






ORIGINAL RESEARCH

Prevalence of sarcopenia in patients with rheumatoid arthritis using the revised EWGSOP2 and the FNIH definition

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ABSTRACT

Objective In rheumatoid arthritis (RA), chronic inflammation can enhance the development of sarcopenia with a depletion of muscle mass, strength and performance. Currently, a consensus definition for sarcopenia and solid results for the prevalence of sarcopenia in patients with RA are lacking.

Methods In this cross-sectional study, 289 patients ≥ 18 years with RA were recruited. Dual X-ray absorptiometry was performed to measure appendicular lean mass. Assessment of muscle function included grip strength, gait speed and chair rise time. Prevalence of sarcopenia was defined using the updated European Working Group on Sarcopenia in Older People (EWGSOP2) and the Foundation for the National Institutes of Health (FNIH) definition. In addition, the RA study population was compared with existing data of healthy controls (n=280).

Results 4.5% of patients (59.4 \pm 11.3 years) and 0.4% of controls (62.9 \pm 11.9 years) were affected by sarcopenia according to the EWGSOP2 definition. Body weight (OR 0.92, 95% CI 0.86 to 0.97), body mass index (BMI) (OR 0.70, 95% CI 0.57 to 0.87), C reactive protein (CRP) (OR 1.05, 95% CI 1.01 to 1.10), disease duration (OR 1.08, 95% CI 1.02 to 1.36), current medication with glucocorticoids (OR 5.25, 95% CI 2.14 to 24.18), cumulative dose of prednisone equivalent (OR 1.04, 95% CI 1.02 to 1.05) and Health Assessment Questionnaire (HAQ) (OR 2.50, 95% CI 1.27 to 4.86) were associated with sarcopenia in patients with RA. In contrast, the prevalence was 2.8% in patients compared with 0.7% in controls when applying the FNIH definition, and body height (OR 0.75, 95% CI 0.64 to 0.88), BMI (OR 1.20, 95% CI 1.02 to 1.41), CRP (OR 1.06, 95% CI 1.01 to 1.11) and HAQ (OR 2.77, 95% CI 1.17 to 6.59) were associated with sarcopenia.

Conclusion Sarcopenia is significantly more common in patients with RA compared with controls using the EWGSOP2 criteria. The FNIH definition revealed sarcopenia in individuals with high BMI and fat mass, regardless of the presence of RA.

Trial registration number It was registered at the German Clinical Trials Registry (DRKS) as well as WHO Clinical Trials Registry (ICTRP) (DRKS00011873, registered on 16 March 2017).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sarcopenia in rheumatoid arthritis (RA) is a common manifestation and is significantly more frequent than in healthy controls.

WHAT THIS STUDY ADDS

⇒ This is the first study to compare the updated European Working Group on Sarcopenia in Older People (EWGSOP2) and the Foundation for the National Institutes of Health (FNIH) definitions between patients with RA and healthy controls. Patients with RA more commonly had sarcopenia than healthy controls using the current EWGSOP2 definition. In contrast, the FNIH definition did not reveal significant differences in terms of the prevalence of sarcopenia between patients and healthy individuals. Parameters suggestive of chronic inflammation such as C reactive protein elevation and treatment with glucocorticoids increased the odds of sarcopenia. The association of sarcopenia with decreased daily function expressed in the Health Assessment Questionnaire score was clinically important.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study shows the importance of a common definition of sarcopenia. The data highlight the importance of assessing for sarcopenia in patients with RA. Further research is needed to accurately determine muscle mass independent of body size parameters.

INTRODUCTION

‘Primary sarcopenia’ was described previously as an age-related loss of muscle mass, whereas more recent definitions additionally recommend using the evaluation of muscle function in terms of strength and performance.^{1 2} Age-related loss of muscle mass tends to be accompanied by an increasing infiltration of fat tissue into skeletal muscles, which correlates with poor health outcomes, for example, a higher risk for the subjects’ falling.³ Further

studies showed that low muscle density due to fat infiltration, muscle strength and muscle performance are all associated with an increased risk of hospitalisation, limitations in activities of daily living and an increased risk for falls and fractures in ageing adults.^{4,5}

In rheumatoid arthritis (RA), the prevalence of sarcopenia was found to be increased compared with healthy peers.^{6–10} As a manifestation of an altered body composition, Giles *et al* observed the reduction of lean mass in patients with RA, while fat mass remained constant or even increased.¹¹ Presumably, this process is triggered by augmented circulating inflammatory cytokines, like TNF- α and Interleukin 1 β , causing an intensified metabolism as well as an increasing peripheral insulin resistance. Moreover, the influence of glucocorticoids—a common medication used for patients with RA—on body composition can enhance these alterations, leading to a gain of trunk fat mass and glucocorticoid myopathy.¹² This shift of fat mass from the extremities towards the trunk enforces the risk of developing cardiovascular diseases.^{13,14} In addition, patients with RA have an increased risk of falling compared with healthy people.^{15,16} The incidence of falls in people with RA and concomitant sarcopenia is twice as high as in patients with RA without sarcopenia.⁹ Thus, the identification of sarcopenic patients with RA should occur at an early stage to initiate preventive measures like functional training, optimisation of nutrition and treat-to-target DMARD therapy, in order to reduce inflammation and glucocorticoid dose.¹⁷

Currently, no consensus definition for sarcopenia exists. However, all definitions proposed recently include the assessment of muscle mass and muscle strength, yet different thresholds are being applied to determine these parameters. Hence, the existing data on the prevalence of sarcopenia vary, depending on the definition used and the respective population studied.¹⁸ However, it is well known that sarcopenia increases with advanced age. Whereas the amount of sarcopenia is found to be around 15% in 65 years, it rises up to 40% in 85-year-old healthy ambulatory subjects.¹⁹

One issue concerning sarcopenia that remains to be addressed adequately is whether the depletion of muscle mass in patients with RA is accompanied by a reduction of muscle strength and performance to an equivalent extent compared with subjects without RA.

