Osteoporosis International (2019) 30:541–553
https://doi.org/10.1007/s00198-018-04828-0

REVIEW ARTICLE

The relationship between sarcopenia and fragility fracture—a systematic review

R. M. Y. Wong[1] · H. Wong[1] · N. Zhang[1] · S. K. H. Chow[1,2] · W. W. Chau[1] · J. Wang[1] · Y. N. Chim[1] · K. S. Leung[1] · W. H. Cheung[1,2]

Received: 11 June 2018 / Accepted: 21 December 2018 / Published online: 4 January 2019

Summary

Sarcopenia is a common geriatric syndrome characterized by progressive decrease of muscle mass and function leading to an increased risk of physical disability, poor quality of life, and mortality. Increasing evidence shows that sarcopenia is related with fragility fractures. This systematic review aimed to summarize the following: (1) the prevalence of sarcopenia in patients with fragility fracture and (2) the associated risk factors for fragility fracture in patients with sarcopenia. Literature search was conducted in PubMed and Cochrane databases. Studies with the prevalence of sarcopenia in elderly patients with fragility fracture and associated risk factors in patients with sarcopenia were included. A total of 15 papers were included, with 10 reporting sarcopenia prevalence, and 5 on fracture risk in patients with sarcopenia. The prevalence of sarcopenia after fracture ranged from 12.4 to 95% in males and 18.3 to 64% in females. The prevalence of sarcopenia in elderly patients with fragility fracture was high, especially in men. Two studies showed that sarcopenia was a risk factor for fragility fracture when associated with low bone mineral density (BMD) but only in men. Caution should be taken for male patients with sarcopenia and low BMD, which is related to significantly increased risk of fractures. There is a pressing need for further research on sarcopenia and its risk on fragility fracture to better understand the relationship, pathophysiology, and mechanisms, which may shed light on potential interventions to improve clinical outcomes.

Keywords Fracture risk · Fragility fracture · Prevalence · Sarcopenia · Systematic review

Introduction

Sarcopenia is a common geriatric syndrome. In normal aging, muscle mass usually decreases at a rate of 1% annually after the age of 40 years [1]. The disease is characterized by progressive loss of lean body mass and function leading to an increased risk of physical disability, poor quality of life, and mortality [2]. The prevalence of sarcopenia among community-dwelling people ranges from 1 to 29% [3]. The disease is also one of the indicators of frailty in the elderly [4].

Several definitions of sarcopenia have emerged in recent years. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) developed a clinical definition of sarcopenia [2]. The EWGSOP recommends using the presence of both low muscle mass and function (strength or performance) for the diagnosis of sarcopenia [2]. In 2011, the International Working Group on Sarcopenia (IWGS) emphasized assessment of physical function including the ability to rise from chair or gait speed to be included in targeting sarcopenia [5]. In 2014, the Asian Working Group for Sarcopenia (AWGS) and the Foundation for the National Institutes of Health (FNIH) of the USA also established the consensus for sarcopenia diagnosis for their respective regions [6, 7]. Table 1 summarizes the definition of sarcopenia recommended by the above working groups. However, due to several definitions, the same population adopting different definitions recommended by the EWGSOP, IWGS, AWGS, and

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-018-04828-0) contains supplementary material, which is available to authorized users.

✉ W. H. Cheung
louis@ort.cuhk.edu.hk

[1] Department of Orthopaedics and Traumatology, 5/F, Clinical Sciences Building, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, SAR, China

[2] The CUHK-ACC Space Medicine Centre on Health Maintenance of Musculoskeletal System, The Chinese University of Hong Kong Shenzhen Research Institute, Shenzhen, People's Republic of China

Table 1 Different definitions of sarcopenia and prevalence of sarcopenia in Hong Kong

