employed keywords were

development, validation and scale, tool or test or instrument or screening or index or battery. The inclusion criteria were the following: consensuses on the diagnosis of sarcopenia and studies developing and validating sarcopenia screening tools in older adults written in English or Spanish. On the other hand, studies focused on evaluating sarcopenia on specific diseases (i.e., diabetes, cancer, or cardiovascular diseases) were excluded.

As a result of the literature search, several scales were found; of these, we selected the most relevant according to their clinimetric properties and practical usefulness for the screening of sarcopenia. The most outstanding and the most studied in different populations and languages were SARC-F and SARC-F-Calf (13, 27). However, within their theoretical models, they include an item for falls ("How many times have you fallen in the past year?"), which is considered a geriatric syndrome and a negative outcome of sarcopenia; therefore, it must not be included in the theoretical model of sarcopenia (strength, muscle mass, and slow gait speed or low score in the Chair stand test). In addition, something that has characterized SARC-F is its low sensitivity in different studies and populations (13, 27–29). As shown in several studies, adding the calf circumference to the SARC-F improves its sensitivity (SARC-CalF) (15, 28, 29). Other scales like the Mini Sarcopenia Risk Assessment (MSRA) questionnaire (16) and SarSA-Mod (17) are focused on evaluating characteristics related to the risk of sarcopenia and not specifically to its presence.

2.3.2 Second stage: contextualization of the theoretical model

A multidisciplinary team that included geriatricians, internists, rehabilitation physicians, nutritionists, and physiotherapists analyzed the selected literature to build the theoretical model of sarcopenia and design the preliminary components of the scale. The team concluded that the items related to the three dimensions of sarcopenia (muscle strength, muscle mass, and gait speed) on which the current consensuses agree (9–11, 16) should be included in the scale.

2.3.3 Third stage: conformation of the scale

The first preliminary version of the scale included an item pool with 41 subjective items. Following the Delphi (30) method, the multidisciplinary team evaluated the face validity and the content validity of each one of the items.

In the first work session, 80% of the team agreed to eliminate 31 items due to insufficient face or content validity. The second preliminary subjective version included 10 items that were tested in a pilot group of 15 adults aged 50 years or older to assess the comprehension of the questions. In the second work session, the team discussed the comprehension of the questions, and it was concluded that the participants of the pilot study had good comprehension of the questions. Therefore, the team decided to include the 10 items in the three rounds of the FraDySMex cohort (2014, 2015, and 2019). In a third work session, the team concluded that the main problem of subjective scales was their low sensitivity versus international consensuses. This could be due to the comparison between subjective items and objective criteria. To improve the above in the new scale, the team agreed to include subjective items and affordable objective proxy tests to evaluate muscular strength and muscle mass. The chosen tests were the Chair stand test and the measurement of calf circumference, based on their predictive validity for different outcomes (15, 29, 31–33). The inclusion of calf circumference to SARC-F has demonstrated an improvement in the criterion validity (sensitivity, specificity, and AUC) (15, 29). The addition of the Chair stand test in the SARCO-GS was considered since the low muscular strength that this test is able to assess has been proposed by international consensuses as a part of sarcopenia (confirmed or severe) (10), and because it has proven to be an excellent proxy to evaluate the strength of leg muscles (quadriceps muscle group). The cut-off points for these measurements were: >15 seconds on the Chair stand test (10) and ≤33 cm and ≤34 cm of calf circumference for women and men, respectively (15).

2.3.3.1 Optimization of the scale length

In a fourth work session, the team analyzed the inter-item correlation. If the correlation between items was rho ≥ 0.90, then the items were discarded. Five items were eliminated, resulting in the final version of the SARCO-GS seven-item [one subjective item of gait speed, two subjective items of muscle strength, two subjective items of muscle mass, the Chair stand test, and calf circumference (Table 1)].

2.3.3.2 Translation–retranslation

Once the final version was established, we translated the SARCO-GS into English to encourage its use among non-Spanish-speaking populations, following a standardized procedure (translation and retranslation) to adapt scales (34) (Table 1).

2.4 Validation (validity and reliability)

The final version of the SARCO-GS seven-item was subjected to reliability and validity analyses. All the analyses except those of predictive validity were performed with data from the 2019 round of FraDySMex since the sample size (n=852) was greater than the size of other rounds.

2.4.1 Criterion validity

2.4.1.1 Cut-off point selection

To determine the cut-off points, the AUC was estimated using the SARCO-GS total score versus the EWGSOP2 consensus, and the cut-off point with better sensitivity, specificity, and AUC was chosen.

Once the cut-off point of SARCO-GS was determined, we analyzed the sensitivity, specificity, AUC, and likelihood ratios of SARCO-GS versus EWGSOP2, FNIH, AWGS, SARC-F, and SARC-CalF as reference standards.

Additionally, to strengthen the criterion validity, we compared the AUC between SARCO-GS, SARC-F, and SARC-CalF (screening scales) using as reference the EWGSOP2 (10), FNIH (11), and AWGS (9) consensuses in order to evaluate which scale had the better AUC.

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TABLE 1 SARCO-GS, Spanish and English versions.

Spanish Version			
Dimensiones	Items	Categorías	Puntaje
Velocidad de la marcha subjetiva	1. Desde hace 3 meses ¿Ha notado que camina…	Nada lento (normal)	0
		Un poco lento	1
		Muy lento o incapaz	2
Medición subjetiva de fuerza muscular	2. ¿Cuánta fuerza tiene para cargar algo pesado de 4 kilogramos o más? Ejemplo: cargar una cubeta o barrica o garrafón de llenas de agua o cargar dos bolsas de mandado o supermercado	Mucha	0
		Poca	1
		Nada o incapaz	2
	3. ¿Cuánta dificultad tiene para subir un piso de escaleras?	Ninguna	0
		Poca	1
		Mucha	2
Medición subjetiva de cantidad de masa muscular	4. En los últimos 3 meses: ¿Ha notado que sus piernas y/o brazos han enflaquecido?	Nada	0
		Poco	1
		Mucho	2
	5. En los últimos 3 meses: ¿Ha notado que sus piernas y/o brazos están más flacos o delgados comparado con las personas de su misma edad?	Nada	0
		Poco	1
		Mucho	2
Medición objetiva de fuerza muscular	6. Prueba de levantarse de la silla 5 veces	≤ 15 segundos	0
		≥ 16 segundos	2
Medición objetiva de cantidad de masa muscular	7. Circunferencia de pantorrilla	Mujer: >33 Hombre: >34	0
		Mujer: ≤33 Hombre: ≤34	2
Sarcopenia = ≥ 3 puntos del puntaje total.			
English Version			
Dimensions	Items	Categories	Score
Subjective gait speed	In the past 3 months, you have noticed that you walk…	Not slowly at all (normal)	0
		A little slowly	1
		Very slowly or unable	2
Subjective muscular Strength	1. How able do you feel to carry a heavy object? (at least 4 kilograms or 9 pounds) Example: carrying a bucket, barrel, or jug full of water or carrying two supermarket bags	Very	0
		Little	1
		Not at all or unable	2
	How difficult is it for you to climb up a flight of stairs?	Not at all	0
		A little	1
		Very	2
Subjective muscle mass	In the last three months, have you noticed that your legs and/or arms have become thinner?	Not at all	0
		A little	1

(Continued)

TABLE 1 Continued

English Version			
Dimensions	Items	Categories	Score
		Much	2
	In the last 3 months: Have you noticed that your legs and/or arms are skinnier or thinner compared to people your same age?	Not at all	0
		A little	1
		Much	2
Objective muscular strength	Chair stand test (Stand up from a chair 5 times)	≤ 15 seconds	0
		≥ 16 seconds	2
Objective muscle mass	Calf circumference	Female: >33 Male: >34	0
		Female: ≤33 Male: ≤34	2
Sarcopenia = ≥ 3 points.			

2.4.2 Construct validity

To test if the SARCO-GS had adequate construct validity (convergent validity with other measurements), Spearman's and Pearson's correlation coefficients were estimated between each item and the total score versus the total score of other measurements related to the construct. The remaining related measurements were quality of life, IADL, ADL, presence of depressive symptoms, comorbidity, nutritional status, gait speed, physical performance, hand grip strength, and phase angle.

2.4.3 Predictive validity

To strengthen the validity, we assessed whether sarcopenia was associated with an increased risk of functional disability. To evaluate the functional dependency, the ability to perform instrumental activities that could be considered complex was evaluated with the Lawton Instrumental Activities of Daily Living Scale (20). We chose this tool considering that the study participants were non–institutionalized adults who had to attend the evaluation centers; therefore, they were expected to have more independence in daily basic activities. To assess the above, we considered the basal measurements of the participants in the study (2014–2015) and the follow-up measurement of functional disability in 2019. A Cox model was performed, adjusting by the following potential confounder variables: age, sex, BMI, education, marital status, comorbidity, and cognitive impairment.

2.4.4 Consistency (reliability)

Spearman's correlation coefficients between items (inter-item) and the total score (item-total) were estimated to assess internal reliability. It was considered sufficient correlation if the coefficient between each item and the total score was significant and higher than 0.30 (35). In addition, the Cronbach's alpha was estimated.

2.5 Statistical analysis

In the descriptive analysis, means ± SD were used for continuous variables, as well as frequencies and percentages for categorical variables.

2.5.1 Criterion validity

The cut-off point was determined with a frequency table and the AUC.

The sensibility, specificity, AUC, and likelihood ratios between SARCO-GS and EWGSOP2, FNIH, and AWGS were assessed through a frequency table and the AUC.

The AUC between SARCO-GS, SARC-F, and SARC-CalF using as reference the EWGSOP2, FNIH, and AWGS consensuses were graphed and compared to evaluate which scale had the better AUC.

2.5.2 Construct validity

Spearman's and Pearson's (normal distribution) correlation coefficients between each item of the scale and the total score versus the total score of the other related measurements were estimated.

2.5.3 Predictive validity

To evaluate if sarcopenia screening by SARCO-GS was an independent risk factor for functional dependence, the Hazard Ratios (HR) were estimated with a Cox regression model adjusting for other variables.

A p-value <0.05 was considered significant and we considered 95% confidence intervals (CI). All the analyses were conducted in STATA/SE 15.0.