The primary objective was to determine the prevalence of sarcopenia in patients with RA compared with healthy controls on the basis of the revised definition on sarcopenia determined by the European Working Group of Sarcopenia in Older People (EWGSOP2).²⁰ For the sake of comparison, a second definition on sarcopenia was applied, namely by the Foundation for the National Institutes of Health (FNIH).²¹ Secondary objectives were the comparisons between patients with RA and sarcopenia and those without sarcopenia concerning muscle function, physical activity, quality of life and laboratory parameters.

METHODS

Study design and patient recruitment

This single-centre, cross-sectional study was conducted at the Charité—Universitätsmedizin Berlin between November 2017 and April 2019. Inclusion criteria comprised a diagnosis of RA according to the 2010 American College of Rheumatology classification criteria,²² age ≥ 18 years and ambulatory ability. Subjects were excluded from the study if an injury occurred in the last 3 months affecting muscle function, acute disease or acute worsening of a chronic disease that negatively affected muscle function, simultaneous participation in another study and pregnancy. All participants gave their written informed consent prior to being included in the study. The sample size of 289 was calculated on an assumed sarcopenia prevalence of 25% in patients with RA with a two-sided 95% CI and was determined using nQuery+n-Test V.3.0 software.

For comparison, existing data of a healthy control cohort ($n=280$, age 18–90 years) without chronic inflammatory disease, which had already been collected at the Centre of Muscle and Bone Research at Charité—Universitätsmedizin Berlin, was used. In this study, subjects were excluded who (1) had metal implants or artificial prostheses; (2) had oedema; (3) took medication affecting water-mineral homeostasis; (4) needed a walking aid; (5) had contraindications for X-ray exposure; (6) were pregnant and (7) were unable to provide written informed consent or were unable to follow the instructions. Study participants underwent scans and physical function assessment in the same laboratory using identical equipment and methods as subjects with RA.

Demographics and disease measures

Body weight, measured in underwear without shoes, was determined to the nearest 0.1 kg. Stature was assessed to the nearest 0.1 cm using a digital weight scale and stadiometer (Seca 764). Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Disease duration, rheumatoid factor (RF) seropositivity, current RA-specific medication, cumulative doses of glucocorticoids and life style factors such as smoking, alcohol consumption, sports, daylight exposure and diet were recorded. Disease Activity Score out of 28 joints and C reactive protein (CRP) blood level (Disease Activity Score of 28 joints including C reactive protein, DAS28_{CRP}) were calculated.²³ Furthermore, the disease-related fatigue was assessed using the Bristol RA Fatigue-Numerical Rating Scale, with zero indicating no fatigue and 10 indicating a high level of fatigue.²⁴

Assessment of physical function and disability

The chair rise test (CRT) was performed on a chair of 45 cm height. Time was taken to stand up to full extent and sitting down five times at maximum speed without break and without using the arms.²⁵ For grip strength measurement, subjects were positioned on a standard chair with back support and arm rests, wrists just over

the end of the arm of the chair and wrists in a neutral position.²⁶ Grip width was adjusted to the participants' hand size. Maximal grip force was assessed once at each side using a digital grip dynamometer (Novotec Medical, Pforzheim, Germany, Software BAS V.4.4). Self-selected gait speed was examined on a 6.45 m walk at usual pace along a quiet corridor using a stop watch (m/s). If necessary, participants were allowed to use canes or walkers.

The Activity-specific Balance Confidence Scale was used for the assessment of balance confidence.²⁷ Subjects rated their balance confidence for performing activities on a 16-item self-report measure. An overall score of zero represents no confidence; an overall score of 100 indicates complete confidence. Disability was assessed using the Health Assessment Questionnaire (HAQ), which evaluates impairments in eight categories of daily life activities: dressing and grooming, arising, eating, walking, hygiene, reach and grip. A score of zero indicates no disability, whereas a score of 3 indicates a high level of impairment.²⁸

Physical activity

For the assessment of physical activity, the short version of the International Physical Activity Questionnaire was completed.²⁹ This measure determines the types and intensity of physical activity and sitting time that people complete as part of their daily lives during the last 7 days and estimates total physical activity in the metabolic equivalent in minutes per week. The higher the value, the higher the activity level.

DXA body composition

So as to determine body composition, a whole-body scan using dual X-ray absorptiometry (DXA) (Lunar iDXA, GE Medical Systems, Wisconsin, USA; EnCore Software V.16.1) was applied according to the standard GE LUNAR Operator's Manual. In order to ensure consistency and follow standard quality control procedures, all scanning and analyses were performed by the same operator. Fat mass was described as percentage fat mass of total body mass. Appendicular lean mass (ALM) was defined as the sum of arms and legs lean mass (kg).³⁰ Relative ALM indices were obtained by adjusting ALM to squared height (ALM/ht²) and to BMI (ALM/BMI).²⁰

Operationalisation of sarcopenia

To assess sarcopenic changes in the study population, two different sarcopenia definitions were applied: In contrast to the previous EWGSOP1 definition,² the updated EWGSOP2 definition provides specific diagnostic thresholds and the classification into probable, confirmed and severe sarcopenia.²⁰ According to this revised clinical algorithm, sarcopenia is probable when low muscle strength was detected such as low grip strength (<27 kg in men and <16 kg in women) and/or a prolonged chair rise time of >15 s. Sarcopenia is confirmed if, in addition to low muscle strength, an ALM/ht² <7.0 kg/m² in men and <5.5 kg/m² in women is to be found. Sarcopenia in combination with a slow gait speed of less than 0.8 m/s is classified as severe sarcopenia.^{2 20}

The FNIH defines sarcopenia as low muscle mass with an ALM/BMI <0.789 m² in men and <0.512 m² in women in combination with weakness associated with low grip strength <26 kg in men and <16 kg in women²¹ (table 1).

Patient and public involvement

In order to guarantee the patient perspective, two patient representatives mediated by the German Rheuma League supported the study. Both patients completed a 2-day training course prior to becoming research partners. The methodical approach relied on recommendations of the EULAR for the involvement of patient representatives in research projects.³¹ The patients provided their input to adjust and refine the research questions, commented on the findings and contributed to the dissemination plan. Moreover, the patient and public involvement representatives were involved in writing a plain language summary leaflet of the findings for dissemination to their peers.