Definition	Muscle mass	Muscle strength	Physical performance
EWGSOP	ASM/height^2	Grip strength	**OR**
	< 6.52 kg/m^2 for men	≤ 30 kg for men	Gait speed
	< 5.44 kg/m^2 for women	≤ 20 kg for women	< 0.8 m/s
IWGS	ASM/height^2		Gait speed
	≤ 7.23 kg/m^2 for men ≤ 5.67 kg/m^2 for women		< 1 m/s
AWGS	ASM/height^2	Grip strength	**AND**
	< 7.0 kg/m^2 in men	< 26 kg for men	Gait speed
	< 5.4 kg/m^2 in women.	< 18 kg for women	< 0.8 m/s
FNIH	Definition 1: low ASM/BMI and low grip strength		
	Definition 2: definition 1 + slow gait speed		
	ASM/BMI	Grip strength	Gait speed
	< 0.789 for men <0.512 for women.	< 26 kg for men < 16 kg for women	< 0.8 m/s

FNIH leads to the prevalence of sarcopenia ranging from 2.6%–22.1% in men to 1.3%–18.25% in women as shown in a study conducted in Hong Kong [8].

Recent evidence showed that sarcopenia was associated with low bone mineral density (BMD) and osteoporosis in elderly men [9, 10]. In postmenopausal women, low lean body mass was associated negatively with femoral neck BMD [11] and structural parameters of bone [12].m

Elderly people with sarcopenia are three times more likely to fall [13]. Increasing evidence showed that sarcopenia is closely related to fragility fracture [14–16]. Most importantly, high prevalence of sarcopenia in patients with fragility fractures has been reported recently, which is alarming to clinicians. However, there is currently still few clinical data demonstrating a causal relationship between osteoporosis and sarcopenia. There is a pressing need to understand more on this relationship. The objective of this systematic review and meta-analysis is to summarize the prevalence of sarcopenia in patients with fragility fracture in different countries and risk factors of fragility fracture with sarcopenia.

Methods

Search strategy

Literature search was carried out on PubMed and Cochrane databases. The keywords, "sarcopeni*" AND "fracture*," were used to search in all fields. Last access to both databases was on Nov. 2, 2018. PRISMA guidelines was used.

Search criteria

Inclusion criteria were as follows: (1) clinical studies that investigate the relationship (prevalence or risk) between sarcopenia and fragility fracture; (2) full-text literature published in English. Exclusion criteria were as follows: (1) non-English papers; (2) not fragility fracture-related; (3) young subjects included; (4) review papers or conference abstracts.

Selection of studies

Two reviewers conducted study selection independently. Duplicates were removed. Irrelevant papers were screened out through the title and abstract by inclusion and exclusion criteria. Full text of potential relevant papers was then retrieved and further assessed for the eligibility. Disagreements were settled by discussion and consensus.

Data extraction

For the studies investigating sarcopenia prevalence, the following data were extracted and presented in tables: (1) study design and sample size; (2) mean age and gender; (3) fracture site; (4) definition of sarcopenia; (5) interval between time of fracture and measurement; (6) prevalence of sarcopenia.

For the studies that investigated risk of fracture in people with sarcopenia, the following data were extracted: (1) sample size; (2) mean age and gender; (3) definition of sarcopenia; (4) follow-up period; (5) fracture risk in term of hazard or odd ratio.

Assessment of quality of selected studies

Two authors independently performed quality assessment of the included studies. Disagreements were resolved by discussion. The methodological quality was assessed using the Newcastle-Ottawa Scale, which has been proven to be valid for nonrandomized studies [32]. The form assigns a maximum

of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome.

Data analysis

All the studies included in this review were clinical studies but there was variability in terms of methodology. Qualitative analysis was performed for studies on prevalence of sarcopenia after fracture, due to the heterogeneity. Subgroup meta-analysis on sarcopenia in patients with history of fragility fracture was performed by computing hazard ratios (HRs) using fixed-effects model. Quantitative analyses were performed on time-to-event basis and were confined to data derived from the period of follow-up. HRs and 95% confidence intervals of fracture were calculated. CMA software version 3.3 was used for all analyses and production of plots. The inverse variance method was used to weight the study effect size.

Results

Results of the search

In the search, 354 and 33 papers were identified in PubMed and Cochrane databases respectively. Three hundred sixty-six papers were excluded based on the selection criteria after screening the titles and abstracts. The full texts of the 21 papers selected were retrieved for further assessment of eligibility. After screening the full text in detail, 2 duplicated papers and 4 papers with duplicated population were excluded. Therefore, 15 papers were finally recruited for analysis in this review. Figure 1 shows the selection process of the included papers.