3 Results

3.1 Sample characteristics

The characteristics of the study sample (FraDySMex round 2019) in which SARCO-GS was validated are in Table 2. The average age was 68.9 years (SD 10.21) and 80.1% were female, almost half (48.8%) were married or in a consensual union, and 71% were overweight or obese (40.9% and 30.4%, respectively). Regarding comorbidities, 77.5% had low comorbidity according to the Charlson Index.

3.2 Criterion validity

3.2.1 Cut-off point selection

The final total score of SARCO-GS was set from 0 to 14 points. The selected cut-off point to screen sarcopenia with SARCO-GS was ≥3 from the total score (Table 2). This value had better sensitivity (77.68%), specificity (53.71%), and AUC (0.73) (considering the EWGSOP2 consensus as a reference) (Table 3).

SARCO-GS had higher values of sensitivity and AUC than SARC-F and SARC-Calf using EWGSOP2 and FINH as references. Regarding specificity, SARC-F and SARC-Calf obtained higher values than SARCO-GS (Table 4).

Figures 1A-C show the comparative AUC between SARCO-GS, SARC-F, and SARC-CalF, considering EWGSOP2 (Figure 1A), FNIH (Figure 1B), and AWGS (Figure 1C) as references. SARCO-GS had a higher AUC than SARC-F and SARC-CalF when the EWGSOP2 and the FNIH were considered as references. However, when AWGS was used as a reference, SARCO-GS had a better AUC than SARC-F but not better than SARC-CalF.

3.3 Construct validity

The SARCO-GS had adequate construct validity (convergent) since there was a significant correlation between the dimension that evaluates each item, the total score, and other objective/subjective measurements (Table 5). Item 1 (subjective gait speed) was correlated with IADL and ADL, Charlson Index, depression symptoms, gait speed, hand grip strength, and physical performance; items 2 and 3 (subjective muscular strength) were correlated with quality of life, IADL and ADL, depression symptoms, nutritional status, gait speed, hand grip strength, and physical performance; both items 4 and 5 (subjective muscular mass) were correlated with nutritional status and item 4 was also correlated with depression symptoms, physical performance, and angle phase. The results of the Chair stand test were correlated with IADL and ADL, nutritional status, hand grip strength, physical performance, and angle phase, whereas calf circumference only correlated with angle phase. All the assessed measurements were correlated with the SARCO-GS total score.

3.4 Predictive validity

Sarcopenia screened by SARCO-GS increased the risk of functional dependence (HR: 2.33, CI 95% 1.02-4.88, p-value=0.046) in adults aged 50 years or older in 4.2 years (average) of follow-up (Table 6). Therefore, SARCO-GS had predictive validity concerning functional dependence, which is an adverse outcome of sarcopenia.

TABLE 2 Baseline characteristics of the participants of FraDySMex cohort, Mexico City.

Age (years)	% (n)
50-69	56.2 (479)
≥70	43.8 (373)
Sex	
Female	80.1 (423)
Male	19.9 (105)
Marital status	
Married/consensual union	48.8 (415)
Single/divorced	26.12 (222)
Widower/widow	25.06 (213)
Body Mass Index (kg/m^2)	
Normal (18.5-24.9)	28.0 (236)
Low weight (<18.5)	0.7 (6)
Overweight (25-29.9)	40.9 (345)
Obesity (≥30)	30.4 (256)
Comorbidity (Charlson Index)	
Low comorbidity (<3 points)	77.5 (606)
High comorbidity (≥3 points)	22.5 (192)
Sarcopenia (SARCO-GS)	
No sarcopenia (<3 points)	45.4 (383)
With sarcopenia (≥3 points)	54.6 (461)

TABLE 3 Different cut-off points of SARCO-GS and their sensibility, specificity, and likelihood ratios versus EWGSOP2.

Cut-off point	Sensitivity (%)	Specificity (%)	LR (+)	NLR (-)
≥0	100.00	0.00	1.00	–
≥1	93.30	24.03	1.23	0.28
≥2	88.55	40.12	1.48	0.32
≥3*	**77.68**	**53.71**	**1.68**	**0.42**
≥4	66.96	67.58	2.10	0.49
≥5	50.89	80.23	2.37	0.63
≥6	37.95	88.43	3.02	0.71
≥7	29.46	93.12	3.89	0.76
≥8	20.54	94.44	3.35	0.85
≥9	14.29	96.34	3.54	0.89
≥10	8.93	98.24	4.61	0.93
≥11	3.12	99.12	3.23	0.98
≥12	1.34	99.56	2.77	0.99
≥13	0.45	99.71	1.38	1.00
≥14	0.00	99.85	0.00	1.00

AUC = 0.73.
*Selected cut-off point to screen sarcopenia.
Positive likelihood ratio (LR+), negative likelihood ratio (LR+), European Working Group on Sarcopenia in Older People (EWGSOP).

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TABLE 4 Criterion validity of SARCO-GS (≥ 3 points), SARC-F and SARC-CalF versus sarcopenia consensuses.

	Sensitivity (%)	Specificity (%)	LR (+)	NLR (-)	AUC
EWGSOP2					
SARCO-GS	77.68	53.71	1.68	0.4156	0.73
SARC-F	22.77	91.49	2.68	0.84	0.62
SARC-CalF	37.95	85.07	2.54	0.73	0.69
FNIH					
SARCO-GS	74.15	52.44	1.56	0.49	0.67
SARC-F	23.90	92.39	3.14	0.82	0.62
SARC-CalF	31.22	83.50	1.89	0.82	0.62
AWGS					
SARCO-GS	77.57	48.71	1.52	0.46	0.70
SARC-F	17.76	88.51	1.54	0.93	0.56
SARC-CalF	50.47	83.24	3.012	0.59	0.74

European Working Group on Sarcopenia in Older People (EWGSOP), Foundation for the National Institutes of Health (FNIH), Asian Working Group for Sarcopenia (AWGS 2019), positive likelihood ratio (LR+); negative likelihood ratio (LR-).

3.5 Consistency (Reliability)

Table 7 shows the internal reliability of SARCO-GS. The Spearman's correlation coefficients between each item and the total score were in a range from 0.50 to 0.70 (moderate and good correlations). The Cronbach's alpha was 0.67, which is close to 0.70, an acceptable value for reliability (36).

4 Discussion

The structure of the new SARCO-GS (subjective items on strength, muscle mass, and gait speed plus the Chair stand test and calf circumference) proposes an innovative manner to screen the sarcopenia construct based on the recommendations of international consensuses on sarcopenia (9–11). This mixed composite structure (subjective and objective) was built based on current evidence that has reported that the inclusion of objective items ameliorates the low sensitivity showed by totally subjective scales such as SARC-F (this low sensitivity is observed when subjective scales are compared with objective diagnosis criteria). In our study, the sensitivity demonstrated by SARCO-GS versus EWGSOP2, FNIH, and AWGS was good. SARCO-GS demonstrated a higher sensibility than SARC-F and SARC-CalF versus EWGSOP2, FNIH, and AWGS. The low sensitivity of SARC-F observed in our study is consistent with that reported in multiple studies (13, 27–29) and summarized in a systematic review and meta-analysis (14) in which values from 28.9% to 55.3% were reported versus EWGSOP2, FNIH, and AWGS. Similarly, SARC-CalF sensitivity has obtained a range from 15.7% to 60.7% versus the mentioned consensuses in other studies (28, 29, 37, 38). Regarding the specificity, SARC-F and SARC-CalF obtained higher values than SARCO-GS versus the three consensuses used as references. However, in a scale intended for population screening, a higher sensitivity is more desirable than specificity due to the importance of decreasing the number of false negatives (14, 39). In other studies, it has been observed that SARC-F has higher values of specificity than of sensibility (range value from 15% to 96.5% versus EWGSOP2; 79.3% to 99.2% versus FNIH; 15.1% to 98.4% versus AWGS); this is also the case for SARC-CalF (29, 38, 40, 41).

Another property of SARCO-GS is that its AUC reflected a good quality when EWGSOP2 was used as a reference. This value was higher than the one obtained by SARC-F (0.62). In other studies (14, 29), a wide range of AUC values has been observed for SARC-F versus EGWSOP from 0.51 to 0.87. Also, SARCO-GS had a higher AUC (0.67) than SARC-F (0.62) versus FNIH. In other studies (14, 29, 37, 40), SARC-F obtained AUC values from 0.68 to 0.89. Regarding AWGS, the AUC of SARCO-GS (0.70) was higher than that of SARC-F (0.56); the AUC of SARC-F reported in this study was inside the range reported in other studies (0.53 to 0.92) (14, 29, 37). On the other hand, the AUC of SARCO-GS was also higher than SARC-CalF (0.69) versus EWGSOP and FNIH; other studies (29, 37, 38, 40) have reported that this value ranges from

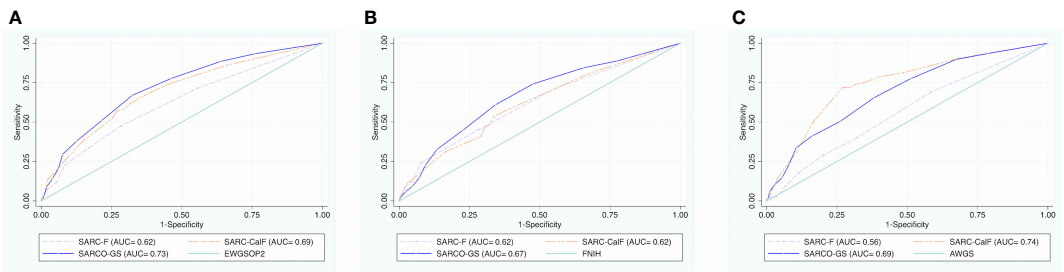

FIGURE 1
Comparative AUC between SARCO-GS, SARC-F, and SARC-CalF versus EWGSOP2, FNIH, and AWGS criteria. **(A)** Comparative AUC between SARCO-GS, SARC-F, and SARC-CalF versus EWGSOP2 criteria. **(B)** Comparative AUC between SARCO-GS, SARC-F, and SARC-CalF versus FNIH criteria. **(C)** Comparative AUC between SARCO-GS, SARC-F, and SARC-CalF versus AWGS criteria.