Statistical analysis

Sociodemographic and clinical parameters are expressed as absolute and relative frequency for categorical parameters, and as mean±SD or median and IQR for continuous data. Group comparisons were calculated with the χ^2 test, Students' t-test or Wilcoxon rank-sum test. Parameters that presented with a p<0.25 in bivariate analysis were used for logistic regression analysis. Associations between ALM/ht² and ALM/BMI with anthropometrics were

Table 1 Sarcopenia definitions and cut-off values

Working group	Muscle mass	Muscle strength	Muscle function
Updated EWGSOP2 ²⁰	Low muscle mass (ALM/ht ²) Men ≤7.0 kg/m ² Women ≤5.5 kg/m ²	Low grip strength Men <27 kg Women <16 kg	Slow gait speed ≤ 0.8 m/s and/or Prolonged chair rise time of >15 s
FNIH ²¹	Low muscle mass (ALM/BMI) Men <0.789 m ² Women <0.512 m ²	Weakness: Low grip strength Men <26 kg Women <16 kg	
ALM, appendicular lean mass; BMI, body mass index; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health.			

Table 2 Baseline characteristics in RA and controls

Variable	n	RA	n	Controls
Age (years), mean±SD	289	59.4±11.3	280	62.9±11.9*
Females, n (%)	289	230 (80)	280	153 (55)***
Height (m), mean±SD	289	1.67±0.08	280	1.69±0.1**
Weight (kg), mean±SD	289	74.9±13.8	280	76.9±14.3 ns
BMI (kg/m ²), mean±SD	289	27.0±4.5	280	26.8±4.0 ns
Fat mass (%), mean±SD	289	38.8±7.4	280	35.3±7.2***
RF seropositivity, n (%)	289	229 (79)		–
ACPA positive, n (%)	289	200 (87)		–
DAS28 _{CRP} median (IQR)	285	2.1 (1.3)		–
CRP (mg/L), median (IQR)	274	2.2 (3.5)		–
Disease duration (years), median (IQR)	289	9 (12)		–
HAQ (0–3), median (IQR)	289	0.5 (0–1.3)		–
Medication current, n (%)	280			–
Jak inhibitors, n (%)		22 (8)		–
cDMARDs, n (%)		190 (68)		–
bDMARDs, n (%)		130 (46)		–
Glucocorticoids, n (%)		147 (53)		–
Cumulative dose prednisone equivalent (g), median (IQR)	275	10.0 (21)		–

*p<0.01, **p<0.001, ***p<0.0001.

ACPA, anticitrullinated peptide antibodies; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; cDMARDs, conventional disease-modifying antirheumatic drugs; CRP, C reactive protein; DAS28_{CRP} Disease Activity Score of 28 joints including C reactive protein; HAQ, Health Assessment Questionnaire; ns, non-significant; RA, rheumatoid arthritis; RF, rheumatoid factor.

assessed visually with scatter plots and Pearson correlation coefficient was calculated.

Correlates for sarcopenia are presented in ORs with 95% CIs using logistic regression analysis. ORs were determined before and after considering age and sex as potential confounders. A p-value <0.05 was used as the level of significance. The statistical calculations were performed by way of the SAS V.9.4 (SAS Institute).

RESULTS

Table 2 shows baseline demographics and disease characteristics. The mean age for patients with RA was 59±11 years. They were predominantly female (80%), mostly seropositive (79.2%) with a median disease duration of 9 years and a low disease activity score (median DAS28_{CRP}=2.1). 68% of the patients received conventional disease-modifying drugs, 46% received biological disease-modifying drugs and 53% currently received glucocorticoids. Median cumulative dose of prednisone equivalent was 10.0 g. With a mean age of 63±12 years, controls were slightly older (p<0.01) and showed a lower proportion of females (55%; p<0.0001). Regarding anthropometric parameters, the two groups differ in terms of body height with the controls being slightly taller (p<0.001). Fat mass as percentage fat mass of total body mass is higher in patients with RA (39%) than in controls (35%).

Table 3 shows baseline characteristics of sarcopenia parameters and proportions of sarcopenia for RA and controls according to the sarcopenia definitions. Patients with RA show significant lower values for ALM/ht², ALM/BMI and grip strength, and slower chair rise time than controls (p<0.0001). Based on the cut-off values of the EWGSOP2 definition, almost twice as many individuals with RA presented with a reduced ALM/ht² (13% vs 7%, p=0.03) and with a prolonged chair rise time (7% vs 4%, p=0.05) compared with controls (**table 3**). Low grip strength was significantly more prevalent in RA than in controls (20% vs 2%, p<0.0001). The frequency of probable sarcopenia was five times higher in RA compared with controls (25% vs 5%, p<0.0001). Confirmed sarcopenia was 11 times more frequent in patients with RA than in controls (4.5% vs 0.4%, p=0.001). Severe sarcopenia did not occur in either group.

Applying the FNIH definition, the prevalence of sarcopenia based on weakness with a low ALM/BMI was observed in 2.8% of the patients with no significant difference to the control group (**table 3**).