Quality of selected studies

Tables 2, 3, and 4 summarize the quality of the 15 studies using the Newcastle-Ottawa Quality Scale. All studies were of high quality and suitable for qualitative or quantitative analysis.

Prevalence of sarcopenia

Fracture sites

A total of 10 included papers reported the prevalence of sarcopenia in patients with fragility fracture. The prevalence of sarcopenia after fracture ranged from 12.4%–95% in males to 18.3%–67.7% in females. Eight of the 10 papers estimated the prevalence of sarcopenia after hip fracture (17.1%–95%) [17, 19, 20, 22–26]. The remaining 2 papers estimated the prevalence of sarcopenia after distal radius fracture (30%) [18] and vertebral fracture (42.3%) [21]. Table 5 summarizes the details and the prevalence in the 10 studies.

Definitions of sarcopenia

With the new consensus on the definition of sarcopenia, an increasing number of papers have used the criteria recommended by the working groups to define sarcopenia. Most of the 10 included papers related to sarcopenia prevalence used recommended definitions of sarcopenia except 1 in 2009 [26], 2 in 2012, and 2 in 2013 [24, 25].

In hip fracture studies (8 out of 10 studies), 5 using the recommended definition of sarcopenia had prevalence ranging from 12.4%–73.6% in males to 18.3%–67.7% in females after the fracture [17, 19, 20, 22, 23]. The remaining 3 papers did not use the recommended definitions but instead used Skeletal Muscle Index (SMI) or Appendicular Lean Mass

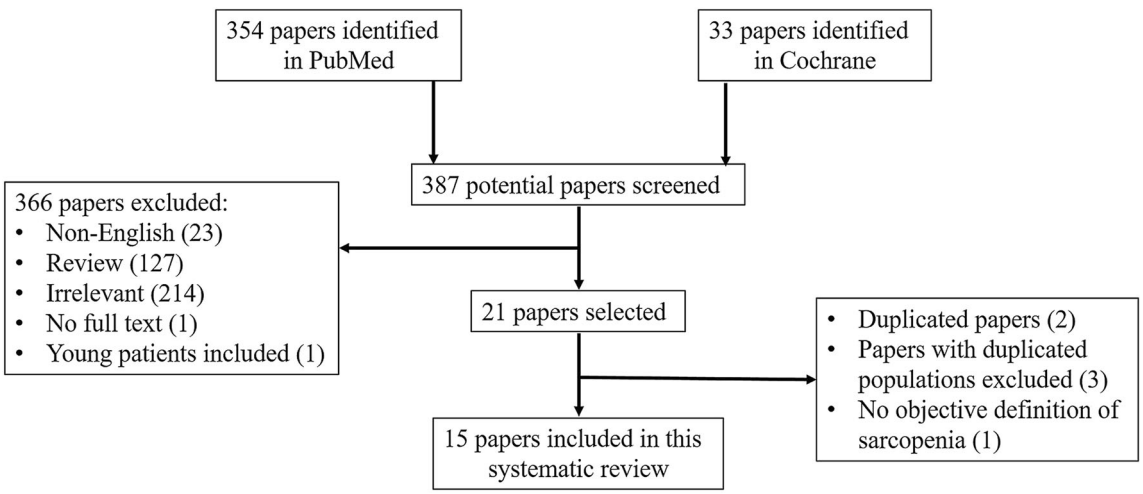

Fig. 1 Papers recruited for analysis

Table 2 Study quality assessment using Newcastle-Ottawa Scale for case-control studies

	Selection				Comparability	Exposure			Total score
Case-control studies	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Yoo et al. 2016, South Korea [23]	Based on AWGS criteria*	Consecutive recruitment of cases*	From the Korean National Health and Nutrition Survey recruits*	No fracture*	Patients age and sex matched**	Not blinded	Yes*	Same rate for both groups*	8

The asterisk represents the 'star or point' awarded for the quality of the study in each category. A maximum of 4 points from 'selection', 2 'points' for comparibility and 3 'points' for exposure or outcome. Please refer to our methodology: assessment of quality of selected studies

(ALM) [24–26]. Two had a prevalence of 81.8%–95% in males and 44.7%–64% in females, after hip fracture [24, 25], while the remaining 1 paper had an overall prevalence of 58% for both sexes [26].

