BMC Geriatrics

RESEARCH

Open Access

Sarcopenia as a predictor of nutritional status and comorbidities: a cross-sectional and mendelian randomization study

Chao Liu[1,2], Guanyi Chen[1], Yu Xia[1,2], Pingxiao Wang[1,2], Ziyue Zhao[1,2], JiaLin Zhang[1,2], Tao Xiao[1,2] and Hui Li[1,2*]

Abstract

Background With the advancement of world population aging, age-related sarcopenia (SP) imposes enormous clinical burden on hospital. Clinical research of SP in non-geriatric wards has not been appreciated, necessitating further investigation. However, observational studies are susceptible to confounders. Mendelian randomization (MR) can effectively mitigate bias to assess causality.

Objective To investigate the correlation between SP and comorbidities in orthopedic wards, and subsequently infer the causality, providing a theoretical basis for developing strategies in SP prevention and treatment.

Methods Logistic regression models were employed to assess the correlation between SP and comorbidities. The MR analysis was mainly conducted with inverse variance weighted, utilizing data extracted from the UK and FinnGen biobank (Round 9).

Results In the cross-sectional analysis, SP exhibited significant associations with malnutrition ($P=0.013$) and some comorbidities, including osteoporosis ($P=0.014$), body mass index (BMI) ($P=0.021$), Charlson Comorbidity Index (CCI) ($P=0.006$). The MR result also provided supporting evidence for the causality between SP and hypertension, osteoporosis and BMI. These results also withstood multiple sensitivity analyses assessing the validity of MR assumptions.

Conclusion The result indicated a significant association between SP and BMI, CCI, malnutrition, and osteoporosis. We highlighted that SP and comorbidities deserved more attention in non-geriatric wards, urging further comprehensive investigation.

Keywords Sarcopenia, Comorbidity, Malnutrition, Osteoporosis, Mendelian randomization

Introduction

Sarcopenia (SP) is an age-related skeletal muscle disease characterized by the progressive decline of skeletal muscle mass, accompanied by diminished muscle strength and/or reduced physical performance [1]. The prevalence of SP in older adults worldwide ranges from 10 to 27% [2] and was notably higher among hospitalized older adults [3]. SP has been associated with severe physiological and clinical consequences, including cognitive impairment, functional decline, falls, fractures, disability, hospital admissions, postoperative complications and mortality [4–8]. The risk factors for SP are also diverse, encompassing aging, physical inactivity, malnutrition, cachexia, and various chronic diseases [9]. Furthermore, SP often coexists with other age-related or metabolic diseases, such as dementia, cardiovascular diseases, diabetes mellitus [9], cirrhosis [10], which imposes a growing economic and public health burden. Consequently, exploring the role

*Correspondence:
Hui Li
lihuix@csu.edu.cn
[1] Department of Orthopedics, the Second Xiangya Hospital of Central South University, 139 Renmin Road, Changsha, Hunan 410011, People's Republic of China
[2] Orthopedic Biomedical Materials Engineering Laboratory of Hunan Province, Changsha 410011, People's Republic of China

of SP in routine clinical practice is of paramount importance to meet the public health challenge effectively.

SP has garnered growing interest across several hospital departments. However, most observational studies have been concentrated in acute geriatric wards [11], and geriatric rehabilitation wards [12], where inpatients exhibit a notably high prevalence of SP. Meanwhile, scant attention has been paid to the relationship between SP and common comorbidities in orthopedic inpatients. SP has the potential to serve as a valuable predictor for identifying orthopedic patients who need improved preoperative interventions and postoperative rehabilitation.

At present, SP related clinical studies were basically limited to cross-sectional investigations, lacking in-depth exploration of the genetic relationship between SP and comorbidities. The Mendelian randomization (MR) approach can effectively mitigate bias from uncontrolled confounders, reverse causality and selective bias, all of which are frequently encountered challenges in conventional observational epidemiological studies [13]. Therefore, MR was employed to deduce the causality between exposure and outcome, using independent single nucleotide polymorphisms (SNPs) as instrumental variables (IVs). Our primary objective was to briefly estimate the correlation between SP and comorbidities in orthopedic patients. After that, the causal relationship was verified by MR, based on the results of the observational study.

Materials and methods

Cross-sectional study design

Study Design and patients

This study was designed as a cross-sectional investigation, continuously recruiting older patients from orthopedic wards at the Second Xiangya Hospital of Central South University. Ethical approval was obtained from the Medical Ethics Committee of our institute (Ethics number: LYF2022221), and all participating patients signed the consent forms. Wave 1 data were analyzed, comprising patients admitted from March 1, 2023 to July 1, 2023. Exclusion criteria were (a) patients in intensive care unit, unable to participate; (b) patients with pacemakers or metal implants. (c) patients who had undergone amputation.

Patient characteristics

Age, sex, length of stay, hospitalization cost, living area, and duration of disease were extracted from the patients' medical records. Mini-mental State Examination (MMSE) [14], The Barthel index (BI) [15], and The Mini Nutritional Assessment (MNA) [16] were completed by nurses to assess the patients' status at admission. The MMSE is a valid test of cognitive function, which includes eleven questions, requires only 5–10 min to administer, and is therefore practical to use serially and routinely [14]. The BI is a tool for assessing the ability to perform basic activities of daily living. It consists of 10 items including eating, bathing, dressing, personal hygiene, walking, and so on [15]. The MNA was designed and validated to provide a single, rapid assessment of nutritional status in elderly patients. It has been translated into several languages and validated in many clinics around the world [16]. The Blood biochemical parameters were also measured within the first 24 h of hospitalization: albumin (ALB), total protein (TP), alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), and serum creatinine (SCR).

Assessment of Sarcopenia and comorbidities

According to Asian Working Group on Sarcopenia in Older People criteria, bioelectrical impedance analysis (Biospace, InBody 770, Korea) was used to calculate skeletal muscle mass index and body mass index (BMI) [1]. Dynamometer(ASP Global, Jamar Plus+, USA)were used to measure handgrip strength. Experienced physicians completed the medical history and Charlson Comorbidity Index (CCI) [17]. CCI is designed to help doctors assess the patient's chronic disease and comorbid burden through CCI score. Comorbidity severity was categorized based on the total CCI score: none = 0, mild = 1–2, moderate = 3–4, and severe ≥ 5 [18].