Subjects with RA and confirmed sarcopenia according to the EWGSOP2 definition showed a significant lower body weight (p<0.02), lower BMI (p<0.0001), longer disease duration (p=0.002), current glucocorticoid medication (p<0.02), higher cumulative dose prednisone equivalent (p=0.0003), a higher HAQ score (p<0.001) and a lower physical activity

Table 3 Comparison of sarcopenia parameter in RA and controls

Variable	RA n=289	Controls n=280	P value
ALM (kg), mean±SD	19.1±4.0	21.1±4.0	<0.0001
ALM/ht ² (kg/m ²), mean±SD	6.8±1.0	7.3±1.2	<0.0001
ALM/BMI (kg/BMI), mean±SD	0.72±0.14	0.80±0.18	<0.0001
Grip strength (kg), mean±SD	23.9±9.0	32.8±9.5	<0.0001
Chair rise time (s), mean±SD	9.6±3.4	8.5±6.0	<0.0001
Gait speed (m/s), mean±SD	1.23±0.21	–	
Sarcopenia EWGSOP2			
Low grip strength, n (%)	59 (20.4)	6 (2.1)	<0.0001
Prolonged chair rise time, n (%)	21 (7.3)	10 (3.6)	0.05
Slow gait speed, n (%)	13 (4.5)	6 (2.1)	0.12
Low muscle mass ALMI/ht ² , n (%)	36 (12.5)	20 (7.1)	0.03
Probable sarcopenia*, n (%)	71 (24.6)	15 (5.4)	<0.0001
Confirmed sarcopenia, n (%)	13 (4.5)	1 (0.4)	0.001
Severe sarcopenia, n (%)	0	0	–
Sarcopenia FNIH			
Weakness, n (%)	59 (20.4)	6 (2.1)	<0.0001
Low muscle mass ALM/BMI, n (%)	18 (6)	22 (7.9)	0.45
Weakness and low ALM/BMI, n (%)	8 (2.8)	2 (0.7)	0.11

p<0.05 significant. Data on gait speed in controls are only available as a dichotomous variable.

bold values: significant

*Low grip strength and/ or prolonged chair rise time.

ALM, appendicular lean mass; BMI, body mass index; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; RA, rheumatoid arthritis.

(p=0.04) compared with patients without sarcopenia (table 4). No significant group differences were found for age, sex, body height, disease activity, medication on disease-modifying drugs, disease related fatigue, self-reported balance confidence and lifestyle factors. Applying the FNIH definition, those patients with RA and sarcopenia were significantly shorter (1.6±0.1 vs 1.7±0.1, p=0.005), and they presented with a higher BMI (30.5±4.9 vs 26.9±4.4, p=0.02) and a higher percentage of fat mass (44.2±9.5 vs 38.6±7.3, p=0.04) (table 4).

Only two subjects (both males) were equally identified as sarcopenic in both definitions (table 5). Participants with sarcopenia using the EWGSOP2 definition tended to have a lower body weight and a lower BMI (figure 1C,E, table 5). Those classified as sarcopenic using the FNIH criteria were short persons and presented with a higher weight, BMI and fat mass (figure 1B,F,G, table 5). A positive linear association was found between ALM/ht² and body weight (figure 1C, r=0.79) and BMI (figure 1E, r=0.63), suggesting that subjects with a low body weight or low BMI are more likely to be classified with low ALM/ht² as was observed using the EWGSOP2 definition. In contrast, a positive linear association was found between ALM/BMI and body height (r=0.85), indicating that shorter individuals are more likely to be classified with low ALM/BMI than taller individuals, as was observed when applying the

FNIH definition (figure 1B, table 5). In addition, those identified with low ALM/BMI presented with a higher body weight (r=0.27), higher percentage of fat mass (r=–0.75) and a higher BMI (r=–0.26) (figure 1D,F,H and table 5).

With regard to logistic regression analysis, confirmed sarcopenia based on EWGSOP2 definition was associated with lower body weight (OR 0.92, 95% CI 0.86 to 0.97), lower BMI (OR 0.70, 95% CI 0.57 to 0.87), higher CRP level (OR 1.05, 95% CI 1.01 to 1.10), longer disease duration (OR 1.08, 95% CI 1.02 to 1.36), current medication with glucocorticoids (OR 5.25, 95% CI 2.14 to 24.18), a higher cumulative dose of prednisone equivalent (OR 1.04, 95% CI 1.02 to 1.05) and a higher HAQ score (OR 2.50, 95% CI 1.27 to 4.86), independent of age and sex (table 6).

In contrast, sarcopenia based on FNIH definition was associated with a smaller body height (OR 0.75, 95% CI 0.64 to 0.88), higher BMI (OR 1.20, 95% CI 1.02 to 1.41), higher percentage fat mass (OR 1.21, 95% CI 1.07 to 1.38), higher CRP level (OR 1.06, 95% CI 1.01 to 1.11) and a higher HAQ score (OR 2.77, 95% CI 1.17 to 6.59), independent of age and sex (table 6).

A logistic regression analysis revealed that RA was associated with higher ORs in both definitions, independent of sex and age (EWGSOP2 (OR 17.4, 95% CI 2.2 to 138.5); FNIH (OR 7.3, 95% CI 1.4 to 37.7)) when compared with controls (data not shown).