Out of the 5 papers using recommended definitions for hip fracture, 2 used the EWGSOP criteria to define sarcopenia in hip fracture patients. The prevalence of sarcopenia was 58.0% and 12.4% in males; 34.9% and 18.3% in females for these 2 papers [19, 20]. Meanwhile, 2 used AWGS criteria to define sarcopenia in hip fracture patients. The prevalence of sarcopenia in hip fracture patients was 73.6% and 68.2% in males; 67.7% and 44.3% in females [22, 23]. Only 1 study used FNIH recommendation, which reported the prevalence of sarcopenia at 72% in males and 28% in females [17].

Time of measurement

For hip fracture studies, the prevalence of sarcopenia was higher if the measurement was taken post-operatively. Using the EWGSOP criteria, the study by Steihaug et al. [19] with measurements after hip surgery had a higher prevalence of sarcopenia (females 34.9%; males 58.0%) compared to the study by González-Montalvo et al. [20] (females 18.3%; males 12.4%) with measurements before the operation. The results were similar using the AWGS criteria. The study by Ho et al. [22] with measurements after hip surgery had a higher prevalence of sarcopenia (females 67.7%; males 73.6%) compared to the study by Yoo et al. [23] (females 44.3%; males 68.2%) with measurements before the operation.

Gender difference

Of the 10 included papers, 8 papers provided the prevalence of sarcopenia separately for both sexes. Seven of the 8 papers showed that the prevalence of sarcopenia after fracture was higher in males [17–19, 22–25]. In contrast, González-Montalvo et al. [20] showed that the prevalence of sarcopenia was higher in females (18.3%) compared to males (12.4%) after hip fracture.

Patient vs. control

Of the 10 included papers, 4 papers used case-control study design [18, 21, 23, 24]. All of them showed that the prevalence of sarcopenia was higher in the fracture group (30% to 50.1%) compared to the control group (10.8% to 33.5%).

Fracture risk of sarcopenia

Definition of sarcopenia

Five prospective cohort studies evaluated sarcopenia status of subjects at baseline and analyzed fracture risks, with a follow-

Table 3 Study quality assessment using Newcastle-Ottawa Scale for cross-sectional studies

Cross-sectional studies	Selection				Comparability	Outcome		Total score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Subjects in different outcome groups comparable. Confounding controlled	Assessment of the outcome	Statistical test	
Landi et al. 2017, Italy [17]	Representative of the average in the target population*	Not justified	No description	Based on FNIH criteria**	(age and sex)**	Objective measurements**	Clearly described*	8
Roh et al. 2017, South Korea [18]	Representative of the average in the target population*	Justified and satisfactory*	No description	Based on AWGS criteria**	(age and sex)**	Objective measurements**	Clearly described*	9
Steihaug et al. 2017, Norway [19]	Representative of the average in the target population*	Not justified	No description	Based on EWGSOP criteria**	(age and sex)**	Objective measurements**	Clearly described*	8
González-Montalvo et al. 2016, Spain [20]	Representative of the average in the target population*	Not justified	No description	Based on EWGSOP criteria**	(age and sex)**	Objective measurements**	Clearly described*	8
Hida et al. 2016, Japan [21]	Representative of the average in the target population*	Not justified	No description	Based on DXA measurement**	(age)*	Objective measurements**	Clearly described*	7
Ho et al. 2016, Hong Kong SAR [22]	Representative of the average in the target population*	Not justified	No description	Based on AWGS criteria**	(age and sex)**	Objective measurements**	Clearly described*	8
Hida et al. 2013, Japan [24]	Representative of the average in the target population*	Not justified	Response satisfactory*	Based on DXA measurement**	(age and sex)**	Objective measurements**	Clearly described	8
Di Monaco et al. 2012, Italy [25]	Representative of the average in the target population*	Justified and satisfactory*	No description	Based on DXA measurement**	(age and sex)**	Objective measurements*	Clearly described	7