Bidirectional MR study design

Data source

The diagnostic criteria for SP primarily involved appendicular lean mass (ALM), grip strength, and walking speed [1]. The ALM-related summary-level genome-wide association study (GWAS) datasets were sourced from the UK Biobank cohort, comprising 450,243 participants. These datasets were quantified by the sum of fat-free mass, and adjusted for appendicular fat mass and other covariates [19]. Walking pace statistics were extracted from an UK Biobank cohort of 459,915 individuals [20]. The low grip strength GWAS data, involving 256,523 individuals of European descent, were extracted from a genome-wide meta-analysis study, adjusted for sex, age, and population substructure [21]. The selection of comorbidities for Mendelian randomization (MR) analysis was informed by the results of our observational study. FinnGen combines imputed genotype data from Finnish biobanks and digital health record data from Finnish health registries, with nearly 500,000 participants. GWAS summary statistics for the chosen comorbidities were extracted from the FinnGen biobank (Round 9) (Supplementary Table 1) [22]. Further detail could be found in their website (https://www.finngen.fi/en) and the published article [19–21].

MR approaches

Genetic IVs with F statistics > 10 were meticulously chosen for exposure ($p < 5 \times 10^{-8}$, clumping $r^2 = 0.001$ and kb = 10,000) [23]. The number of malnutrition-related IVs below 3, so we relaxed the P-value threshold to 1×10^{-5} and reevaluated it. After harmonization processes, MR-pleiotropy residual sum and outlier (MR-PRESSO) was executed to eliminate IVs with potential pleiotropy [24]. These valid IVs satisfied the three assumptions: [1] IVs were significantly associated with the exposure; [2] IVs were not related to any potential confounders; [3] IVs affect outcome solely through exposure [13]. The inverse-variance weighted (IVW) method was employed as the main MR analysis, which could effectively estimate the causality in the absence of directed pleiotropy ($p > 0.05$ in the MR-Egger intercept test) [25]. The Cochran's Q test assessed these selected IVs to determine appropriate IVW effects model. Additionally, Weighted median and MR Robust Adjusted Profile Score(MR RAPS) were also performed to assess the robustness and sensitivity [26, 27]. MR Egger was utilized to calculate the intercept value to evaluate horizontal pleiotropy [28]. Finally, MR Steiger was employed to test whether causal relationship was valid.

Statistical analyses

All statistical analyses were conducted in the R statistical software (Version 4.1.3). In the analysis of observational study, Continuous variables are presented as

Table 1 Patient characteristics

Variables	Sarcopenia group ($n = 17$)	Non-sarcopenia group ($n = 103$)	*P*
Age (years)	73.24 ± 5.90	68.10 ± 5.687	**0.001**
Sex (female)	13(0.76)	77(0.75)	0.88
Height (cm)	152.68 ± 5.34	156.84 ± 6.64	**0.016**
Weight (kg)	51.31 ± 5.11	63.12 ± 9.01	**< 0.001**
BMI (kg/m^2)	22.05 ± 1.66	25.64 ± 3.38	**< 0.001**
ASM/height^2	5.58 ± 0.39	6.50 ± 0.74	**< 0.001**
Handgrip Strength (kg)	16.50 ± 4.83	23.94 ± 7.66	**< 0.001**
Live in rural area	12(0.71)	56(0.54)	0.211
Duration of disease(years)	6.30 ± 8.59	10.86 ± 11.97	0.135
Hospitalization cost (thousand yuans)	37.44 ± 10.76	35.47 ± 12.77	0.549
LOS (day)	10.59 ± 3.30	11.50 ± 4.49	0.427
CCL			
None	0(0)	0(0)	**0.013**
Mild (1–2 conditions)	2(0.12)	47(0.46)	
Moderate (3–4 conditions)	11(0.65)	48(0.47)	
Severe (≥ 5 conditions)	4(0.24)	8(0.08)	
Abnormal ALT	3(0.18)	8(0.08)	0.191
Abnormal AST	1(0.06)	9(0.09)	0.693
Abnormal BUN	8(0.47)	37(0.36)	0.38
Abnormal SCR	3(0.18)	3(0.03)	**0.01**
Abnormal TP	7(0.41)	36(0.35)	0.62
Abnormal ALB	11(0.65)	50(0.49)	0.22
Thrombus of lower limb	3(0.18)	10(0.10)	0.329
Hypertension	5(0.29)	57(0.55)	**0.047**
Diabetes	6(0.35)	15(0.15)	**0.037**
Osteoporosis	16(0.94)	50(0.49)	**< 0.001**
Dementia (MMSE)	2(0.12)	8(0.08)	0.581
Need nursing (BI)	9(0.53)	27(0.26)	**0.026**
MNA			
Well-nourished (≥ 24)	6(0.35)	87(0.84)	**< 0.001**
Nutrition risk (17-23.5)	11(0.65)	16(0.16)	
Malnourished (< 17)	0(0)	0(0)	

Abbreviations: *BMI* Body mass index, *ASM* Appendicular skeletal muscle mass, *LOS* Length of stay, *CCL* Charlson Comorbidity Index, *ALT* Alanine transaminase, *AST* Aspartate transaminase, *BUN* Blood urea nitrogen, *SCR* Serum creatinine, *TP* Total protein, *ALB* Albumin, *MMSE* Mini-mental State Examination, *BI* Barthel index, *MNA* Mini Nutritional Assessment

Table 2 Risk factors of Sarcopenia according to logistic regression analysis

Variables	B	SE	Wald	*P*-value
BMI (kg/m2)	-0.501	0.217	5.322	0.021
CCL	2.183	0.791	7.610	0.006
Osteoporosis	3.223	1.315	6.009	0.014
MNA	2.661	1.067	6.224	0.013
Duration of disease(years)	-0.118	0.050	5.593	0.018

Abbreviations: *BMI* Body mass index, *CCL* Charlson Comorbidity Index, *MNA* Mini Nutritional Assessment

means ± standard deviations, while categorical variables are expressed as numbers (percentages). The differences between the SP and non-SP groups were evaluated by independent sample t-tests for normally distributed data and chi-squared tests for categorical data. Backward stepwise binomial logistic regression ($p<0.10$) was performed to correct for the possible influencing factors and determine the associations between potential risk factors and SP.