Table 4 Comparison between RA subjects with and without confirmed sarcopenia

Variable	n	Sarcopenia EWGSOP2			Sarcopenia FNIH		
		Yes n=13	No n=276	P value	Yes n=8	No n=281	P value
Age (years), mean±SD	289	62±8.0	59±11.4	0.35	66±8.4	59±11.3	0.12
Sex, n (%)	289			0.26			0.21
Female		9 (69.2)	221 (80.1)		5 (62.5)	225 (80.7)	
Male		4 (30.8)	55 (19.9)		3 (37.5)	56 (20.0)	
Height (m), mean±SD	289	1.7±0.1	1.7±0.1	0.13	1.6±0.1	1.7±0.1	0.005
Weight (kg), mean±SD	289	66.5±8.7	75.3±13.9	0.02	77.4±16.2	74.8±13.8	0.61
BMI (kg/m ²), mean±SD	289	23.0±2.6	27.1±4.5	<0.0001	30.5±4.9	26.9±4.4	0.02
Fat mass (%), mean±SD	289	38.3±6.7	38.8±7.5	0.79	44.2±9.5	38.6±7.3	0.04
DAS28 _{CRP} median (IQR)	285	2.8 (1.1)	2.1 (1.3)	0.12	2.7 (1.1)	2.1 (1.3)	0.08
CRP (mg/L), median (IQR)	274	3.3 (6.9)	2.2 (3.2)	0.24	3.3 (8.3)	2.2 (3.4)	0.41
Disease duration (years), median (IQR)	289	22 (10)	9 (12)	0.002	15.5 (14)	9 (13)	0.19
bDMARDs, n (%)	280	9 (69.2)	121 (45.3)	0.09	6 (75.0)	124 (45.6)	0.15
cDMARDs, n (%)	280	9 (69.2)	181 (67.8)	1.0	5 (62.5)	185 (68.0)	0.71
Glucocorticoids current, n (%)	280	11 (84.6)	136 (50.9)	0.02	7 (87.5)	140 (51.5)	0.07
Cumulative prednisone dose (g), median (IQR)	275	36.9 (63.6)	9.6 (20.4)	0.0003	29.4 (48.2)	9.9 (20.6)	0.06
Current smoking, n (%)	288	3 (23.1)	56 (20.4)	0.52	1 (12.5)	58 (20.7)	1.0
Regular alcohol consumption, n (%)	289	0	2 (0.7)	1.0	0	2 (0.7)	1.0
≥1 × sports/ week, n (%)	285	7 (53.9)	194 (70.0)	0.23	3 (37.5)	194 (70.0)	0.11
Sunlight exposure, n (%)	289			0.46			0.49
<30 min/ day		8 (61.5)	141 (51.1)		3 (37.5)	146 (52.0)	
≥30 min/ day		5 (38.5)	135 (48.9)		5 (62.5)	135 (48.0)	
Nutrition, n (%)	286			1.0			1.0
vegetarian/vegan diet		1 (7.7)	27 (9.9)		0	28 (10.1)	
mixed diet		12 (92.3)	246 (90.1)		8 (100)	250 (89.9)	
HAQ (0–3), median (IQR)	289	1.5 (1.3)	0.5 (1.2)	0.01	1.6 (2.0)	0.5 (1.3)	0.14
BRAF-NRS Fatigue (0–10), mean±SD	289	4.4±2.9	4.4±2.4	0.98	4.6±3.2	4.4±2.4	0.79
ABC-scale (0–100), median (IQR)	289	88.2 (36.3)	90.5 (22.2)	0.07	70.0 (43.5)	90.0 (22.5)	0.21
IPAQ total MET(min/week), median (IQR)	289	1470 (2670)	4246 (4884)	0.04	3432 (2486)	4158 (4974)	0.35

Bold values: p<0.05 significant.

ABC-scale, Activities-specific Balance Confidence Scale; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; BRAF-NRS, Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale; CRP, C reactive protein; DAS28_{CRP}, Disease Activity Score of 28 joints including C reactive protein; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; HAQ, Health Assessment Questionnaire; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; MTX, Methotrexate; RA, rheumatoid arthritis.

DISCUSSION

This study was aimed at defining the prevalence of sarcopenia using the revised definition determined by the European Working Group of Sarcopenia in Older People²⁰ and the FNIH definition²¹ in patients with RA compared with controls without inflammatory disease. To the best of the authors' knowledge, this study is the first to compare both definitions between patients with RA and healthy controls.

Sarcopenia in RA is a common manifestation and occurs significantly more frequently than in healthy controls.^{8,32} According to the updated EWGSOP2 guideline, we found a prevalence of a confirmed sarcopenia in

4.5% of patients with RA and 0.4% of controls without a difference in sex. This means the prevalence of sarcopenia was 11 times higher in patients with RA compared with the control group.

In recent years, various studies on sarcopenia in RA have been published, yet the prevalence of sarcopenia varied considerably between 8% and 89%, depending on the underlying sarcopenia definition, measurement method and the population.^{6,7,9–11,33–40} Most of the studies reported a higher prevalence than this study, and often no healthy control group was included. The few studies with controls consistently reported a higher prevalence for patients with RA than for controls,^{6,41,42} but the ratio

Table 5 Overlap definitions according to baseline characteristics in patients with RA and confirmed sarcopenia

Variable	EWGSOP2 n=11	FNIH n=6	Both n=2
Males, n	2	1	2
Age (years), median (IQR)	63 (11)	68 (12)	60 (14)
Weight (kg), median (IQR)	63 (5)	73 (22)	79 (2)
Height (m), median (IQR)	1.72 (0.10)	1.54 (0.15)	1.70 (0.10)
BMI (kg/m ²), median (IQR)	21.9 (2.7)	31.1 (2.7)	27.4 (3.9)
Fat mass (%), median (IQR)	38.4 (11.6)	48.1 (14.6)	36.5 (7.0)
DAS28 _{CRP} median (IQR)	2.6 (1.3)	2.5 (0.7)	3.3 (1.1)
HAQ (0–3), median (IQR)	1.5 (1.3)	1.6 (1.8)	1.1 (2.3)

BMI, body mass index; CRP, C reactive protein; DAS28_{CRP} Disease Activity Score of 28 joints including C reactive protein; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis.

was dependent on the underlying definition and different threshold values.

Due to the varying approaches to define low ALM using the DXA method, a considerable inconsistency can be found among the results.^{6 7 11 34–37 40 43 44} In addition, several Asian studies use thresholds from Asian reference data,^{9 34 38 42} which limits direct comparisons of results.

In this study, 13% of the patients with RA showed a low ALM/ht² according to the cut-off values suggested by the EWGSOP2,^{2 20} which is considerably less compared with other published data. Ngeuleu *et al*⁷ reported a higher prevalence with 38.8%, using the same ALM/ht² threshold in females. However, their patients displayed a higher disease activity (CRP mean 22±28 mg/L) than this study cohort. A second study⁶ used a higher threshold value of 5.75 kg/m² for women and found a higher prevalence of 43.3% for reduced ALM/ht² in RA. Again, CRP values were more elevated (mean 8.9±12.3 mg/L) than in this study population. Giles *et al*¹¹ described a prevalence for reduced muscle mass of 26% at a threshold of 5.75 kg/m² for women and 8.5 kg/m² for men. In this case, disease activity was comparatively low with a mean CRP of 2.8 mg/L (IQR 1.13–7.69).