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TABLE 5 Construct validity of SARCO-GS (convergent and divergent) by correlations with other measurements.

Variable	Item 1		Item 2		Item 3		Item 4		Item 5		Item 6		Item 7		Total score	
Total score	rho	P	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Quality of life EQ-VAS	-0.14	<0.001	-0.20	<0.001	-0.25	<0.001	-0.15	0.001	-0.12	<0.001	-0.15	0.002	-0.02	0.5487	-0.22	<0.001
ADL Barthel Index	-0.28	<0.001	-0.30	<0.001	-0.34	<0.001	-0.18	<0.001	-0.09	0.007	-0.27	<0.001	-0.10	0.002	-0.33	<0.001
IADL Lawton scale	-0.29	<0.001	-0.40	<0.001	-0.36	<0.001	-0.14	<0.001	-0.10	0.002	-0.37	<0.001	-0.19	<0.001	-0.41	<0.001
Depression symptoms CESD-7	0.29	<0.001	0.28	<0.001	0.29	<0.001	0.23	<0.001	0.19	<0.001	0.19	<0.001	0.04	0.238	0.34	<0.001
Comorbidities Charlson Index	0.24	<0.001	0.20	<0.001	0.20	<0.001	0.13	<0.001	0.09	0.012	0.17	<0.001	-0.006	0.856	0.24	<0.001
Nutritional status MNA	-0.35	<0.001	-0.31	<0.001	-0.32	<0.001	-0.32	<0.001	-0.30	<0.001	-0.23	<0.001	-0.17	<0.001	-0.45	<0.001
Gait speed (m/seg)	-0.25	<0.001	-0.25	<0.001	-0.23	<0.001	-0.18	<0.001	-0.13	<0.001	-0.09	0.013	-0.15	<0.001	-0.36	<0.001
Grip strength (kg)	-0.28	<0.001	-0.37	<0.001	-0.33	<0.001	-0.18	<0.001	-0.11	0.002	-0.27	<0.001	-0.19	<0.001	-0.36	<0.001
Physical performance SPPB	-0.39	<0.001	-0.41	<0.001	-0.40	<0.001	-0.23	<0.001	-0.19	<0.001	-0.64	<0.001	-0.13	<0.001	-0.57	<0.001
Angle phase (°)	-0.18	<0.001	-0.19	<0.001	-0.18	<0.001	-0.21	<0.001	-0.16	<0.001	-0.35	<0.001	-0.22	<0.001	-0.36	<0.001

EuroQol visual analog scale (EQ-VAS), basic activities of daily living (ADL), instrumental activities of daily living (IADL), Center for Epidemiologic Studies Depression Scale Short Form (CESD-7), Mini Nutritional Assessment (MNA), Short Physical Performance Battery (SPPB).

0.59 to 0.85 using the EWGSOP2 as a reference and from 0.68 to 0.89 using the FNIH consensus. SARC-CalF had a higher value of AUC (0.74) than the value observed for SARCO-GS versus AWGS. In other populations (29, 38), the AUC range for the SARC-CalF versus AWGS was between 0.73 and 0.92. The above could be explained by the high specificity of SARC-CalF.

The variability in the AUC values of SARC-F and SARC-CalF could be explained by the differences in the prevalence of sarcopenia, the adjusted cut-off points, and the specific characteristics of each studied population.

Taking into account the results obtained in the evaluation of the criterion validity, SARCO-GS had a better ability to detect sarcopenia cases than SARC-F and SARC-CalF using as references EWGSOP2 and FNIH.

Additionally, the results obtained from the construct validity assessment verified that all SARCO-GS items (subjective and objective) and the total score are correlated with the proxy objective constructs included in the FraDySMex cohort. For example, the gait speed item (Item 1) was correlated with gait speed as measured by the GAITRite, which has proven to be a gold standard for gait speed assessment (41). The muscle strength items (2 and 3) that assessed the strength to carry a heavy object (upper extremity, item 2) and to climb stairs (lower extremity, item 3) were correlated as expected with hand grip strength and with the SPPB; both tests have been considered in the EWGSOP2 as proxy assessments of arm and leg muscle strength (10). The items of subjective perception of muscle mass (items 4 and 5) were correlated with the phase angle, which is a proxy measurement for assessing muscle mass and has been associated with frailty and sarcopenia (42). Moreover, these items were also correlated with the MNA, which evaluates the risk of malnutrition, which is an indicator related to muscle mass quantity (43).

The Chair stand test was correlated with hand grip strength and phase angle. The above had concordance with the existing evidence; this test has been associated with muscular strength (44) and muscle mass (32). The calf circumference had a significant correlation with the phase angle that reflected the quantity of muscle mass (42) and MNA. Since these items are quantifiable, their inclusion in SARCO-GS improves the capacity of the scale to identify individuals affected by sarcopenia. Other constructs such as quality of life, depression, disability, and comorbidity were correlated with the SARCO-GS total score; these findings agree with the evidence on the association between these constructs and sarcopenia (27).

Regarding predictive validity, functional disability is one of the main adverse outcomes of sarcopenia (45, 46) and our results using the SARCO-GS are congruent with these findings. Sarcopenia evaluated by SARCO-GS increased the risk of functional disability in a follow-up period of 4.2 years. Therefore, the proposed cut-off point ≥3 is useful for intervention and longitudinal studies to prevent this outcome. These results strengthen the criterion validity of SARCO-GS.

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TABLE 6 Predictive validity of SARCO-GS: Adjusted Hazard ratios for functional dependence.

	Hazard ratio	p-value	CI 95%
Sarco-GS			
No sarcopenia (<3 points)	1.00		
With sarcopenia (≥3 points)	2.22	0.046	1.01-4.88
Sex			
Female	1.00		
Male	0.61	0.238	0.27-1.39
Age (years)			
50-69	1.00		
≥70	2.31	0.014	1.19-4.49
Body Mass Index (kg/m^2)			
Normal (18.5-24.9)	1.00		
Low weight (<18.5)	0.81	0.533	0.43-1.55
Overweight (25-29.9)	0.59	0.148	0.29-1.21
Obesity (≥30)			
Marital Status			
Married/consensual union	1.00		
Single/divorced	1.12	0.741	0.56-2.26
Widow/widower	0.88	0.648	0.46-1.66
Education (years)			
≥13	1.00		
7-12	1.43	0.389	0.63-3.26
<7	1.81	0.199	0.73-4.49
Comorbidity (Charlson Index)			
Low comorbidity (<3 points)	1.00		
High comorbidity (≥3 points)	1.06	0.859	0.58-1.92
Cognitive impairment (MMSE)			
No	1.00		
Yes	0.84	0.679	0.37-1.91

MMSE, Mini-Mental State Examination (score ≤23 in the case when the years of study were ≥5; score ≤19 if the years of study were between 1 and 4; score ≤ 16 if the years of study were <1).

This predictive capacity of SARCO-GS confirms that the inclusion of calf circumference and Chair stand test strengthens the construct of sarcopenia (10) and provides support to be included in the screening stage.

The internal reliability by inter-item and item-total was acceptable. Even though this scale is composed of objective and subjective measurements, it shows that all the items belong to this same construct of sarcopenia. The Cronbach alpha of 0.69 was reasonable; although this coefficient is helpful for comparative purposes between other populations, it belongs to classical theories of psychometry and has the disadvantage that, when it is employed to analyze the internal structure of scales that combine subjective and objective clinical evaluations with different variances, the value may be low. In these cases, its interpretation should be considered carefully (47).

It is important to consider some limitations of the present study. The studied population in which SARCO-GS was validated is a representative sample of three districts in the southeast of Mexico City; therefore, it considers unique characteristics of this population. Another limitation is the lack of evaluation of the external reliability (test re-test or inter-rater agreement). Considering these limitations, it is crucial to validate SARCO-GS in populations other than Mexico and worldwide. Some strengths should be mentioned: the present study comprised data from a longitudinal cohort study that included the measurements assessed by objective tools like DXA, hand dynamometer, and GAITRite.

TABLE 7 Internal Reliability of SARCO-GS, by correlation inter-item, item total, and Cronbach's alpha (rho, p-value).

Domain	Item	1	2	3	4	5	6	7	Total score
Subjective gait speed	**1**	1.00							0.59 <0.001
Subjective muscular strength	**2**	0.43 <0.001	1.00						0.62 <0.001
Subjective muscular strength	**3**	0.45 <0.001	0.53 <0.001	1.00					0.59 <0.001
Subjective muscle mass	**4**	0.22 <0.001	0.23 <0.001	0.18 <0.001	1.00				0.57 <0.001
Subjective muscle mass	**5**	0.20 <0.001	0.24 <0.001	0.21 <0.001	0.58 <0.001	1.00			0.54 <0.001
Muscular strength	**6**	0.30 <0.001	0.32 <0.001	0.35 <0.001	0.19 <0.001	0.16 <0.001	1.00		0.62 <0.001
Muscle mass	**7**	0.06 0.031	0.11 0.001	0.07 0.057	0.21 <0.001	0.22 <0.001	0.13 <0.001	1.00	0.51 <0.001

Cronbach Alpha: 0.67.

5 Conclusions

SARCO-GS is a new scale to screen sarcopenia that combines subjective items with objective measurements. The SARCO-GS yielded satisfactory results in terms of sensitivity, AUC versus the most used consensuses, predictive validity for functional disability, construct validity, and internal reliability. SARCO-GS could narrow the gap of subjective scales in terms of sensitivity to timely screening of sarcopenia in community-dwelling adults and prevent adverse outcomes. Furthermore, it could be used in different clinical and research settings since its measurements do not require specialized equipment and are easy to conduct.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Institute of Geriatrics (DI-PI-002/2014). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: OR-C. Methodology: OR-C, IO-G, AIG-G, and AL-L. Data analysis: IO-G and OR-C. Writing—Original Draft Preparation: OR-C and IO-G. Writing—Review and Editing: OR-C, IO-G, AIG-G, and AL-L. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The relationship between sarcopenia and mortality in Chinese community-dwelling adults: a 7-year cohort study with propensity score matching and Mendelian randomization

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Background: Sarcopenia has been linked to adverse health outcomes, including an increased risk of mortality. This study aimed to assess the 7-year mortality risk of sarcopenia in a community-based population in China and explore the causal relationship between components of sarcopenia and any death.