Table 4 Study quality assessment using Newcastle-Ottawa Scale for cohort studies

Cohort studies	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for out-comes to occur	Adequacy of follow-up of cohorts	
Singh et al. 2009, Australia [26]	Representative of the average in the target population*	Drawn from same community*	Structured interview*	Yes*	(age and sex)**	Objective measurements*	Yes*	> 85% follow-up*	9
Harris et al. 2017, USA [27]	Representative of the average in the target population*	Drawn from same community*	Some cases were self-report	Yes*	(age and race)**	Objective measurements*	Yes*	No statement	7
Schaap et al. 2017, The Netherlands [28]	Representative of the average in the target population*	Drawn from same community*	Structured interview*	Yes*	(age and sex)**	Objective measurements*	Yes*	Complete*	9
Hars et al. 2016, Switzerland [29]	Representative of the average in the target population*	Drawn from same community*	Structured interview*	Yes*	(age and sex)**	Objective measurements*	Yes*	> 80% follow-up*	9
Chalhoub et al. 2015, USA [30]	Representative of the average in the target population*	Drawn from same community*	Self report	Yes*	(age)*	Objective measurements*	Yes*	No statement	6
Yu et al. (2014) Hong Kong	Representative of the average in the target population*	Draw from same community*	Self report	Yes*	(age and education)**	Objective measurements*	Yes*	No statement	7

The asterisk represents the 'star or point' awarded for the quality of the study in each category. A maximum of 4 points from 'selection', 2 'points' for comparibility and 3 'points' for exposure or outcome. Please refer to our methodology: assessment of quality of selected studies

Table 5 Prevalence of sarcopenia after fracture (*F* females, *M* males, *SMI* Skeletal Muscle Index, *ALM* appendicular lean mass)

Included studies, countries	Country	Study design sample size	Age (years)	Fracture site	Definition of sarcopenia	Assessments used	Time of fracture–measurement interval	Statistics	Prevalence
Landi et al. 2017, Italy [17]	Italy	Cross-sectional 127 (82F, 45 M)	81.3 ± 4.8	Hip	FNIH	DXA	< 48 h of admission to RU (days before RU admission 3.8 ± 2.2)	Logistic regression	All 33.9% (F: 28%, M: 72%)
Roh et al. 2017, South Korea [18]	Korea	Cross-sectional patient (132: 91F, 41M), control (132: 91F, 41M)	Patient 62.4 ± 7.2 Control 62.1 ± 7.3	Distal radius	AWGS	DXA, grip strength	Post-op	Pearson's correlation, univariate/multiple logistic regression	Patient 30% (F: 27%, M: 34%) Control 17% (F: 19%, M: 15%)
Steihaug et al. 2017, Norway [19]	Norway	Cross-sectional 202 (152F, 50M)	79.4 [76–86]	Hip	EWGSOP	Triceps skinfold, grip strength, walk	Post-op	Logistic regression	All 37% (F: 34.9%, M: 58.0%)
González-Montalvo et al. 2016, Spain [20]	Spain	Cross-sectional 479 (382F, 97M)	85.3 ± 6.8	Hip	EWGSOP	BIA, grip strength	Pre-op < 72 h	Multiple logistic regression	All 17.1% (F: 18.3%, M: 12.4%)
Hida et al. 2016, Japan [21]	Japan	Cross-sectional patient (216F) Control (1608F)	Patient 79.9 ± 8.1* Control 69.1 ± 10.9	Vertebra	SMI < 5.46 kg/m^2	DXA	< 48 h of admission	Mantel-Haenszel analysis, multiple logistic regression	Patient 42.3% Control 25.0%
Ho et al. 2016, Hong Kong SAR [22]	HKSAR, China	Cross-sectional 239 (167F, 72M)	F: 82.2 M: 81.5	Hip	AWGS	DXA, grip strength	Post-op 14.2 days (3–28 days)	Pearson's correlation	All 69.5% (F: 67.7% M: 73.6%)
Yoo et al. 2016, South Korea [23]	Korea	Case control 359 (272F, 87M)	F: 78.3 ± 9.8 M: 75.3 ± 8.6	Hip	AWGS	DXA	Pre-op	Multiple regression, Mantel-Haenszel analysis, multiple logistic regression	Patient 50% (F: 44.3%, M: 68.2%) Control 10.8% (F: 7.1%, M: 16.1%)
Hida et al. 2013, Japan [24]	Japan	Cross-sectional patient (357: 304F, 53M) Control (2511: 1893F, 618M)	Patient (F: 82.7 ± 9.3, M: 80.3 ± 9.4)* Control (F: 70.5 ± 11.1, M: 67.5 ± 12.9)	Hip	SMI F: < 5.46 kg/m^2 M: < 6.87 kg/m^2	DXA	< 48 h	Pearson's correlation	Patient 50.1% (F: 44.7%, M: 81.1%) Control 33.5% (F: 27.2%, M: 52.8%)
Di Monaco et al. 2012, Italy [25]	Italy	Cross-sectional 581 (531F, 60M)	F: 80.0 ± 7.4 M: 81.4 ± 7.5	Hip	ALM/ht^2 F: < 5.45 kg/m^2 M: < 7.26 kg/m^2	DXA	F: 18.3 ± 8.8 days M: 19.4 ± 8.2 days	Binary logistic regression	F: 64% M: 95%
Singh et al. 2009, Australia [26]	Australia	Prospective cohort study 193 (139F, 54M)	80.6 ± 8.4	Hip	SMI F: < 7.0 kg/m^2 M: < 9.5 kg/m^2	BIA, grip strength, walk	Start around 2 weeks after fracture	Logistic regression	116 patients measured 58% sarcopenia