According to the FNIH definition, eight subjects with RA and two subjects in the control group were affected by sarcopenia (2.8% vs 0.7%). A New Zealand study³⁷ which applied the FNIH definition without grip strength, the prevalence of reduced ALM/BMI in RA was considerably higher (17.1%) than in our study (6%). Study participants also exhibited higher inflammatory activity

(CRP 8.8±13.3 mg/L), which might explain the higher prevalence.³⁷

The results suggest that the CRP level, that is, the activity of inflammation, has an influence on the development of sarcopenia. As in this study, the mean CRP value (2.2±3.5 mg/L) and the disease activity (2.1±1.3) were comparatively low; the low prevalence rate is not unexpected. This finding is supported by a recent meta-analysis which concluded that high CRP and RF seropositivity, thus RA activity, has a strong influence on muscle loss in patients with RA regardless of age.¹⁰ These results match those observed in populations with 'primary sarcopenia'. Bano *et al* concluded that sarcopenic subjects show particularly increased CRP levels leading to muscle wasting in the context of an imbalance between protein synthesis and catabolism (muscle proteolysis, myocyte apoptosis).⁴⁵ Effective inflammation management can counteract the catabolic effect and reduce muscle breakdown.⁴⁶

The above-mentioned studies defined sarcopenia exclusively according to reduced muscle mass and neglected muscle function. If sarcopenia was defined as reduced muscle mass in combination with low handgrip strength,³³ a prevalence of sarcopenia of 20.8% in RA was reported. In a Japanese study using the BIA method, a prevalence for reduced ALM/ht² of 30% was found.³⁸ If low handgrip strength and reduced walking speed were added to the definition of sarcopenia, the prevalence decreased to 13%. In contrast, a systematic review and meta-regression analysis by Li *et al*¹⁰ estimated a pooled prevalence of 30.6% by solely evaluating low muscle mass of 14 enrolled studies. The estimated pooled prevalence increased to 31.1% by evaluating both muscle mass and muscle strength.¹⁰

Using the EWGSOP2 definition, a proportion of subjects with reduced muscle strength five times higher was found in RA compared with controls (25% vs 5%), while with regard to reduced muscle mass (ALM/ht²), the difference between patients with RA and control was less pronounced (13% vs 7%). These results support the idea that muscle strength is reduced to a greater extent than muscle mass in patients with RA compared with healthy controls. However, adding muscle mass to muscle strength for confirming a probable sarcopenia results once again in a prevalence of sarcopenia roughly five times higher in patients with RA compared with controls. Hence, subjects with RA with low muscle strength (probable sarcopenia) tend to have an additionally reduced muscle mass (confirmed sarcopenia) than healthy controls with low muscle strength. The reduced muscle mass cannot account alone for the muscle weakness leading to a higher prevalence of sarcopenia by including muscle function in patients with RA.⁴⁷ Specifically, handgrip strength was found to be significantly weaker in RA than controls. This difference was not as evident when testing leg strength using the CRT. The question arises whether this muscle function in the hands thrice worse is caused by muscle atrophy or, that is, by pain or