For MR analysis, a Bonferroni corrected significance level ($p<0.05/15=0.003$) was applied. All analyses were conducted with the R packages "MendelianRandomization", "TwosampleMR", and "MRPRESSO".

Results

Cross-sectional analysis

The patient characteristics across groups with and without SP are showed in Table 1. Patient in orthopedic wards diagnosed with SP exhibited reduced ASM/height^2 and weaker handgrip strength. Compared with patient without SP, those with SP presented with older age, lower BMI, and higher CCI. The statistical difference result revealed that SP patients were more prone to require nursing care, suffer from hypertension, diabetes, osteoporosis, and malnutrition. Although there were notable

Table 3 Primary mendelian randomization estimates of comorbidities on Sarcopenia-related traits

Exposures	Outcomes	No. of IVs	IVW		Weighted median		RAPS	
			Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*
BMI	ALM	187	0.180(0.153, 0.207)	**1.779e-38****	0.205(0.174, 0.235)	**2.727e-39****	0.162(0.130, 0.193)	**5.562e-24****
BMI	Low grip strength	221	-0.025(-0.086, 0.036)	0.427	-0.010(-0.096, 0.076)	0.823	-0.014(-0.075, 0.047)	0.647
BMI	Walking pace	213	-0.104(-0.119, -0.089)	**3.908e-42****	-0.085(-0.102, -0.067)	**3.315e-21****	-0.100(-0.115, -0.085)	**5.517e-38****
Hypertension	ALM	106	-0.013(-0.031, 0.004)	0.137	-0.011(-0.029, 0.008)	0.257	-0.012(-0.033, 8.428e-03)	0.247
Hypertension	Low grip strength	159	0.007(-0.026, 0.040)	0.680	0.027(-0.015, 0.069)	0.210	0.017(-0.015, 0.049)	0.290
Hypertension	Walking pace	156	-0.023(-0.030, -0.016)	**6.277e-11****	-0.018(-0.027, -0.010)	**8.275e-06****	-0.024(-0.031, -0.017)	**4.067e-11****
Osteoporosis	ALM	37	0.004(-0.007, 0.015)	0.471	0.005(-0.008, 0.018)	0.481	0.003(-0.006, 0.012)	0.527
Osteoporosis	Low grip strength	44	0.002(-0.022, 0.027)	0.841	-0.008(-0.051, 0.036)	0.727	-0.007(-0.032, 0.019)	0.610
Osteoporosis	Walking pace	44	0.004(-2.782e-4, 0.008)	0.067	0.005(-0.003, 0.012)	0.206	0.005(3.063e-4, 0.009)	**0.036***
Dementia	ALM	10	0.009(-0.003, 0.021)	0.149	0.014(-0.003, 0.030)	0.106	0.006(-0.002, 0.014)	0.163
Dementia	Low grip strength	12	0.034(-0.024, 0.092)	0.256	0.052(-0.004, 0.108)	0.066	0.041(0.013, 0.068)	0.004*
Dementia	Walking pace	7	-0.001(-0.012, 0.009)	0.793	-0.009(-0.022, 0.005)	0.215	0.004(-0.005, 0.014)	0.360
Malnourished	ALM	10	7.577e-4(-0.004, 0.005)	0.753	5.866e-4(-0.004, 0.005)	0.811	-1.385e-04(-0.001, 9.603e-4)	0.805
Malnourished	Low grip strength	10	0.004(-0.009, 0.017)	0.559	-0.002(-0.020, 0.016)	0.788	0.003(-0.002, 0.008)	0.219
Malnourished	Walking pace	10	0.002(-5.236e-4, 0.004)	0.135	0.002(-9.467e-4, 0.005)	0.176	0.002(-8.265e-4, 0.004)	0.197

Abbreviations: *BMI* Body mass index, *ALM* Appendicular lean mass, *MR* Mendelian randomization, *CI* Confidence interval, *IVW* Inverse variance weighted, *MR-RAPS* Mendelian Randomization Robust Adjusted Profile Score

P value* denotes nominal association ($P<0.05$)

P value** denotes statistical significance after the Bonferroni correction. ($P<0.003$)

differences in SCR in the blood biochemical indexes, but not in BUN. The backward stepwise binomial logistic regression model was conducted and five significant factors were detected (Table 2). Notably, the analysis revealed significant associations between SP and BMI, CCI, osteoporosis in orthopedic wards.

MR analysis between comorbidities and SP-related traits

The IVW result revealed a significant causal effect of BMI on SP after the Bonferroni correction (Table 3; Fig. 1) [ALM-related analysis: Beta = 0.180, 95% confidence interval (CI) = (0.153, 0.207), $p = 1.779e\text{-}38$; walking pace-related analysis: Beta (95% CI) =-0.104(-0.119, -0.089), $p = 3.908e\text{-}42$]. Furthermore, the IVW results also indicated that a significant negative causal effect of hypertension on SP [walking pace-related analysis: Beta (95% CI) =-0.023(-0.030, -0.016), $p = 6.277e\text{-}11$]. Consistently, the weighted median and the RAPS further reinforcing the hypothesized relationships. Osteoporosis and dementia exhibited nominal causal effects on SP-related traits.

The impact of SP on comorbidities was also thoroughly evaluated. The result showed that SP exerted a substantial causal effect on BMI after the Bonferroni correction (Table 4; Fig. 2) [ALM-related analysis: Beta (95% CI) = 0.049(0.028, 0.069), $p = 3.975e\text{-}06$; walking pace-related analysis: Beta (95% CI) =-1.120(-1.295, -0.945), $p = 5.550e\text{-}36$]. The IVW results also supported that SP had a significant negative causal effect on hypertension [ALM-related analysis: Beta (95% CI) =-0.096(-0.140, -0.052), $p = 2.153e\text{-}05$; walking pace-related analysis: Beta (95% CI) =-1.341(-1.716, -0.967), $p = 2.207e\text{-}12$], and SP had a noteworthy positive causal effect on osteoporosis [low grip strength-related analysis: Beta (95% CI) = 0.367(0.146, 0.589), $p = 0.001$]. SP also had a nominal causal effect on dementia. However, the current results did not support for the causality between malnutrition and SP-related traits.