*$P < 0.05$ when compared to control group

Table 6 Risk of fracture in people with sarcopenia

Included studies, countries	Country	Study design sample size	Mean age (years)	Definition of sarcopenia	Assessments used	Prevalence of sarcopenia	Follow-up period (year)	Statistics	Risk of fracture
Harris et al. 2017, USA [27]	USA	Cohort 10937F	Normal 60.8 ± 7.0 Sarcopenia 62.0 ± 7.2* Low BMD 65.0 ± 7.1* Low BMD and sarcopenia 65.3 ± 7.0*	ALM values following a previously developed approach	DXA	19.9% (w/low BMD 12.8%)	15.9	Cox-proportional hazards analysis	HR of fracture (95% CI)+ Sarcopenia alone 0.58 (0.23–1.49) Low BMD alone 2.42 (1.63–3.59) Low BMD and sarcopenia 2.78 (1.78–4.34)
Schaap et al. 2017, The Netherlands [28]	The Netherlands	Cohort *N* = 496 250F, 246M Ages 55–85 years	75.2 ± 6.4	EWGSOP FHIN 1 FHIN 2	DXA, Grip strength, Walk	EWGSOP—31.9% FHIN 1–7.9% FHIN 2–6.3%	3	Cox-proportional hazards analysis	HR of fracture (95% CI)^ EWGSOP—0.94 (0.54–1.64) FHIN 1–1.53 (0.70–3.31) FHIN 2–1.41 (0.58–3.43)
Hars et al. 2016, Switzerland [29]	Switzerland	Cohort *N* = 913 729F, 184M ages 63–67 years	No Sarcopenia 65.0 ± 1.4 Sarcopenia 65.0 ± 1.4	EWGSOP 1	DXA	11.2%	3.4 ± 0.9	Univariate/multivariate logistic regression	OR (95% CI)^^ Sarcopenia alone 2.32 (1.04–5.18)* Low BMD and sarcopenia 3.39 (1.54–7.46)*
Chalhoub et al. 2015, USA [30]	USA	*N* = 6658 1114F, 5544 M Ages 63–67 years	Females Normal 75.6 ± 4.2 Sarcopenia 77.0 ± 3.5* Low BMD 78.3 ± 4.3* Low BMD and sarcopenia 79.1 ± 4.0* Males Normal 72.8 ± 5.5 Sarcopenia 80.5 ± 6.0* Low BMD 74.6 ± 6.0* Low BMD and sarcopenia 79.6 ± 6.3*	EWGSOP	DXA, grip strength, walk	Females 16.2% (w/low BMD 9.2%) Males 3.4% (w/low BMD 2.0%)	Females 8 Males 9	Cox-proportional hazards analysis, multivariate adjusted model	HR of non-traumatic and non-spine fracture (95% CI)++ Females: Sarcopenia alone 1.27 (0.55–2.92) Low BMD alone 2.42 (1.59–3.68) Low BMD and sarcopenia 2.14 (1.27–3.58) Males: Sarcopenia alone 1.20 (0.64–2.28) Low BMD alone 1.82 (1.55–2.13) Low BMD and sarcopenia 4.08 (2.79–5.96)
Yu et al. (2014) Hong Kong [31]	HKSAR, China	2000M Age > 65 years	No Sarcopenia 71.98 ± 4.71 Sarcopenia 76.44 ± 5.88*	AWGS	DXA, grip strength, walk	9.35%	11.3	Cox-proportional hazards analysis	All fracture HR (95% CI)^^^ Sarcopenia alone 2.33 (1.48–3.67)* Low BMD alone 2.40 (1.63–3.54)* Low BMD and sarcopenia 3.49 (1.76–6.90)*