Methods: Data were sourced from the China Health and Retirement Longitudinal Study (CHARLS) conducted between 2011 and 2018. Sarcopenia was diagnosed using the Asian Working Group for Sarcopenia (AWGS) 2019 criteria. Logistic regression, Kaplan–Meier (KM) survival analysis, and propensity score matching with inverse probability of treatment weighting were used. Mendelian randomization (MR) analyses, conducted using European population data, were utilized to assess causality between sarcopenia and any death.

Results: The study included 9,006 participants: 3,892 had no sarcopenia, 3,570 had possible sarcopenia, 1,125 had sarcopenia, and 419 had severe sarcopenia. Over 7 years of follow-up, there were 871 deaths, including 196 with sarcopenia and 133 with severe sarcopenia. The KM curves showed that sarcopenia had a higher risk of mortality. Compared to those of no sarcopenia, the odds ratios (ORs) of sarcopenia for 7-year mortality were 1.41 (95% CI, 1.06–1.87) after adjusting for confounding variables ($p < 0.05$). The ORs of severe sarcopenia were 2.11 (95% CI, 1.51–2.95). Propensity score matching analysis and inverse probability of treatment weighting analysis confirmed these findings. The

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adjusted ORs of sarcopenia and 7-year mortality were 2.94 (95% CI, 1.6–5.39) in the 45–60 age group, 1.72 (95% CI, 1.11–2.68) in the 60–80 age group, and 5.03 (95% CI, 0.48–52.65) in the ≥80 age group. The ORs of severe sarcopenia and 7-year mortality were 6.92 (95% CI, 1.95–24.5) in the 45–60 age group, 2.59 (95% CI, 1.61–4.17) in the 60–80 age group, and 12.52 (95% CI, 1.18–133.18) in the ≥80 age group. The MR analyses, leveraging the inverse variance weighted (IVW) method, unveiled substantial causal links between low hand grip strength in individuals aged 60 and older, the usual walking pace, and mortality risk.

Conclusion: This study underscores the significant impact of sarcopenia and its components on mortality risk within the Chinese population. Particularly, low hand grip strength and usual walking pace emerged as noteworthy contributors to mortality risk.

KEYWORDS

the CHARLS, sarcopenia, mortality risk, the propensity score matching, Mendelian randomization

Introduction

Sarcopenia, characterized by loss of muscle mass and function, is a common condition in older adults that has been associated with increased disability, falls, hospitalization, and mortality (1–5). It has been reported to be prevalent in various groups, with estimates ranging from 9.9% to 40.4% among community-dwelling adults and 2% to 34% in outpatient settings, and affects as many as 56% of hospitalized patients (6–9). As the global population ages, the prevalence of sarcopenia is expected to increase significantly (10). Despite its growing recognition as a significant public health issue, there are limited data on the association between sarcopenia and mortality risk in Chinese community-dwelling adults. Moreover, the relationship between sarcopenia and mortality can be confounded by chronic diseases and other factors that commonly occur with aging. Propensity score matching has been used in previous research to account for these confounding factors, but typically for a single disease (11–14).

Sarcopenia is linked to a doubling of mortality risk in both community-dwelling adults and nursing home residents and a tripling of risk in cancer patients (11–14). As the world's population continues to age, addressing the health implications of sarcopenia has become a critical priority. However, despite the increasing recognition of sarcopenia's importance, there are still gaps in our understanding of its causal relationship with mortality.

This study aims to contribute to this understanding by investigating the causal links between different components of sarcopenia—specifically, appendicular lean mass, low hand grip strength, and usual walking pace—and the risk of mortality in a comprehensive manner. Our research combines data from a longitudinal study conducted among Chinese adults aged 45 years and older with a Mendelian randomization study utilizing European population data. By applying Mendelian randomization methods, we can better elucidate the causal relationships between these sarcopenia components and mortality risk.

Methods

Longitudinal study

Population

The China Health and Retirement Longitudinal Study (CHARLS), established in 2011, is a national longitudinal study of community-dwelling adults in China, with its detailed validity and methodology previously documented (15, 16). The CHARLS protocol was approved by the Peking University Ethical Review Committee (IRB00001052-11015) following the Declaration of Helsinki. Informed consent was obtained from all participants. Data from Harmonized CHARLS 2011–2018 were included. Missing data on sex (n = 8), age (n = 305), weight (n = 4,099), height (n = 58), no-grip strength, walking speed, sitting test (n = 7,501), no follow-up (n = 1,345), blood sample data (n = 3,259), and age < 18 years (n = 3) were excluded. A total of 9,006 participants (≥18 years) were enrolled in the study (Figure 1).

Evaluation of sarcopenia status

Asian Working Group for Sarcopenia (AWGS) 2019 algorithm was used to evaluate sarcopenia status in the CHARLS, including assessment of muscle mass, muscle strength, and physical

performance (1). The muscle mass values, the appendicular skeletal muscle mass (ASM), were imputed using an anthropometric equation (ASM = 0.193 * body weight + 0.107 * height − 4.157 * sex − 0.037 * age − 2.631) mainly validated in Asia populations as described in previous studies (17, 18). The handgrip strength of the dominant hand was recorded by a Yuejian TM WL-1000 dynamometer. The participants carried out the gait speed and five-time chair stand tests, and the methods employed in the CHARLS have been described (15, 17).

Mortality data

From April 2011 to March 2019, all deaths were recorded, and the survival status of the participants was determined during the baseline investigation in 2011–2012, prior to follow-up. Death data were collected from life history surveys conducted in 2013, 2014, 2015, and 2018, with the follow-up period spanning approximately 8 years. The survival status of participants was ascertained through field investigations conducted by interviewers during four separate follow-up periods. Interviewers visited the residences of participants and, in the event of the participant's death, collected relevant information by interviewing household members who lived with the deceased (19).

Covariates

Sociodemographic and medical covariable data were extracted from the CHARLS 2011. These variables included age, gender (male or female), marital status (single, married, divorced, or widowed or others), education (elementary school or less, or secondary school or above), dwelling locations (urban or rural), drinking, smoking, and multimorbidity (20). The multimorbidity covariate consisted of self-reported data on 12 medically diagnosed conditions, including hypertension, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive diseases, memory-related diseases, arthritis or rheumatoid arthritis, and asthma (20, 21).

Statistical analysis

For continuous variables, confidence intervals (CIs) of 95% were supplied, whereas percentage frequencies were provided for categorical variables. To compare continuous and categorical data, *t*-tests and χ^2 were utilized. With the use of logistic regression models, the risk of mortality is determined. The Kaplan–Meier curves are depicted visually. To reduce potential selection bias, propensity score matching (PSM) was utilized to balance covariates between participants with and without sarcopenia or severe sarcopenia. After individual propensity scores were computed using a logistic regression model, the nearest-neighbor matching technique with a caliper width of 0.2 standard deviations of the propensity score was used to pair patients from the lowest hand grip strength (HGS) group with those from other groups. Then, a regression analysis was conducted using the inverse probability of treatment weighting (IPTW) (22). Statistical analyses were carried out using the R software package (http://www.R-project.org, The R Foundation) and the Free Statistics software version 1.7. Statistical significance was determined by a two-sided *p*-value <0.05.

Mendelian randomization study

Data source

The Mendelian randomization study was conducted using European populations to examine the causal relationship between sarcopenia and any death. The exposures analyzed were appendicular lean mass, low hand grip strength in those aged 60 years and older, and usual walking pace. Appendicular lean mass data were obtained in 2020 from 205,513 samples genotyped for 18,164,071 single-nucleotide polymorphisms (SNPs) (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90000026/). Low hand grip strength was analyzed in 2021 using 256,523 samples genotyped for 9,336,415 SNPs (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90007526/). The usual walking pace was examined in 2018 with 459,915 samples genotyped for 9,851,867 SNPs (https://gwas.mrcieu.ac.uk/datasets/ukb-b-4711/). The outcome was any cause mortality, analyzed in 2021 with 218,792 samples genotyped for 16,380,466 SNPs (https://gwas.mrcieu.ac.uk/datasets/finn-b-DEATH/). Sample sizes ranged from 205,513 to 459,915; SNPs analyzed spanned 9,336,415 to 18,164,071; years of data collection were from 2018 to 2021 (Supplementary Table 1).

Selection of SNPs and statistical analysis

The Mendelian randomization (MR) analysis was conducted employing the inverse variance weighted (IVW) method. The SNP selection process involved several methodologies: a significance threshold of $p < 5 \times 10^{-8}$ was applied to identify SNPs, achieving genome-wide significance. A threshold of $r^2 < 0.001$ (with a clumping distance of 10,000 kb) was set to exclude SNPs that were in a state of linkage disequilibrium. In addressing potential pleiotropy, the PhenoScanner database was utilized for SNP identification and subsequent exclusion. Weak instrumental variables, as indicated by an F-statistic < 10, were systematically excluded from the analysis. The MR–pleiotropy residual sum and outlier (MR-PRESSO) method was employed before each MR analysis to eliminate potential outliers. Additionally, palindromic SNPs were eliminated through data harmonization between the any death dataset and the exposure dataset. Following this meticulous screening process, the remaining SNPs were retained for subsequent analyses. To validate the findings, alternative methods including MR-Egger, weighted median, and weighted mode were applied alongside IVW. Heterogeneity was assessed using Cochran's Q test, while pleiotropy was evaluated through MR-Egger intercept testing and leave-one-out analysis. All statistical analyses were conducted using R software (version 4.3.0) for both MR analyses and sensitivity assessments.

Results

Longitudinal study

Demographics

The study included 9,006 participants, of which 45.9% were male and 54.1% were female. Among them, 3,892 had no

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TABLE 1 The baseline characteristics of the study population in the CHARLS.