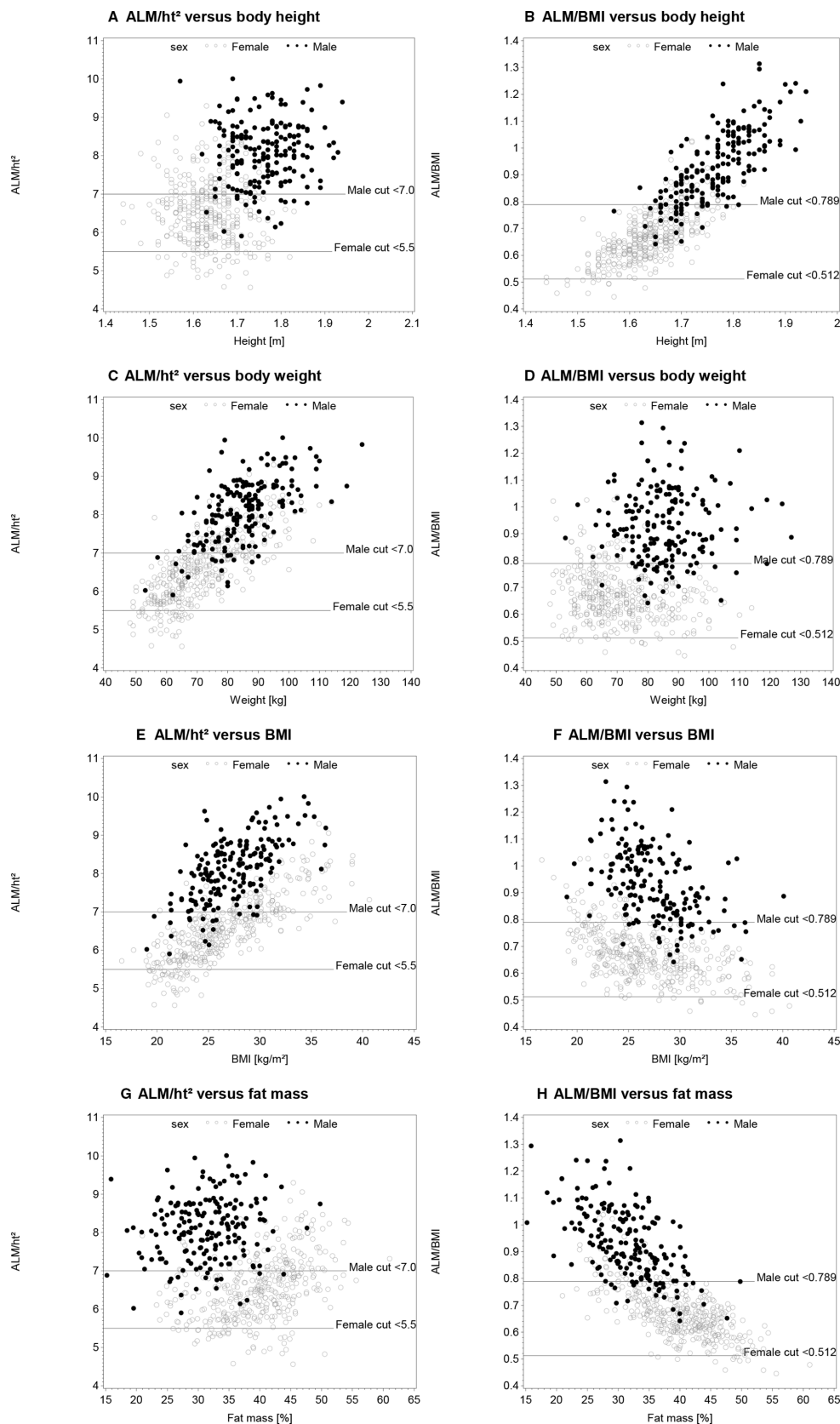


Figure 1 (A–H): Association between ALM/ht² (EWGSOP2), respectively, ALM/BMI (FNIH) and anthropometrics in RA and controls: (A) ALM/ht² vs height ($r=0.44^{***}$), (B) ALM/BMI vs height ($r=0.85^{***}$), (C) ALM/ht² vs weight ($r=0.79^{***}$), (D) ALM/BMI vs weight ($r=0.27^{***}$), (E) ALM/ht² vs BMI ($r=0.63^{***}$), (F) ALM/BMI vs BMI ($r=-0.26^{***}$), (G) ALM/ht² vs fat mass ($r=-0.13^{*}$), (H) ALM/BMI vs fat mass ($r=-0.75^{***}$). * $p<0.05$, *** $p<0.0001$. ALM, appendicular lean mass; BMI, body mass index; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; RA, rheumatoid arthritis.

Table 6 Association between RA disease characteristics and sarcopenia

	EWGSOP2				FNIH			
	Crude ORs (95% CI)	P value	Adjusted* ORs (95% CI)	P value	Crude ORs (95% CI)	P value	Adjusted* ORs (95% CI)	P value
Sex								
Male	ref.		–	–	ref.		–	–
Female	0.56 (0.17 to 1.89)	0.35	–	–	0.42 (0.10 to 1.79)	0.34	–	–
Age (years)	1.03 (0.97 to 1.08)	0.36	–	–	1.10 (1.00 to 1.14)	0.12	–	–
Height (cm)	1.05 (0.99 to 1.13)	0.13	1.08 (0.98 to 1.19)	0.14	0.87 (0.78 to 0.96)	0.006	0.75 (0.64 to 0.88)	0.0003
Weight (kg)	0.95 (0.90 to 0.99)	0.03	0.92 (0.86 to 0.97)	0.006	1.01 (0.96 to 1.01)	0.61	1.01 (0.95 to 1.07)	0.82
BMI (kg/m ²)	0.74 (0.62 to 0.90)	0.002	0.70 (0.57 to 0.87)	0.001	1.18 (1.02 to 1.36)	0.03	1.20 (1.02 to 1.41)	0.03
Fat mass (%)	0.99 (0.92 to 1.10)	0.80	1.00 (0.92 to 1.10)	0.92	1.12 (1.01 to 1.25)	0.04	1.21 (1.07 to 1.38)	0.004
DAS28 _{CRP}	1.34 (0.82 to 2.19)	0.25	1.38 (0.85 to 2.24)	0.19	1.56 (0.87 to 2.79)	0.14	1.63 (0.93 to 2.85)	0.09
CRP(mg/L)	1.06 (1.02 to 1.10)	0.008	1.05 (1.01 to 1.10)	0.02	1.10 (1.01 to 1.11)	0.02	1.06 (1.01 to 1.11)	0.03
Disease duration (years)	1.07 (1.02 to 1.12)	0.005	1.08 (1.02 to 1.36)	0.006	1.05 (0.98 to 1.11)	0.17	1.04 (0.97 to 1.11)	0.25
CG current								
No	ref.		ref.		ref.		ref.	
Yes	5.3 (1.15 to 24.4)	0.03	5.25 (2.14 to 24.18)	0.03	6.6 (0.80 to 54.37)	0.08	6.5 (0.78 to 53.56)	0.08
bDMARDs current								
No	ref.		ref.		ref.		ref.	
Yes	2.72 (0.82 to 9.0)	0.10	2.80 (0.84 to 9.40)	0.10	3.6 (0.71 to 18.1)	0.12	3.87 (0.75 to 19.95)	0.11
Cumulative dose prednisone equivalent (g)	1.04 (1.02 to 1.05)	<0.0001	1.04 (1.02 to 1.05)	<0.0001	1.02 (1.00 to 1.04)	0.04	1.02 (1.00 to 1.04)	0.05
≥1 × sports/ week								
No	ref.		ref.		ref.		ref.	
Yes	0.5 (0.16 to 1.54)	0.23	0.51 (0.17 to 1.60)	0.25	0.26 (0.06 to 1.10)	0.07	0.26 (0.06 to 1.13)	0.07
HAQ (score 0–3)	2.20 (1.17 to 4.10)	0.02	2.50 (1.27 to 4.86)	0.008	2.31 (1.10 to 5.04)	0.04	2.77 (1.17 to 6.59)	0.02
ABC-scale (0–100)	0.98 (0.96 to 1.00)	0.11	0.98 (0.96 to 1.00)	0.11	0.97 (0.95 to 1.00)	0.09	0.98 (0.95 to 1.00)	0.10
IPAQ (total METs)	1.00 (1.00 to 1.00)	0.26	1.00 (1.00 to 1.00)	0.27	1.00 (1.00 to 1.00)	0.26	1.00 (1.00 to 1.00)	0.30

Bold values: p<0.05 significant.

*Analyses adjusted for age and sex.

ABC-scale, Activity-specific Balance Confidence Scale; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CG, glucocorticoids current; CRP, C reactive protein; DAS28_{CRP}, Disease Activity Score of 28 joints including C reactive protein; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; HAQ, Health Assessment Questionnaire; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; RA, rheumatoid arthritis.

osteodestructive joint lesions in patients with erosive RA. Therefore, future studies should assess pain intensity by joint using the Visual Analogue Scale and the presence of erosive joint lesions in addition to disease activity.