F females, *M* males, *ALM* appendicular lean mass, *BMD* bone mineral density, *HR* hazard ratio, *OR* odd ratio, *CI* confidence interval

* $P < .05$ when compared to normal group

+ Adjusted for age, race, study assignment, physical function, history of fracture, history of self-report falls in past year, hormone use, physical activity, alcohol consumption, smoking status, corticosteroid use, body mass index, dietary calcium intake, dietary vitamin D intake

++ Adjusted for age, race, fall history, previous fracture, current smoking, corticosteroids, rheumatoid arthritis, alcohol consumption, instrumental activity of daily living impairments, and physical activity

^ Adjusted for age, sex, and total body fat

^^ Adjusted for gender, age, length of follow-up and FRAX probability with femoral neck BMD

^^^ Adjusted for age, education levels, socioeconomic status ladder-Hong Kong, presence of chronic obstructive pulmonary disease, diabetes mellitus, hypertension, heart diseases, and stroke, smoking, physical activity (PASE total score), dietary protein intake, dietary vitamin D intake, dietary energy intake, cognitive function (CSI-D categories), and body weight

up period ranging from 3 to 15.9 years [27–31]. All of the papers used the definitions of sarcopenia recommended by the working groups, including EWGSOP and AWGS, except the study by Harris et al. [27]. Table 6 summarizes the details and fracture risk of sarcopenic patients in each study.

Sarcopenia alone

Only 2 of the 5 papers concluded that sarcopenia was associated with increased fracture risk. Yu et al. [31] found that multivariate-adjusted fracture risk for those with sarcopenia alone in community-dwelling men aged 65 years or older was 2.33 times more (95% CI, 1.48–3.67) when compared to those with normal BMD and without sarcopenia. Hars et al. [29] also found a higher fracture risk in healthy 63- to 67-year-old community-dwelling elderly with an odds ratio of 2.31 (95% CI, 1.04–5.18) after multi-variable adjustment. However, Chalhoub et al. [30], Harris et al. [27], and Schaap et al. [28] were unable to show a higher fracture risk in sarcopenic patients.

Sarcopenia and low bone mineral density (BMD)

Two studies showed that men had a much higher fracture risk if they were sarcopenic and osteoporotic. Yu et al. [31] found that men with osteoporosis and sarcopenia had a significantly increased risk of fracture (HR, 3.49, 95% CI, 1.76–6.90) than those with sarcopenia alone (HR = 2.33, 95% CI, 1.48–3.67) or low BMD alone (HR = 2.4, 95% CI, 1.63–3.54). Chalhoub et al. [30] also found similar results of significantly higher risk of fracture in sarcopenic and osteoporotic men (HR = 4.08, 95% CI, 2.79–5.96) than those with sarcopenia alone (HR = 1.20, 95% CI, 0.64–2.28) or low BMD alone (HR = 1.82, 95% CI, 1.55–2.13). Meanwhile, the fracture risk in women was higher with low BMD, but the addition of sarcopenia did not further increase the fracture risk [27, 30].

Subgroup analysis on different nationalities and sarcopenia assessment

Asian sarcopenia prevalence, in general, is higher (30–69.5%) compared to Caucasians (17.1–64%). As for the assessments of sarcopenia with different criteria for diagnosis, EWGSOP had a range of 17.1–37%, AWGS 30–69.5%, and SMI 42.3–58% for prevalence.