Characteristic	Total (n = 9,006)	No sarcopenia (n = 3,892)	Possible sarcopenia (n = 3,570)	Sarcopenia (n = 1,125)	Severe arcopenia (n = 419)	*p*-Value
Age, years	58.8 ± 9.6	52.3 ± 6.2	61.8 ± 8.3	67.1 ± 8.3	71.4 ± 8.1	<0.001
Gender, n (%)						0.002
Male	4,138 (45.9)	1,798 (46.2)	1,693 (47.4)	461 (41)	186 (44.4)	
Female	4,868 (54.1)	2,094 (53.8)	1,877 (52.6)	664 (59)	233 (55.6)	
BMI (kg/m^2)	23.5 ± 3.9	24.0 ± 3.9	24.8 ± 3.4	19.3 ± 1.8	19.3 ± 1.9	<0.001
Weight (kg)	58.7 ± 11.7	61.1 ± 11.6	61.9 ± 9.6	45.8 ± 5.5	44.4 ± 5.5	<0.001
Height (m)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	<0.001
ASM (kg)	17.0 ± 4.2	17.9 ± 4.2	17.6 ± 3.7	13.6 ± 3.6	13.0 ± 3.5	<0.001
ASM/Ht^2 (kg/m^2)	6.7 ± 1.1	7.0 ± 1.1	7.0 ± 1.0	5.6 ± 0.9	5.6 ± 1.0	<0.001
Walk speed (m/s)	0.6 ± 0.2	1.1 ± 0.1	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	<0.001
Handgrip strength (kg)	31.7 ± 10.4	35.6 ± 9.7	30.1 ± 9.9	28.1 ± 7.7	17.5 ± 5.9	<0.001
5-time chair stand test (s)	10.8 ± 4.3	8.5 ± 1.9	12.7 ± 4.8	12.0 ± 4.0	14.1 ± 6.3	<0.001
Waist (cm)	84.3 ± 12.6	84.5 ± 11.9	87.7 ± 12.7	75.7 ± 9.2	75.6 ± 10.5	<0.001
Education, n (%)						<0.001
Elementary school or below	6,412 (71.2)	2,258 (58)	2,776 (77.8)	982 (87.3)	396 (94.5)	
Secondary school	2,506 (27.8)	1,590 (40.9)	756 (21.2)	138 (12.3)	22 (5.3)	
College or above	88 (1.0)	44 (1.1)	38 (1.1)	5 (0.4)	1 (0.2)	
Marriage, n (%)						<0.001
Single	57 (0.6)	18 (0.5)	22 (0.6)	7 (0.6)	10 (2.4)	
Married	7,907 (87.8)	3,664 (94.1)	3,082 (86.3)	875 (77.8)	286 (68.3)	
Divorced or widowed or others	1,042 (11.6)	210 (5.4)	466 (13.1)	243 (21.6)	123 (29.4)	
Area, n (%)						<0.001
Urban area	2,972 (33.0)	1,406 (36.1)	1,209 (33.9)	251 (22.3)	106 (25.3)	
Rural area	6,034 (67.0)	2,486 (63.9)	2,361 (66.1)	874 (77.7)	313 (74.7)	
Drinking, n (%)						<0.001
No	6,543 (72.7)	2,665 (68.5)	2,665 (74.6)	885 (78.7)	328 (78.3)	
Yes	2,463 (27.3)	1,227 (31.5)	905 (25.4)	240 (21.3)	91 (21.7)	
Smoking, n (%)						0.261
No	6,307 (70.0)	2,694 (69.2)	2,542 (71.2)	783 (69.6)	288 (68.7)	
Yes	2,699 (30.0)	1,198 (30.8)	1,028 (28.8)	342 (30.4)	131 (31.3)	
Diabetes, n (%)						<0.001
No	7,495 (83.2)	3,326 (85.5)	2,834 (79.4)	989 (87.9)	346 (82.6)	
Yes	1,511 (16.8)	566 (14.5)	736 (20.6)	136 (12.1)	73 (17.4)	
Hypertension, n (%)						<0.001
No	6,640 (73.7)	3,134 (80.5)	2,276 (63.8)	898 (79.8)	332 (79.2)	
Yes	2,366 (26.3)	758 (19.5)	1,294 (36.2)	227 (20.2)	87 (20.8)	

(Continued)

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TABLE 1 Continued

Characteristic	Total (n = 9,006)	No sarcopenia (n = 3,892)	Possible sarcopenia (n = 3,570)	Sarcopenia (n = 1,125)	Severe arcopenia (n = 419)	*p*-Value
Cancer, n (%)						0.878
No	8,922 (99.1)	3,854 (99)	3,535 (99)	1,117 (99.3)	416 (99.3)	
Yes	84 (0.9)	38 (1)	35 (1)	8 (0.7)	3 (0.7)	
Heart disease, n (%)						<0.001
No	7,951 (88.3)	3,557 (91.4)	3,011 (84.3)	1,011 (89.9)	372 (88.8)	
Yes	1,055 (11.7)	335 (8.6)	559 (15.7)	114 (10.1)	47 (11.2)	
Stroke, n (%)						<0.001
No	8,772 (97.4)	3,827 (98.3)	3,445 (96.5)	1,099 (97.7)	401 (95.7)	
Yes	234 (2.6)	65 (1.7)	125 (3.5)	26 (2.3)	18 (4.3)	
Lung disease, n (%)						<0.001
No	8,131 (90.3)	3,643 (93.6)	3,192 (89.4)	945 (84)	351 (83.8)	
Yes	875 (9.7)	249 (6.4)	378 (10.6)	180 (16)	68 (16.2)	
Arthre disease, n (%)						<0.001
No	5,847 (64.9)	2,700 (69.4)	2,174 (60.9)	722 (64.2)	251 (59.9)	
Yes	3,159 (35.1)	1,192 (30.6)	1,396 (39.1)	403 (35.8)	168 (40.1)	
Liver disease, n (%)						0.999
No	8,818 (97.9)	3,810 (97.9)	3,496 (97.9)	1,102 (98)	410 (97.9)	
Yes	188 (2.1)	82 (2.1)	74 (2.1)	23 (2)	9 (2.1)	
Kidney disease, n (%)						0.017
No	8,495 (94.3)	3,699 (95)	3,334 (93.4)	1,067 (94.8)	395 (94.3)	
Yes	511 (5.7)	193 (5)	236 (6.6)	58 (5.2)	24 (5.7)	
Digestive disease, n (%)						0.042
No	6,955 (77.2)	3,037 (78)	2,764 (77.4)	849 (75.5)	305 (72.8)	
Yes	2,051 (22.8)	855 (22)	806 (22.6)	276 (24.5)	114 (27.2)	
Asthma, n (%)						<0.001
No	8,591 (95.4)	3,781 (97.1)	3,378 (94.6)	1,043 (92.7)	389 (92.8)	
Yes	415 (4.6)	111 (2.9)	192 (5.4)	82 (7.3)	30 (7.2)	
Memory-related disease, n (%)						<0.001
No	8,874 (98.5)	3,873 (99.5)	3,490 (97.8)	1,106 (98.3)	405 (96.7)	
Yes	132 (1.5)	19 (0.5)	80 (2.2)	19 (1.7)	14 (3.3)	
7-year mortality, n (%)						<0.001
No	8,135 (90.3)	3,745 (96.2)	3,175 (88.9)	929 (82.6)	286 (68.3)	
Yes	871 (9.7)	147 (3.8)	395 (11.1)	196 (17.4)	133 (31.7)	

CHARLS, China Health and Retirement Longitudinal Study; BMI, body mass index; ASM, appendicular skeletal muscle mass.

sarcopenia, 3,570 had possible sarcopenia, 1,125 had sarcopenia, and 419 had severe sarcopenia. Over 7 years of follow-up, there were 871 deaths, including 147 without sarcopenia, 395 with possible sarcopenia, 196 with sarcopenia, and 133 with severe sarcopenia (Table 1).

Univariate and multivariate logistic regression analyses

The univariate and multivariate logistic regression analyses showed that the risk factors for 7-year mortality were sarcopenia (odds ratios (OR): 1.41, 95% CI, 1.06–1.87), severe sarcopenia (OR = 2.11, 95% CI, 1.51–2.95), age (OR = 1.09, 95% CI, 1.08–1.1), diabetes (OR = 1.51, 95% CI, 1.26 to 1.82), hypertension (OR = 1.31, 95% CI, 1.11 to 1.56), cancer (OR = 4.46, 95% CI, 2.45 to 8.09), stroke (OR = 1.64, 95% CI, 1.13 to 2.38), lung disease (OR = 1.82, 95% CI, 1.45 to 2.28), and memory-related diseases (OR = 2.11, 95% CI, 1.37–3.25) ($p < 0.05$). The protective factors for 7-year mortality were female (OR = 0.52, 95% CI, 0.43–0.63), married (OR = 0.33, 95% CI, 0.17–0.61), and divorced (OR = 0.46, 95% CI, 0.24–0.9) ($p < 0.05$) (Table 2).

The relationship between sarcopenia and all-cause mortality

According to the Kaplan–Meier survival curves, sarcopenia and severe sarcopenia had a higher risk of 7-year mortality (Figure 2). The results from logistic regression analyses are presented in Table 2. Compared to no sarcopenia, the unadjusted OR of sarcopenia for 7-year mortality (model 1) was 5.37 (95% CI, 4.29–6.74), whereas for severe sarcopenia, it was 11.85 (95% CI, 9.1–15.42). After adjusting for age and sex (model 2), the OR of sarcopenia and severe sarcopenia for 7-year mortality was 1.41 (95% CI, 1.07–1.85) and 2.2 (95% CI, 1.59–3.05). Further adjusting for age, sex, education level, marriage status, urban area, drinking, and smoking (model 3), the OR of sarcopenia and severe sarcopenia for 7-year mortality was 1.39 (95% CI, 1.06–1.83) and 2.1 (95% CI, 1.51–2.92). Finally, after adjusting for age, body mass index (BMI),

TABLE 2 Univariate and multivariate logistic analyses of risk factors for 7-year mortality in the CHARLS.