The current overlap analysis of the two sarcopenia definitions with different adjustments for ALM demonstrated that using ALM/ ht^2 (EWGSOP2) resulted in the identification of taller subjects assumed to be sarcopenic with a significantly lower average body weight ($p=0.02$) and thus a lower BMI ($p<0.0001$). Adjusting ALM for BMI, identified subjects were shorter with higher weight and BMI. A comparison of patients with RA with and without sarcopenia showed no significant differences in age and sex that could account for these differences. Furthermore, comparing patients with RA and controls, the adjustment for squared height showed a higher prevalence of sarcopenia in RA than adjusting for BMI (12.5% vs 6%), whereby the result remained comparatively stable in the control group (7.1% vs 7.9%). These results are largely consistent with previously published data,^{6 7 37} in which a significantly lower BMI was also found in patients with RA with sarcopenia. Yet, sarcopenia was defined exclusively by ALM/ ht^2 in all three studies. German data from the Base-II study, in which both operationalisations were applied, showed that the adjustment to BMI leads to lower prevalence data in the general population over 60 years than the adjustment to the squared body size (ALM/BMI 15.8% vs ALM/ ht^2 25.5%).⁴⁸ This also accords with a meta-analysis by Mayhew *et al*, who identified a higher estimated sarcopenia prevalence for ALM/ ht^2 of 30.4% than for ALM/BMI with 24.2% in community-dwelling older adults.⁴⁹ With muscle mass being the largest proportion of the total body weight, at least in the normal BMI range, this finding is not surprising; otherwise it would be an overadjustment using BMI in a study population with a general manifestation of higher fat mass (sarcopenic obesity) and predominantly lower lean mass.⁴¹ Consequently, the assumption arises that the adjustment with squared height is the more suitable approach for assessing sarcopenia in subjects with lower weight and higher disease activity, thus in patients with RA. The FNIH definition is more likely to reveal sarcopenia in individuals with high BMI and fat mass, regardless of the presence of RA. In addition, individuals identified as sarcopenic by FNIH definition were shorter, which obviously results in lower muscle mass by using indices based on adjustments with body size. Therefore, further research is needed to accurately determine muscle mass independent of body size parameters.⁵⁰

Furthermore, this study discovered associations between sarcopenia and a worse score in the HAQ, longer disease duration, a current glucocorticoid medication and a higher cumulative dose of prednisone equivalent. As higher disease activity has already been discussed as a major influence on sarcopenia, this result is not surprising and is confirmed by several studies.^{9 10 33 36 39 41} All in all, it is possible that these risk factors could predict the development of sarcopenia and should be investigated by further

longitudinal studies. The association of sarcopenia with HAQ for both definitions could be a causal relationship in which low muscle mass and function leads to increased disability measured by the HAQ or vice versa. This would be of significant clinical importance, given that interventions such as physical activity and protein rich nutrition which are recommended to treat sarcopenia could then help reduce disability in patients with RA.

There are some limitations in this study. We used both the EWGSOP2 and FNIH criteria, which are validated for older populations and not for the evaluation of 'secondary sarcopenia' in RA. The comparison to a control group without inflammatory disease applying the same criteria showed that subjects with RA are more affected by sarcopenia, low lean mass and poor muscle function. However, with the present data, it was not possible to determine whether joint pain or joint destruction caused by RA influenced grip strength measurement. Therefore, the assessments might be influenced by factors not immediately related to muscle function. However, this does not exclude these patients from having sarcopenia or a higher risk of developing sarcopenia. Therefore, the influence of pain and erosive lesions in particular should be investigated in future studies.

The cross-sectional design of the study does not allow the determination of a causal relationship between sarcopenia and the contributing factors. For example, as mentioned above, it is not clear whether a higher HAQ value in the sarcopenia group is the cause or the result of sarcopenia. Prospective studies are necessary to determine risk factors and optimal cut-off values for muscle mass and muscle function with regard to a clinically relevant outcome.

The median CRP of 2.2 mg/L in the RA sample was much lower than other studies found this to be the case. Hence, selection bias towards subjects with RA and low to moderate disease activity might have influenced the results, leading to an underestimation of the prevalence of sarcopenia. On the other hand, a low CRP reflects appropriate modern and effective therapy management by rheumatologists. In addition, patients with sarcopenia in the RA group were significantly younger than in the control group (59 ± 11 years vs 63 ± 12 years) with a wide range of ages, which might have caused a bias in the occurrence of sarcopenia. However, in this study as well as in other publications,¹⁰ the duration of disease activity was found to explain the occurrence of sarcopenia in patients with RA to a greater extent than age.

The inclusion of a healthy control group added strength to the study. However, the control group could not be matched for age and sex due to the lack of data of a sufficiently large healthy cohort. As subjects with RA and controls differ concerning age and sex, a logistic regression analysis adjusting for these factors was performed. RA was associated with higher ORs in both definitions, independent from sex and age. However, due to the low prevalence of sarcopenia the ORs are imprecise with large CIs.

In conclusion, this study confirmed that patients with RA more commonly had sarcopenia than healthy controls using the current EWGSOP2 definition. The results of this study suggest that the prevalence of sarcopenia in patients with RA depends not only on the underlying sarcopenia definition but also, most notably, on the activity of the rheumatic disease. The prevalence of sarcopenia is significantly higher in populations with higher CRP levels. However, the influence of pain and erosive joint lesions on grip strength measurements should be explored by future research. In addition, a current glucocorticoid medication, a higher cumulative dose of prednisone equivalent and a worse HAQ score are associated with sarcopenia in patients with RA. The association with HAQ alludes to the suggestion that sarcopenia may lead to more disability, which needs to be investigated in future studies. This research is a first step towards a deeper understanding of defining low muscle mass by using different muscle mass indices. The two definitions were found to respond differently to the anthropometric characteristics of the cohort, resulting in different rates of prevalence. This shows the importance of a common definition of sarcopenia and the need for reliable methods to determine low muscle mass and the inclusion of muscle function.

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