To ensure the robustness of our findings, comprehensive sensitivity analyses were conducted, (Table 5; Fig. 3). The Cochran's Q test showed heterogeneity within each pair of datasets. The outliers identified through MR-PRESSO are documented in Supplementary Table 2. MR Egger indicated significantly horizontal pleiotropy of BMI on ALM. The F value of these IVs exceeded 10, indicating their validity in minimizing bias. The proportion of variance explained showed in Supplementary Tables 3, and each pair passed the MR Steiger test, enhancing the effectiveness and reliability of our analyses (Supplementary Table 3).

Discussion

In this study, we conducted a comprehensive analysis combining a cross-sectional investigation in orthopedic wards and a two-sample MR analysis to explore the relationship between SP and comorbidities. The observational research results unveiled a robust association between a higher risk of SP and elevated BMI, as well as an increased risk of osteoporosis and malnutrition in orthopedic wards. The MR analysis further corroborated the causal link between SP and BMI, hypertension, osteoporosis. To our knowledge, this was also the first bi-directional

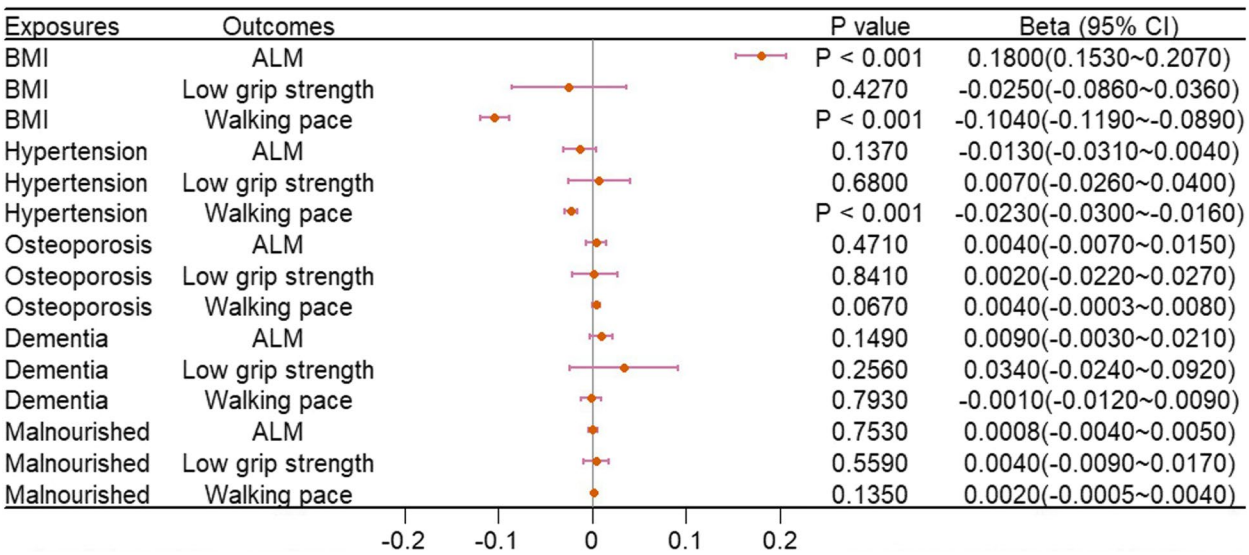

Fig. 1 Forest plot of the MR IVW analyses for comorbidities on SP-related traits. IVW, in verse-variance weighted; MR, mendelian randomization; SP, sarcopenia; AlM, appendicular lean mass; BMI, body mass index; CI, confidence interval

Table 4 Primary mendelian randomization estimates of Sarcopenia-related traits on comorbidities

Exposures	Outcomes	No. of IVs	IVW		Weighted median		RAPS	
			Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*
ALM	BMI	486	0.049(0.028, 0.069)	**3.975e-06****	0.056(0.033, 0.079)	**1.609e-06****	0.044(0.023, 0.066)	**4.923e-05****
Low grip strength	BMI	12	-0.036(-0.088, 0.016)	0.177	-0.059(-0.113, -0.006)	**0.029***	-0.022(-0.120, 0.077)	0.668
Walking pace	BMI	42	-1.120(-1.295, -0.945)	**5.550e-36****	-0.960(-1.132, -0.787)	**1.083e-27****	-1.097(-1.294, -0.899)	**1.143e-27****
ALM	Hypertension	495	-0.096(-0.140, -0.052)	**2.153e-05****	-0.144(-0.197, -0.091)	**1.130e-07****	-0.097(-0.142, -0.052)	**2.208e-05****
Low grip strength	Hypertension	11	0.084(-0.040, 0.207)	0.185	0.038(-0.074, 0.151)	0.501	0.044(-0.060, 0.148)	0.405
Walking pace	Hypertension	42	-1.341(-1.716, -0.967)	**2.207e-12****	-1.381(-1.763, -1000)	**1.329e-12****	-1.273(-1.718, -0.829)	**1.916e-08****
ALM	Osteoporosis	518	0.018(-0.069, 0.106)	0.680	-0.004(-0.141, 0.132)	0.949	0.009(-0.077, 0.095)	0.833
Low grip strength	Osteoporosis	12	0.367(0.146, 0.589)	**0.001****	0.339(0.050, 0.628)	**0.021***	0.316(0.099, 0.534)	**0.004***
Walking pace	Osteoporosis	49	0.164(-0.439, 0.768)	0.593	0.067(-0.800, 0.935)	0.879	0.167(-0.444, 0.779)	0.592
ALM	Dementia	519	-0.064(-0.126, -0.003)	**0.040***	-0.005(-0.100, 0.090)	0.911	-0.065(-0.125, -0.005)	**0.033***
Low grip strength	Dementia	14	-0.041(-0.186, 0.104)	0.581	0.014(-0.194, 0.222)	0.898	-0.025(-0.170, 0.120)	0.737
Walking pace	Dementia	49	-0.009(-0.628, 0.611)	0.978	-0.301(-0.992, 0.390)	0.393	0.035(-0.618, 0.688)	0.917
ALM	Malnourished	521	0.024(-0.277, 0.325)	0.875	-0.192(-0.694, 0.310)	0.454	-0.054(-0.347, 0.240)	0.720
Low grip strength	Malnourished	14	-0.131(-0.897, 0.636)	0.738	-0.132(-1.178, 0.915)	0.806	-0.184(-0.937, 0.570)	0.633
Walking pace	Malnourished	49	0.195(-2.127, 2.518)	0.869	0.877(-2.594, 4.349)	0.620	0.239(-2.267, 2.745)	0.852