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Possible sarcopenia	3.17 (2.61–3.85)	<0.001	1.11 (0.89–1.4)	0.356
Sarcopenia	5.37 (4.29–6.74)	<0.001	1.41 (1.06–1.87)	0.017
Severe sarcopenia	11.85 (9.1–15.42)	<0.001	2.11 (1.51–2.95)	<0.001
Age, years	1.11 (1.1–1.12)	<0.001	1.09 (1.08–1.1)	<0.001
Female	0.5 (0.44–0.58)	<0.001	0.52 (0.43–0.63)	<0.001
Education Secondary school	0.46 (0.38–0.55)	<0.001	0.83 (0.67–1.03)	0.097
Education College or above	0.47 (0.19–1.16)	0.103	0.53 (0.2–1.37)	0.19
Married	0.21 (0.12–0.37)	<0.001	0.33 (0.17–0.61)	0.001
Divorced or widowed or others	0.61 (0.34–1.09)	0.097	0.46 (0.24–0.9)	0.022
Rural area	1.13 (0.97–1.31)	0.122	1 (0.84–1.18)	0.976
Drinking	1.02 (0.88–1.2)	0.761	0.98 (0.82–1.18)	0.852
Smoking	1.41 (1.22–1.63)	<0.001	1.12 (0.93–1.35)	0.237
Diabetes	1.67 (1.41–1.97)	<0.001	1.51 (1.26–1.82)	<0.001
Hypertension	1.64 (1.42–1.9)	<0.001	1.31 (1.11–1.56)	0.002
Cancer	2.77 (1.65–4.64)	<0.001	4.46 (2.45–8.09)	<0.001
Heart disease	1.5 (1.23–1.82)	<0.001	1.24 (0.99–1.54)	0.062
Stroke	2.56 (1.85–3.54)	<0.001	1.64 (1.13–2.38)	0.009
Lung disease	2.47 (2.05–2.97)	<0.001	1.82 (1.45–2.28)	<0.001
Arthre disease	0.99 (0.85–1.14)	0.851	0.89 (0.76–1.05)	0.173
Kidney disease	1.34 (1.02–1.76)	0.037	1.29 (0.95–1.75)	0.107
Digestive disease	0.86 (0.72–1.02)	0.084	0.92 (0.76–1.12)	0.407
Asthma	1.9 (1.45–2.49)	<0.001	0.87 (0.63–1.21)	0.411
Memory-related disease	4.05 (2.77–5.93)	<0.001	2.11 (1.37–3.25)	0.001

CHARLS, China Health and Retirement Longitudinal Study; OR, odds ratio.

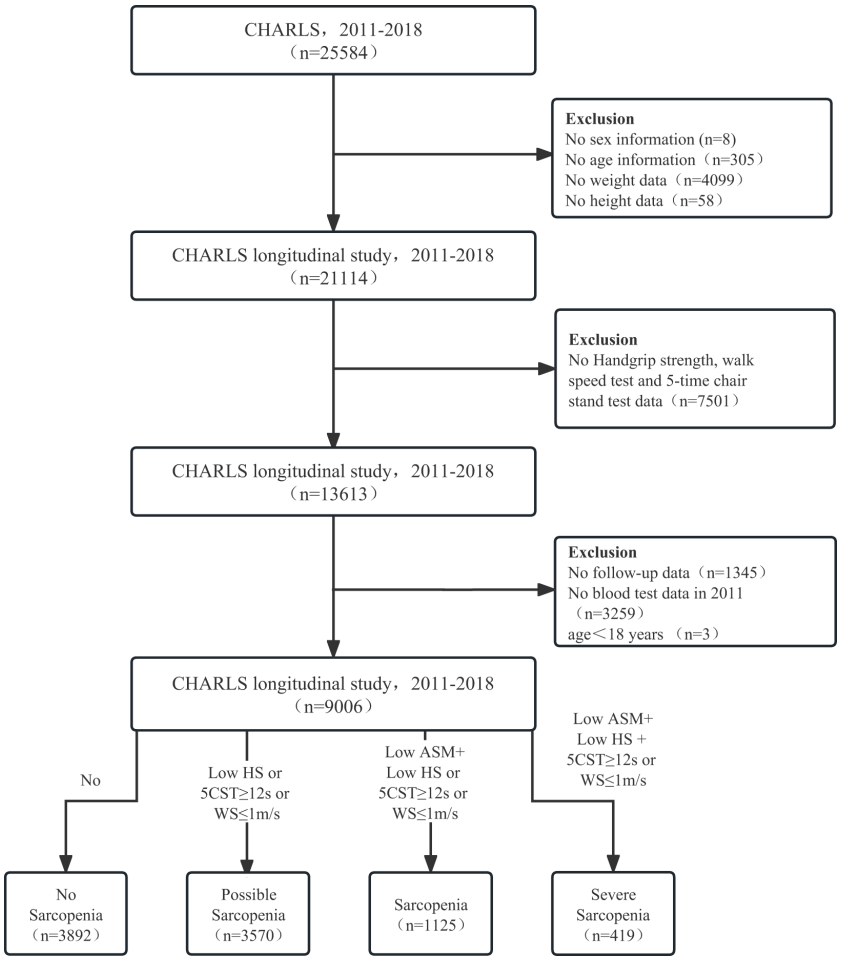

FIGURE 1
The flow diagram for the population in the CHARLS. CHARLS, The China Health and Retirement Longitudinal Study; HS, handgrip strength; CST, 5-time chair stand tests; WS, walk speed; ASM, appendicular skeletal muscle mass.

education level, marriage status, urban area, drinking, smoking, diabetes, hypertension, cancer, heart disease, stroke, lung disease, Arthre disease, liver disease, kidney disease, digestive disease, asthma, and memory-related disease (model 4), the OR of sarcopenia and severe sarcopenia for 7-year mortality was 1.41 (95% CI, 1.06–1.87) and 2.11 (95% CI, 1.51–2.95). All of the unadjusted and adjusted ORs of sarcopenia and severe sarcopenia were statistically significant ($p < 0.05$). The unadjusted OR of possible sarcopenia for the 7-year mortality was 3.17 (2.61–3.85) with a statistical difference ($p < 0.05$), but the adjusted OR was 1.11–1.23 without a statistical difference ($p > 0.05$) (Table 3).

Over a 7-year follow-up period, stratified analysis by age revealed that among individuals aged <45 years, there were 218 cases (4 deaths) of no sarcopenia, 43 cases (0 deaths) of possible sarcopenia, 3 cases (0 deaths) of sarcopenia, and 1 case (0 deaths) of severe sarcopenia. Among those aged ≥45 and <60 years, there were 3,405 cases (112 deaths) of no sarcopenia, 1,182 cases (52 deaths) of possible sarcopenia, 181 cases (14 deaths) of sarcopenia, and 28 cases (3 deaths) of severe sarcopenia. Among those aged ≥60 and <80 years, there were 263 cases (29 deaths) of no sarcopenia, 2,284 cases (317 deaths) of possible sarcopenia, 864 cases (145 deaths) of sarcopenia, and 325 cases (83 deaths) of severe sarcopenia. Among those aged ≥80 years, there were 6 cases (2 deaths) of no sarcopenia, 61 cases (26 deaths) of possible sarcopenia, 77 cases (37 deaths) of sarcopenia, and 65 cases (47 deaths) of severe sarcopenia. A statistically significant interaction between age and sarcopenia was observed in individuals aged ≥45 years ($p < 0.05$), but not in those aged <45 years ($p > 0.05$). The OR values of sarcopenia and 7-year mortality were 2.94 (95% CI, 1.6–5.39), 1.72 (95% CI, 1.11–2.68), and 5.03 (95% CI, 0.48–52.65) in the 45–60, 60–80, and ≥80 age groups, respectively. The OR values of severe sarcopenia and 7-year mortality were 6.92 (95% CI, 1.95–24.5), 2.59 (95% CI, 1.61–4.17), and 12.52 (95% CI, 1.18–133.18) in the 45–60, 60–80, and ≥80 age groups, respectively (Table 4).

The ORs of sarcopenia and severe sarcopenia for 7-year mortality with PSM and IPTW analyses

The sarcopenia and severe sarcopenia were matched as separate groups for propensity score matching. The baseline characteristics

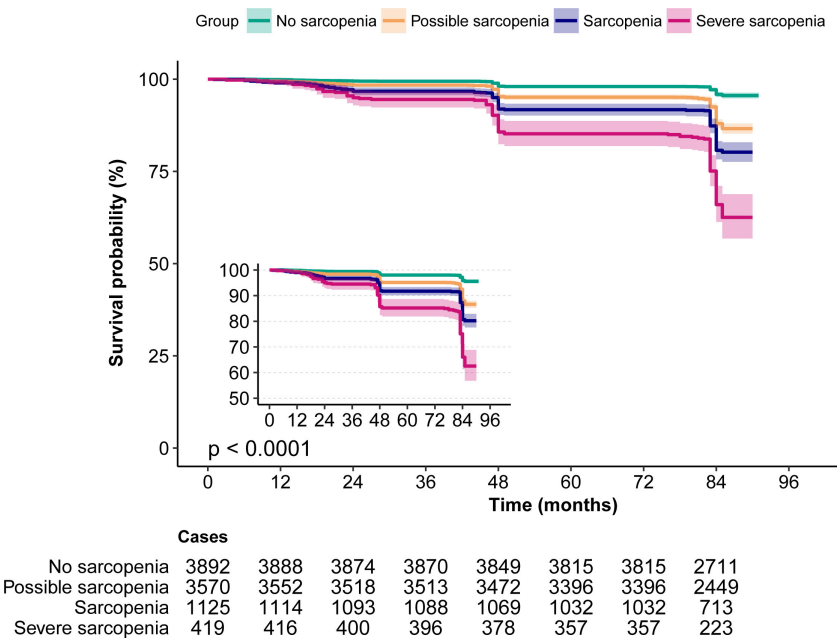

FIGURE 2
The Kaplan–Meier survival curves for sarcopenia associated with all-cause mortality risk. Note the small Kaplan–Meier graph on the left and its enlarged view.

before and after propensity score matching are shown in Supplementary Table 2. In both sarcopenia and severe sarcopenia, there were significantly higher OR for 7-year mortality by PSM and IPTW analyses ($p < 0.05$). Before PSM, the unmatched crude ORs for 7-year mortality were 3.46 (2.98–4.02) for sarcopenia and 4.95 (3.97–6.16) for severe sarcopenia, whereas the multivariable ORs were 1.46 (1.21–1.76) for sarcopenia and 1.74 (1.35–2.24) for severe sarcopenia. After propensity score matching, the ORs for 7-year mortality were 1.33 (1.09–1.63) for sarcopenia and 1.7 (1.25–2.32) for severe sarcopenia. After the inverse probability of treatment weighting regression analysis, the ORs for 7-year mortality were 1.77 (1.49–2.09) and 2.28 (1.69–3.07) for sarcopenia and severe sarcopenia, respectively (Figure 3).

Mendelian randomization study

The effect of appendicular lean mass on any death

This study examined the role of appendicular lean mass, a key component of sarcopenia, in relation to any death. Analyzing 283 SNPs with MR methods, we found significant results with the MR-Egger method (OR = 1.261, 95% CI, 1.056–1.507, $p = 0.011$). The weighted median method resulted in an OR of 0.948 (95% CI, 0.850–1.058, $p = 0.341$), while the IVW method resulted in an OR of 0.954 (95% CI, 0.892–1.021, $p = 0.176$). Heterogeneity ($p > 0.05$) and potential pleiotropy ($p < 0.05$) were assessed (Supplementary Figures 1–4 and Table 5).

TABLE 3 Association of sarcopenia with 7-year mortality in the CHARLS.

7-year mortality	n.total	Death event_%	Model 1	*p*-Value	Model 2	*p*-Value	Model 3	*p*-Value	Model 4	*p*-Value
No sarcopenia	3,892	147 (3.8)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Possible sarcopenia	3,570	395 (11.1)	3.17 (2.61–3.85)	<0.001	1.23 (0.98–1.53)	0.073	1.23 (0.98–1.53)	0.075	1.11 (0.89–1.4)	0.356
Sarcopenia	1,125	196 (17.4)	5.37 (4.29–6.74)	<0.001	1.41 (1.07–1.85)	0.015	1.39 (1.06–1.83)	0.019	1.41 (1.06–1.87)	0.017
Severe Sarcopenia	419	133 (31.7)	11.85 (9.1–15.42)	<0.001	2.2 (1.59–3.05)	<0.001	2.1 (1.51–2.92)	<0.001	2.11 (1.51–2.95)	<0.001
Trend. test	9,006	871 (9.7)	2.19 (2.03–2.37)	<0.001	1.27 (1.15–1.4)	<0.001	1.25 (1.13–1.39)	<0.001	1.28 (1.15–1.42)	<0.001

Model 1: crude model. Model 2: adjusted OR for age and sex. Model 3: adjusted OR for age, sex, education level, marriage status, urban area, drinking, and smoking. Model 4: adjusted OR for age, sex, education level, marriage status, urban area, drinking, smoking, diabetes, hypertension, cancer, heart disease, stroke, lung disease, Arthre disease, liver disease, kidney disease, digestive disease, asthma, and memory-related disease.
CHARLS, China Health and Retirement Longitudinal Study; OR, odds ratio.

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TABLE 4 Subgroup analysis stratified by age of the association between sarcopenia and 7-year mortality.

Subgroup	n.total	Death event (%)	Model 1	*p*-Value	Interaction *p*-Value	Model 2	*p*-Value	Interaction *p*-Value	Model 3	*p*-Value	Interaction *p*-Value
Age < 45 years					0.026			0.016			0.001
No sarcopenia	218	4 (1.8)	1 (Ref)			1 (Ref)			1 (Ref)		
Possible sarcopenia	43	0 (0)	–	–		–	–		–	–	
Sarcopenia	3	0 (0)	–	–		–	–		–	–	
Severe sarcopenia	1	0 (0)	–	–		–	–		–	–	
Trend test	265	4 (1.5)	–	–		–	–		–	–	
45 years ≥ age < 60 years											
No sarcopenia	3,405	112 (3.3)	1 (Ref)			1 (Ref)			1 (Ref)		
Possible sarcopenia	1,182	52 (4.4)	1.35 (0.97–1.89)	0.078		1.41 (1–1.98)	0.051		1.23 (0.87–1.76)	0.245	
Sarcopenia	181	14 (7.7)	2.46 (1.38–4.39)	0.002		2.69 (1.49–4.85)	0.001		2.94 (1.6–5.39)	<0.001	
Severe sarcopenia	28	3 (10.7)	3.53 (1.05–11.86)	0.042		5.24 (1.52–18.05)	0.009		6.92 (1.95–24.5)	0.003	
Trend test	4,796	181 (3.8)	1.49 (1.2–1.85)	<0.001		1.58 (1.26–1.98)	<0.001		1.56 (1.23–1.98)	<0.001	
60 years ≥ age < 80 years											
No sarcopenia	263	29 (11)	1 (Ref)			1 (Ref)			1 (Ref)		
Possible sarcopenia	2,284	317 (13.9)	1.3 (0.87–1.95)	0.202		1.32 (0.88–1.99)	0.182		1.21 (0.8–1.83)	0.367	
Sarcopenia	864	145 (16.8)	1.63 (1.06–2.49)	0.025		1.71 (1.11–2.64)	0.015		1.72 (1.11–2.68)	0.016	
Severe sarcopenia	325	83 (25.5)	2.77 (1.75–4.38)	<0.001		2.64 (1.65–4.22)	<0.001		2.59 (1.61–4.17)	<0.001	
Trend test	3,736	574 (15.4)	1.39 (1.24–1.56)	<0.001		1.37 (1.22–1.55)	<0.001		1.42 (1.25–1.61)	<0.001	
Age ≥ 80 years											
No sarcopenia	6	2 (33.3)	1 (Ref)			1 (Ref)			1 (Ref)		
Possible sarcopenia	61	26 (42.6)	1.49 (0.25–8.74)	0.661		1.31 (0.22–7.89)	0.768		3.49 (0.33–36.86)	0.298	
Sarcopenia	77	37 (48.1)	1.85 (0.32–10.7)	0.492		1.76 (0.3–10.41)	0.534		5.03 (0.48–52.65)	0.177	
Severe sarcopenia	65	47 (72.3)	5.22 (0.88–31.04)	0.069		4.78 (0.79–28.8)	0.088		12.52 (1.18–133.18)	0.036	
Trend test	209	112 (53.6)	1.81 (1.29–2.54)	0.001		1.83 (1.3–2.59)	0.001		1.97 (1.33–2.91)	0.001	

Model 1: crude model. Model 2: adjusted OR for sex, education level, marriage status, urban area, drinking, and smoking. Model 3: adjusted OR for sex, education level, marriage status, urban area, drinking, smoking, diabetes, hypertension, cancer, heart disease, stroke, lung disease, Arthre disease, liver disease, kidney disease, digestive disease, asthma, and memory-related disease. OR, odds ratio.

The effect of low hand grip strength (60 years and older) on any death

In our analysis of the impact of low hand grip strength on any death in individuals aged 60 and older (defined by the European Working Group on Sarcopenia in Older People (EWGSOP) criteria), we employed MR with a dataset of 11 SNPs. The IVW method demonstrated a significant association (OR = 1.310, 95% CI, 1.058–1.621, $p = 0.013$) between low hand grip strength and any

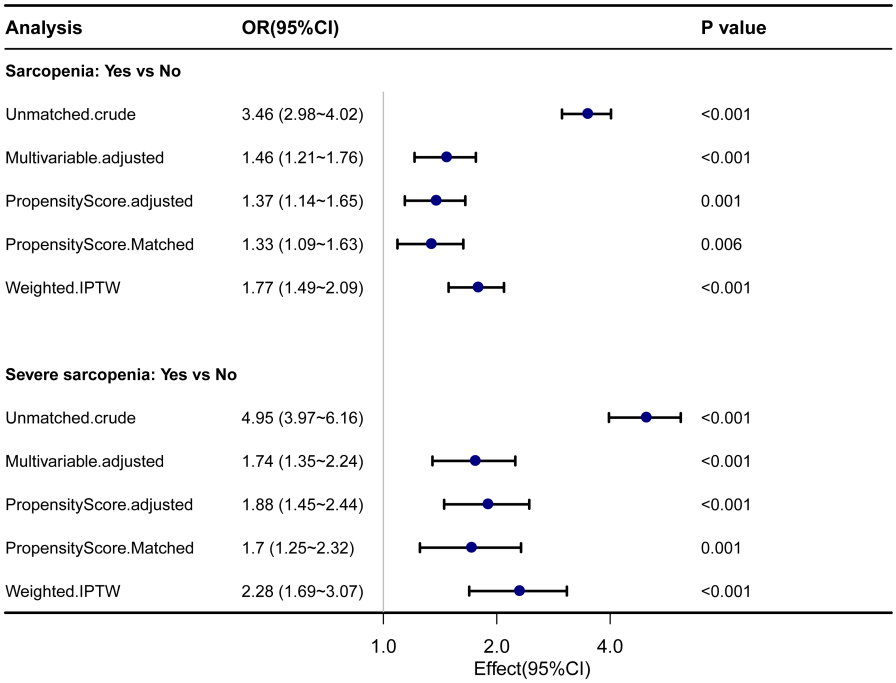

FIGURE 3
Forest plot shows ORs of all-cause mortality in participants with sarcopenia and severe sarcopenia using propensity score matching analysis. IPTW, the inverse probability of treatment weighting regression analysis; ORs, odds ratios.

death. Subsequently, the MR-Egger method showed an OR of 1.077 (95% CI, 0.523–2.218, $p = 0.846$), and the weighted median method yielded an OR of 1.168 (95% CI, 0.902–1.512, $p = 0.238$). Importantly, there was minimal evidence of heterogeneity ($p > 0.05$), and no substantial pleiotropy was observed ($p > 0.05$) (Supplementary Figures 5–8 and Table 5).

The effect of the usual walking pace on any death

Examining the influence of the usual walking pace, another integral component of sarcopenia, on any death, 52 SNPs were analyzed using MR methods. The IVW method indicated a significant association (OR = 0.590, 95% CI, 0.367–0.950, $p = 0.030$) between the usual walking pace and any death. In contrast, the MR-Egger method did not reveal a statistically significant effect on mortality (OR = 0.404, 95% CI, 0.057–2.874, $p = 0.369$), and the weighted median method yielded an OR of 0.587 (95% CI, 0.294–1.173, $p = 0.131$). Similar to the previous exposure, minimal evidence of heterogeneity ($p > 0.05$) was observed, and no substantial pleiotropy was detected ($p > 0.05$) (Supplementary Figures 9–12 and Table 5).