Abbreviations: *BMI* Body mass index, *ALM* Appendicular lean mass, *MR* Mendelian randomization, *CI* Confidence interval, *IVW* Inverse variance weighted, *MR-RAPS* Mendelian Randomization Robust Adjusted Profile Score

P value* denotes nominal association ($P < 0.05$)

P value** denotes statistical significance after the Bonferroni correction. ($P < 0.003$)

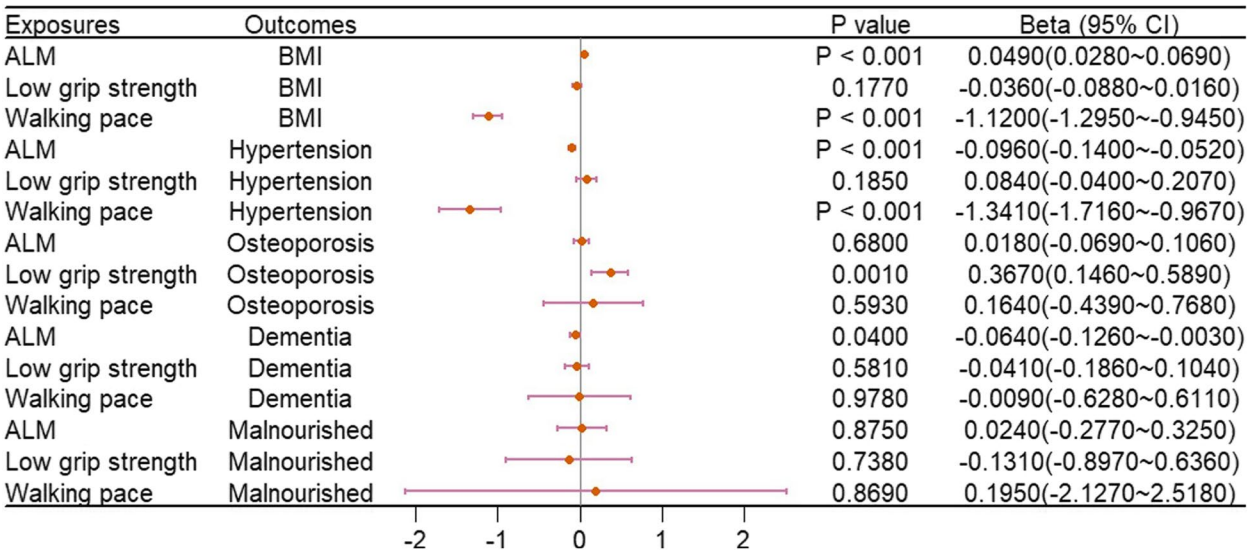

Fig. 2 Forest plot of the MR IVW analyses for SP-related traits on comorbidities. IVW, inverse-variance weighted; MR, mendelian randomization; SP, sarcopenia; AlM, appendicular lean mass; BMI, body mass index; CI, confidence interval

Table 5 Sensitivity analysis of the primary causal association between Sarcopenia-related traits and comorbidities

Exposures	Outcomes	Cochran's Q (*P*)	MR-Egger (*P*)	MR-PRESSO (*P*)	F
BMI	ALM	647.643(2.311e-52)	-0.002(0.038)	3902.053(< 0.001)	NA
BMI	Low grip strength	309.740(6.261e-05)	0.002(0.330)	402.849(< 0.001)	NA
BMI	Walking pace	525.404(1.379e-28)	-4.683e-4(0.329)	737.419(< 0.001)	NA
Hypertension	ALM	363.138(3.821e-30)	5.980e-4(0.676)	3444.765(< 0.001)	48.599
Hypertension	Low grip strength	222.324(5.667e-4)	-0.002(0.560)	281.777(< 0.001)	54.475
Hypertension	Walking pace	327.530(2.074e-14)	-1.425e-4(0.799)	547.166(< 0.001)	54.630
Osteoporosis	ALM	97.843(1.267e-07)	-6.413e-4(0.618)	959.470(< 0.001)	22.882
Osteoporosis	Low grip strength	58.582(0.057)	0.003(0.324)	62.710(0.1)	23.044
Osteoporosis	Walking pace	57.912(0.064)	-4.754e-4(0.400)	81.640(0.003)	23.593
Dementia	ALM	9.870(0.361)	-0.001(0.572)	66.864(0.001)	165.096
Dementia	Low grip strength	23.624(0.014)	-0.008(0.369)	26.204(0.073)	132.622
Dementia	Walking pace	6.214(0.400)	5.801e-4(0.688)	56.503(0.004)	159.466
Malnourished	ALM	18.616(0.029)	0.003(0.300)	21.882(0.367)	21.856
Malnourished	Low grip strength	13.775(0.131)	0.001(0.912)	14.149(0.526)	21.856
Malnourished	Walking pace	6.709(0.667)	-0.001(0.361)	7.712(0.727)	21.798
ALM	BMI	1280.168(5.537e-73)	-6.147e-4(0.252)	4155.172(< 0.001)	NA
Low grip strength	BMI	29.032(0.002)	5.739e-05(0.991)	78.325(< 0.001)	NA
Walking pace	BMI	119.432(1.360e-09)	-8.744e-4(0.797)	1215.148(< 0.001)	NA
ALM	Hypertension	1305.003(1.931e-74)	0.002(0.098)	2635.125(< 0.001)	98.155
Low grip strength	Hypertension	25.216(0.005)	0.006(0.595)	86.217(< 0.001)	38.032
Walking pace	Hypertension	114.748(6.602e-09)	-0.009(0.244)	311.719(< 0.001)	37.714
ALM	Osteoporosis	633.056(3.493e-4)	-0.003(0.241)	773.904(< 0.001)	97.915
Low grip strength	Osteoporosis	7.407(0.765)	0.013(0.535)	37.944(0.010)	37.445
Walking pace	Osteoporosis	41.152(0.747)	-0.007(0.550)	47.296(0.758)	40.362
ALM	Dementia	599.325(0.008)	-9.528(0.547)	725.345(< 0.001)	97.979
Low grip strength	Dementia	18.446(0.141)	-0.008(0.634)	21.508(0.231)	39.249
Walking pace	Dementia	95.561(5.378e-05)	-0.011(0.383)	104.459(< 0.001)	40.362
ALM	Malnourished	447.777(0.990)	0.003(0.669)	535.371(0.967)	98.763
Low grip strength	Malnourished	13.645(0.399)	-0.044(0.558)	15.631(0.549)	39.249
Walking pace	Malnourished	54.481(0.242)	-0.045(0.354)	60.132(0.295)	40.362