In summary, these findings reveal associations between sarcopenia components (appendicular lean mass, low hand grip strength, and usual walking pace) and mortality risk.

Discussion

Our study employed a multifaceted approach by combining longitudinal data from the CHARLS cohort with MR analysis to explore the complex relationships between various components of sarcopenia (appendicular lean mass, low hand grip strength, and usual walking pace) and mortality risk in older adults.

In this study, the prevalence of sarcopenia and severe sarcopenia in our study was 12.5% and 4.7%, respectively, which is consistent with previous studies in China. Our results showed that sarcopenia and severe sarcopenia were associated with a higher risk of 7-year mortality, even after adjusting for several potential confounding factors, consistent with previous studies conducted in other populations (7, 9, 23). Compared to participants without sarcopenia, those with sarcopenia had a 41% higher risk of mortality. Moreover, the risk of mortality was even higher for participants with severe sarcopenia, with a 111% higher risk than those without sarcopenia. This highlights the importance of early detection and intervention for sarcopenia before it progresses to a more severe stage.

Our study also identified several risk factors for mortality, including age, chronic diseases (such as diabetes, hypertension, cancer, stroke, lung disease, and memory-related diseases), and male gender. The association between sarcopenia and mortality risk is more pronounced in older age groups, with the highest risk observed in individuals aged ≥80 years. These findings are consistent with previous studies that have reported an association between these factors and mortality risk (8, 12, 24, 25).

To account for potential confounding by chronic diseases and age, we used propensity score matching, which confirmed the significant association between sarcopenia and mortality risk. While previous research has also utilized this approach, it has mainly focused on examining the relationship between sarcopenia

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TABLE 5 The causal association between sarcopenia and risk of any death.

Exposure	Outcome	nSNP		OR	95% CI	*p*	Heterogeneity test		Pleiotropy_test	
							Cochran's Q	*p*	Intercept	*p*
Appendicular lean mass	Any death	283	MR-Egger	1.261	1.056–1.507	0.011	245.388	0.980	−0.008	0.001
		283	Weighted median	0.948	0.850–1.058	0.341				
		283	IVW	0.954	0.892–1.021	0.176				
Low hand grip strength (60 years and older) (EWGSOP)	Any death	11	MR-Egger	1.077	0.523–2.218	0.846	14.605	0.147	0.012	0.590
		11	Weighted median	1.168	0.902–1.512	0.238				
		11	IVW	1.310	1.058–1.621	0.013				
Usual walking pace	Any death	52	MR-Egger	0.404	0.057–2.874	0.369	38.768	0.896	0.003	0.697
		52	Weighted median	0.587	0.294–1.173	0.131				
		52	IVW	0.590	0.367–0.950	0.030				

SNP, single-nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse variance weighted; EWGSOP, European Working Group on Sarcopenia in Older People.

and mortality in the context of a single disease. For instance, Lin et al. demonstrated that patients with both type 2 diabetes and sarcopenia were at higher risk for mortality than those without sarcopenia (13). Similarly, Bang et al. found that sarcopenia was associated with an increased incidence of postoperative acute kidney injury and overall mortality in patients undergoing surgery for abdominal aortic aneurysms (14). Furthermore, several studies have investigated the impact of sarcopenia on postoperative outcomes in cancer patients (11, 26). After utilizing propensity score matching to account for potential confounding factors, the association between sarcopenia and mortality risk remained significant. This underscores the importance of screening for sarcopenia in older adults and implementing age-specific interventions to address associated health risks.

Furthermore, our MR analysis introduced a causal dimension to this association. While MR results did not uniformly establish causal relationships between all sarcopenia components and mortality, they offered valuable insights. Importantly, the MR analysis using the IVW method demonstrated a significant causal association between low hand grip strength in individuals aged 60 and older and mortality risk. Additionally, the MR analysis using the IVW method of walking pace provided further support for this causal relationship. This highlights the importance of muscle strength as a key factor influencing healthy aging and longevity. However, the MR-Egger and weighted median methods did not provide supportive evidence, indicating potential complexities in this relationship and emphasizing the need for further investigation. Meanwhile, the MR analysis did not establish a significant causal relationship between appendicular lean mass and mortality risk. This discrepancy may warrant further exploration, considering the complexity of measuring muscle mass and the multifaceted nature of sarcopenia. It is possible that muscle quality and function, rather than muscle mass alone, play a more critical role in influencing mortality risk. These subtle differences underscore the need for ongoing research to elucidate underlying mechanisms.

Sarcopenia's impact on mortality extends beyond physical frailty, encompassing a range of physiological and metabolic changes (8). One critical aspect is the increased risk of falls and fractures among individuals with reduced muscle mass and strength (27, 28). These incidents can trigger a chain reaction, leading to complications like infections, immobility, and secondary muscle loss, ultimately contributing to mortality (7, 8, 28). Chronic inflammation, hormonal shifts, and malnutrition are pivotal factors linking sarcopenia to mortality (25, 29). They can initiate or worsen various chronic diseases, significantly elevating the risk of premature death (10, 13). Strategies aimed at managing chronic diseases, reducing inflammation, optimizing hormone levels, and ensuring adequate nutrition can collectively improve the overall wellbeing of sarcopenic individuals, potentially reducing their mortality risk.

Our study has several strengths, including a large sample size, a longitudinal design, and the use of standardized diagnostic criteria for sarcopenia. Additionally, the inclusion of Mendelian randomization analysis, employing multiple methods such as IVW,

MR-Egger, and weighted median, provided a robust basis for establishing causal links between sarcopenia components and mortality. Finally, rigorous adjustments for sociodemographic and medical covariates were performed to mitigate potential confounding effects. However, our study also has some limitations. First, the diagnosis of sarcopenia was based on a single measurement of muscle mass, strength, and function, which may not accurately reflect the individual's sarcopenia status over time. Second, we did not have data on the cause of death, which limits our ability to assess the specific causes of mortality associated with sarcopenia. Finally, our study was based on observational data from Chinese adults, and the generalizability of our findings to other populations may be limited. Additionally, while efforts were made to address pleiotropy, the presence of residual pleiotropic effects cannot be entirely excluded.

In conclusion, our study demonstrates that sarcopenia and severe sarcopenia are strongly linked to higher mortality risk. Further research should explore interventions to mitigate these risks and enhance outcomes for individuals with sarcopenia.

Data availability statement

Publicly available datasets were analyzed in this study. After obtaining permission, the CHARLS data can be found at: https://charls.charlsdata.com/users/profile/index/zh-cn.html.

Ethics statement

The CHARLS is approved by the Biomedical Ethics Review Committee of Peking University, and all participants provide informed consent. The data of the CHARLS are available for free on the Peking University Open Research Data Platform (https://charls.charlsdata.com/). The study used publicly available deidentified data, and informed consent was waived. Based on a publicly accessible database, this study did not require ethical approval or informed consent.

Author contributions

LX: conception of the protocol, data analysis and interpretation, acquisition of the data, statistical analysis and interpretation of the data, and manuscript preparation. TL: manuscript preparation. TG, ZZ, SW, XHW, XYW, JZ, PZ, YL, and LL: study concept and design and interpretation of the results. GY, YL, LL, JZ, and PZ: revision of the manuscript. SY, LK, and ZL: concept and design, final drafting of the manuscript, and study supervision. All authors agreed to be fully accountable for ensuring the integrity and accuracy of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1215512/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The scatter plot of Appendicular Lean Mass on any death.

SUPPLEMENTARY FIGURE 2
The forest plot of Appendicular Lean Mass on any death.

SUPPLEMENTARY FIGURE 3
The leaveoneout plot of Appendicular Lean Mass on any death.

SUPPLEMENTARY FIGURE 4
The funnel plot of Appendicular Lean Mass on any death.

SUPPLEMENTARY FIGURE 5
The scatter plot of Low Hand Grip Strength (60 years and older) on any death.

SUPPLEMENTARY FIGURE 6
The forest plot of Low Hand Grip Strength (60 years and older) on any death.

SUPPLEMENTARY FIGURE 7
The leaveoneout plot of Low Hand Grip Strength (60 years and older) on any death.

SUPPLEMENTARY FIGURE 8
The funnel plot of Low Hand Grip Strength (60 years and older) on any death.

SUPPLEMENTARY FIGURE 9
The scatter plot of the Usual Walking Pace on any death.

SUPPLEMENTARY FIGURE 10
The forest plot of the Usual Walking Pace on any death.

SUPPLEMENTARY FIGURE 11
The leaveoneout plot of the Usual Walking Pace on any death.

SUPPLEMENTARY FIGURE 12
The funnel plot of the Usual Walking Pace on any death.

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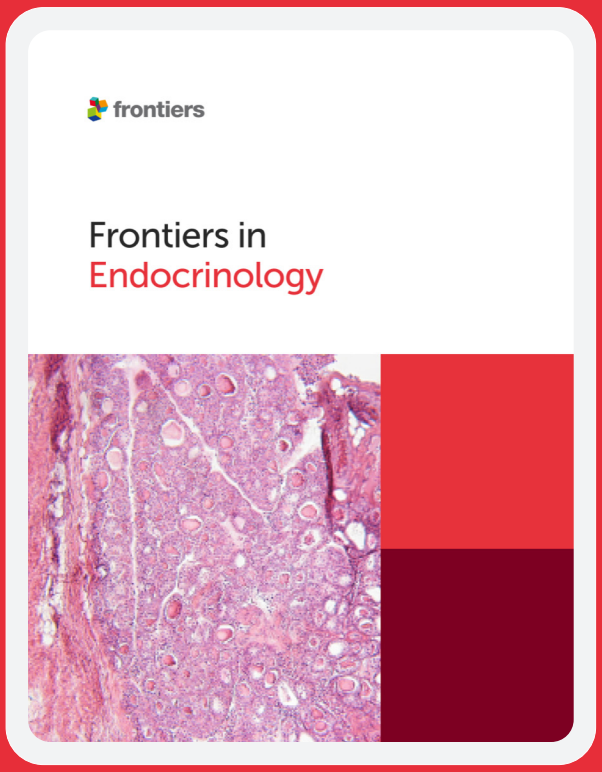

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