NA occurred because of a lack of sample size for BMI

Abbreviations: *BMI* Body mass index, *ALM* Appendicular lean mass, *MR* Mendelian randomization, *MR-PRESSO* Mendelian Randomization Pleiotropy RESidual Sum and Outlier, *NA* Not applicable

MR study to investigate causality between SP and these comorbidities.

Actually, some observational studies with similar themes were reported, but most of these investigations occurred in geriatric wards [12], or several studies only focus on SP related postoperative complications [29]. Extensive meta-analyses have demonstrated that SP is highly prevalent as a comorbid disease in individuals with hypertension [30], diabetes mellitus [9], lower BMI [31], osteoporosis [32], liver cirrhosis [33], chronic kidney disease [34] and malnutrition [35]. Nevertheless, it is crucial to specify the scope to which the conclusions may be applied. When experienced orthopedic surgeons encounter older patients with uncontrolled diabetes, hypertension, or mental illness in outpatient settings, they may recommend the patient to control disease first, and then go to the orthopedic wards for surgery, which makes the condition of SP in orthopedics significantly different from that in geriatrics. Our result revealed a strong correlation between SP and BMI, osteoporosis, and malnutrition in orthopedics department. Suitable nutritional supplementation can be effective in managing fatigue, improving motor, cognitive performance and ALM [36–38]. Meanwhile, hypertension, diabetes, and the blood biochemical parameters cannot well predict SP in orthopedic wards. SP has not received adequate attention in clinical practice and our findings carry crucial implications for comprehending and forecasting SP in non-geriatric medical contexts.

Similarly, SP related MR studied are currently rare. Despite these differences, one MR letter reported a

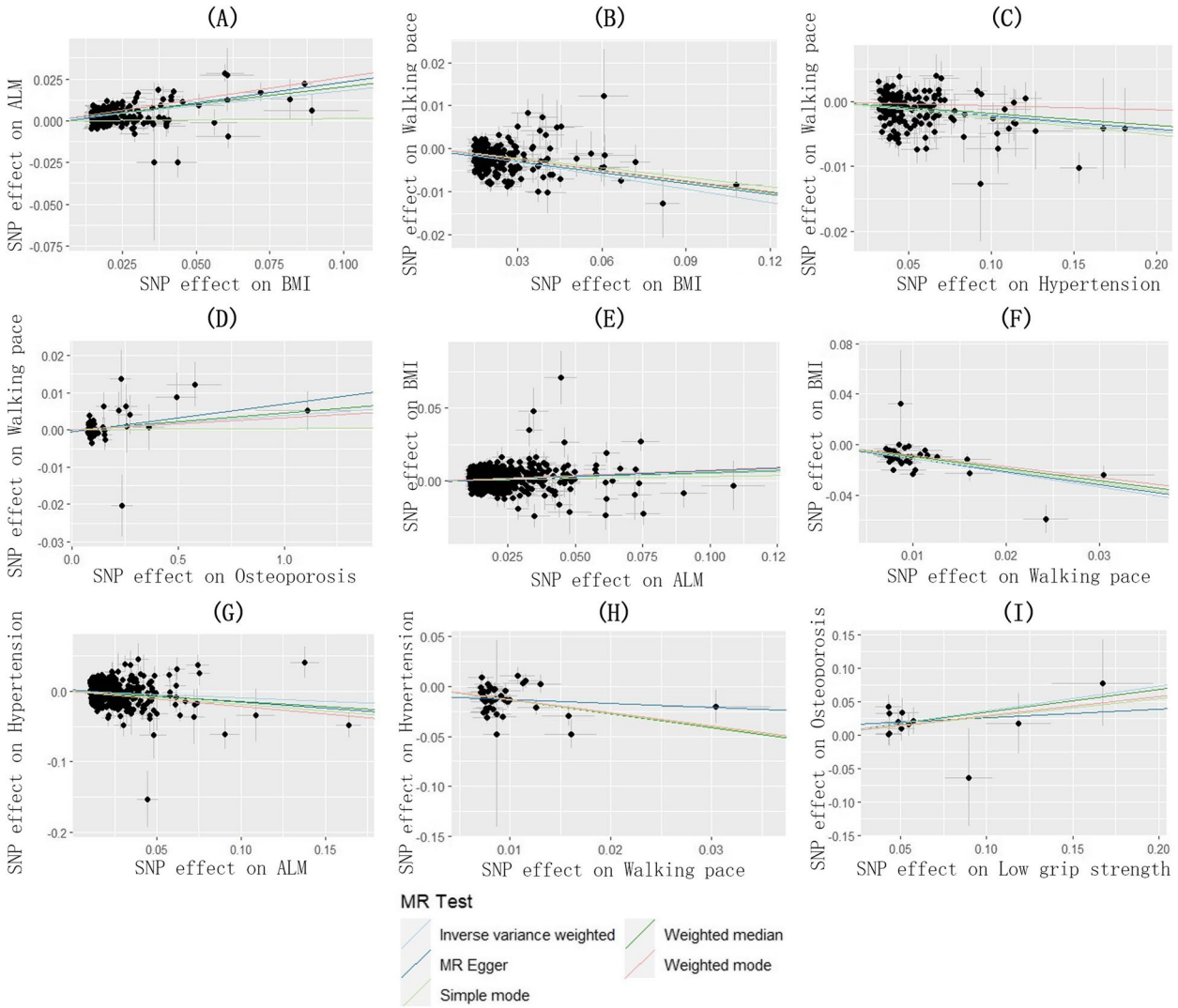

Fig. 3 Scatter plot of the MR estimate for **A** the effect of BMI on AIM; **B** the effect of BMI on walking pace: **C** the effect of hypertension on walking pace; **D** the effect of osteoporosis on walking pace: **E** the effect of AIM on BMI; **F** the effect of walking pace on BMI; **G** the effect of AIM on hypertension; **H** the effect of walking pace on hypertension; **I** the effect of low grip strength on osteoporosis; Abbreviations: BMI; body mass index, AIM: appendicular lean mass, MR: mendelian randomization

significant negative causal effect between BMI and walking pace [39]. Two MR studied revealed a mutual significant causal effect between osteoporosis and SP [39, 40]. Our MR analyses were the first to assess the causality between SP and common comorbidities, including hypertension, dementia, and malnutrition. Somewhat unexpectedly, the MR result did not support causality between SP and malnutrition, warranting scrupulous consideration. The reasons may be that the P-value threshold was relaxed to 1×10^{-5} instead of 1×10^{-8}, which might downgrade the quality of GWAS datasets. Malabsorption, atherosclerosis and stroke may be potential confounding factors to affect the MR process [41–43]. Addressing this requires more rigorous MR methods and improved data sources. Our current MR results remain consistent with the majority of previous studies.

In our observational study, we focused on the role of SP in non-geriatric wards, indicating that older patients with osteoporosis, malnutrition, and lower BMI are more susceptible to developing SP in orthopedic wards. Combined with these observational findings, we identified common comorbidities to perform MR analyses, supporting the bidirectional causality between SP and BMI, hypertension, and osteoporosis. We retrieved data from the UK and FinnGen biobank (Round 9) to meticulously

avoid sample overlapping and minimize bias. The validity of results was checked by strict parameters and diverse MR methods. However, our MR analysis still had several potential limitations. Firstly, more clinical samples in orthopedic wards are still essential to bolster our hypothesis. Secondly, more reliable data sources were still essential, especially for malnutrition. Regrettably, we were unable to find more robust statistic for malnutrition. Thirdly, MR analysis is valid only if the three assumptions mentioned above are strictly satisfied. Although we used six sensitivity analysis methods to ensure that these assumptions were met, more testing methods were also required to ensure the robustness of the results, with the updating of MR methods.

Conclusions

In conclusion, our cross-sectional analysis demonstrated that BMI, osteoporosis, and malnutrition are robust predictors of SP in orthopedic wards, while the MR analyses validated the causal association between SP and BMI, hypertension, osteoporosis. This novel discovery offers valuable insights for improving practices in identifying SP among older patients in non-geriatric wards, who had better absorb adequate nutrition, control weight, and prevent osteoporosis to effectively address SP.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05341-2.

Supplementary Material 1: Additional Table 1. Independent IVs of age-related diseases in the forward MR analysis. Additional Table 2. Independent IVs of sarcopenia-related traits in the reverse MR analysis.

Supplementary Material 2: Supplementary Table 1. Phenotype source and description of age-related comorbidities. Supplementary Table 2. IVs outliers in MR-PRESSO analysis.

Statement

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Authors' contributions

L.C. had the idea and drafted the first draft, Guanyi Chen collected clinical data, Yu Xia performed data analysis, Pingxiao Wang and Ziyue Zhao created the table and figure, JiaLin Zhang gave constructive suggestions during the process. X.T. and L.H drafted the final manuscript. All authors contributed to the final manuscript and agreed to the published version of the manuscript.

Funding

This work was supported by Research Project of Human Health Commission (grant number 202204073071).

Availability of data and materials

GWAS datasets of SP-related traits are available in [https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90007526/], [https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90000025/], [https://gwas.mrcieu.ac.uk/datasets/ukb-b-4711/]. GWAS datasets of comorbidities are available in [https://www.finngen.fi/en/access_results]. Further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate

The study received the necessary ethical approvals from the Medical Ethics Committee of the Second Xiangya Hospital, Central South University (Ethics number: LYF2022221; date: 18 January 2023). The consent that was obtained from all of the participants was informed.

Consent for publication

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no competing interests.

Received: 24 December 2023 Accepted: 28 August 2024
Published online: 11 September 2024

References

1. Chen L-K, Woo J, Assantachai P, Auyeung T-W, Chou M-Y, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc. 2020;21(3):300-e372.
2. Petermann-Rocha F, Balntzi V, Gray SR, Lara J, Ho FK, Pell JP, et al. Global prevalence of Sarcopenia and severe Sarcopenia: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2021;13(1):86–99.
3. Bianchi L, Abete P, Bellelli G, Bo M, Cherubini A, Corica F, et al. Prevalence and clinical correlates of Sarcopenia, identified according to the EWGSOP definition and diagnostic algorithm, in hospitalized older people: the glisten study. J Gerontol Ser A. 2017;72(11):1575–81.
4. Chen L-K, Liu L-K, Woo J, Assantachai P, Auyeung T-W, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.
5. Yeung SSY, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CGM, et al. Sarcopenia and its association with falls and fractures in older adults: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2019;10(3):485–500.
6. Simonsen C, de Heer P, Bjerre ED, Suetta C, Hojman P, Pedersen BK, et al. Sarcopenia and postoperative complication risk in gastrointestinal surgical oncology. Ann Surg. 2018;268(1):58–69.
7. Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association between Sarcopenia and cognitive impairment: a systematic review and meta-analysis. J Am Med Dir Assoc. 2016;17(12):1164 e7- e15.
8. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyere O. Health outcomes of Sarcopenia: a systematic review and meta-analysis. PLoS On. 2017;12(1): e0169548.
9. Pacifico J, Geerlings MAJ, Reijnierse EM, Phassouliotis C, Lim WK, Maier AB. Prevalence of Sarcopenia as a comorbid disease: a systematic review and meta-analysis. Exp Gerontol. 2020;131: 110801.
10. Welch N, Attaway A, Bellar A, Alkhafaji H, Vural A, Dasarathy S. Compound Sarcopenia in hospitalized patients with cirrhosis worsens outcomes with increasing age. Nutrients. 2021;13(2):659.
11. Hao Q, Hu X, Xie L, Chen J, Jiang J, Dong B, et al. Prevalence of Sarcopenia and associated factors in hospitalised older patients: a cross-sectional study. Australas J Ageing. 2018;37(1):62–7.
12. Pacifico J, Reijnierse EM, Lim WK, Maier AB. The association between Sarcopenia as a comorbid disease and incidence of institutionalisation and mortality in geriatric rehabilitation inpatients: REStORing health of acutely unwell adulTs (RESORT). Gerontology. 2022;68(5):498–508.
13. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies

in epidemiology using mendelian randomization: the STROBE-MR statement. JAMA. 2021;326(16):1614–21.
14. He H, Liu M, Li L, Zheng Y, Nie Y, Xiao LD, et al. The impact of frailty on short-term prognosis in discharged adult stroke patients: a multicenter prospective cohort study. Int J Nurs Stud. 2024;154: 104735.
15. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Maryland State Med J. 1965;14:61–5.
16. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition (Burbank, Los Angeles County, Calif). 1999;15(2):116–22.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
18. Lim SK, Beom J, Lee SY, Kim BR, Chun SW, Lim JY, et al. Association between Sarcopenia and fall characteristics in older adults with fragility hip fracture. Injury. 2020;51(11):2640–7.
19. Pei YF, Liu YZ, Yang XL, et al. The genetic architecture of appendicular lean mass characterized by association analysis in the UK Biobank study. Commun Biol. 2020;3(1):608. https://doi.org/10.1038/s42003-020-01334-0.
20. Mitchell RE, Elsworth BL, Mitchell R, Raistrick CA, Paternoster L, Hemani G, Gaunt TR. MRC IEU UK Biobank GWAS pipeline version 2. University of Bristol; 2019. https://doi.org/10.5523/bris.pnoat8cxo0u52p6ynfaekeigi.
21. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021;12(1):654.
22. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613(7944):508–18.
23. Clarke L, Zheng-Bradley X, Smith R, Kulesha E, Xiao C, Toneva I, et al. The 1000 Genomes Project: data management and community access. Nat Methods. 2012;9(5):459–62.
24. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.
25. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. Nat Rev Cardiol. 2017;14(10):577–90.
26. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14.
27. Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. J Ann Stat. 2020;48(3):1742–69, 28.
28. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25.
29. Babu JM, Kalagara S, Durand W, Antoci V, Deren ME, Cohen E. Sarcopenia as a risk factor for prosthetic infection after total hip or knee arthroplasty. J Arthroplast. 2019;34(1):116–22.
30. Bai T, Fang F, Li F, Ren Y, Hu J, Cao J. Sarcopenia is associated with hypertension in older adults: a systematic review and meta-analysis. BMC Geriatr. 2020;20(1):279.
31. Li C, Kang B, Zhang T, Gu H, Man Q, Song P, et al. High visceral fat area attenuated the negative association between high body mass index and Sarcopenia in community-dwelling older Chinese people. Healthcare. 2020;8(4):479.
32. Nielsen BR, Abdulla J, Andersen HE, Schwarz P, Suetta C. Sarcopenia and osteoporosis in older people: a systematic review and meta-analysis. Eur Geriatr Med. 2018;9(4):419–34.
33. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of Sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. PLoS On. 2017;12(10): e0186990.
34. Ribeiro HS, Neri SGR, Oliveira JS, Bennett PN, Viana JL, Lima RM. Association between Sarcopenia and clinical outcomes in chronic kidney disease patients: a systematic review and meta-analysis. Clin Nutr. 2022;41(5):1131–40.
35. Ligthart-Melis GC, Luiking YC, Kakourou A, Cederholm T, Maier AB, de van der Schueren MAE. Frailty, Sarcopenia, and malnutrition frequently (Co-) occur in hospitalized older adults: a systematic review and meta-analysis. J Am Med Dir Assoc. 2020;21(9):1216–28.
36. Giovannini S, Iacovelli C, Loreti C, Lama E, Morciano N, Frisullo G, et al. The role of nutritional supplement on post-stroke fatigue: a pilot randomized controlled trial. J Nutr Health Aging. 2024;28(7): 100256.
37. Giovannini S, Brau F, Forino R, Berti A, D'Ignazio F, Loreti C, et al. Sarcopenia: diagnosis and management, state of the art and contribution of ultrasound. J Clin Med. 2021;10(23):5552.
38. Robinson S, Cooper C, Aihie Sayer A. Nutrition and Sarcopenia: a review of the evidence and implications for preventive strategies. J Aging Res. 2012;2012:1–6.
39. Ran S, Zhao MF, Liu BL. The causal association of Sarcopenia with osteoporosis and obesity: a mendelian randomization analysis. Osteoporos Int. 2023;34(3):613–4.
40. Liu C, Liu N, Xia Y, Zhao Z, Xiao T, Li H. Osteoporosis and sarcopenia-related traits: a bi-directional mendelian randomization study. Front Endocrinol (Lausanne). 2022;13:975647.
41. Ko SH, Shin YI. Nutritional supplementation in stroke rehabilitation: a narrative review. Brain Neurorehabil. 2022;15(1):e3.
42. Wei T, Liu J, Zhang D, Wang X, Li G, Ma R, et al. The relationship between nutrition and atherosclerosis. Front Bioeng Biotechnol. 2021;9:635504.
43. Cammarota G, Cesaro P, Cazzato A, Cianci R, Fedeli P, Ojetti V, et al. The water immersion technique is easy to learn for routine use during EGD for duodenal villous evaluation: a single-center 2-year experience. J Clin Gastroenterol. 2009;43(3):244–8.

Publisher's note