Subgroup meta-analysis of sarcopenia in patients with fragility fracture

In the fixed-effects model, a 1-SD advantage in intelligence was associated with the sarcopenia patients who had fracture history. There was a low degree of heterogeneity indicated by the effect size (effect size = 2.986 (2.402, 3.711), $Q = 7.43$, $I^2 = 32.7\%$, p value = 0.19) (Fig. 2).

Discussion

Most fragility fractures in elderly people are caused by falls from standing height. Reduced skeletal mass and strength were

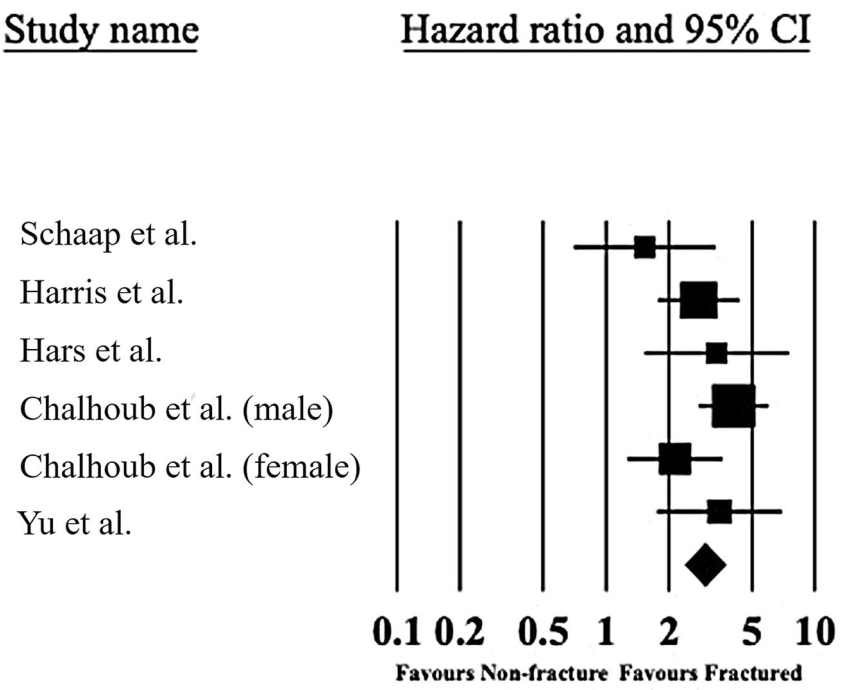

Fig. 2 Fixed-effect model - Forest plot for fragility fractures

associated with impaired balance [12, 33] and frailty [34] in elderly people. A systematic review and meta-analysis [35] concluded that muscle weakness, especially lower limb weakness, was a significant risk factor for recurrent falls. This explains how the 4 case-control studies [18, 21, 23, 24] showed the prevalence of sarcopenia to be higher in patients with fracture than control subjects. Sarcopenia is part of the frailty that leads to fracture. Furthermore, it has been shown in studies that approximately 50% of all rehabilitation patients have sarcopenia [36].

Sarcopenia was more prevalent in older men than women after a fragility fracture [17–19, 22–25]. There are a number of risk factors for sarcopenia, and the decline in sex hormone may be a possible reason for the sex difference. In men, the levels of testosterone and bioavailable testosterone, respectively, decreases by 0.8% and 2% per year from age of 40 [37]. In women, there is a marked reduction in estrogen levels after menopause. Testosterone increase synthesis of muscle protein and higher levels of testosterone are associated with less loss of lean body mass [38, 39]. Evidence also shows that estrogen levels are correlated positively with lean body mass [40]. However, the role of estrogen on the onset of sarcopenia is controversial and further research is still required [41]. The loss of muscle strength in men was nearly two-fold compared to women over 3 years of follow-up in a study [42].

Sarcopenia was more prevalent in patients with hip fracture as our review showed that sarcopenia prevalence was up to 95% [17, 19, 20, 22–26], while those with distal radius and vertebral fracture were 30% [18] and 42.3% [21], respectively. A recent study also showed that sarcopenia was more prevalent in the order of hip fracture (41.5%), vertebral fracture (35%), and distal radius fracture (29.6%) [43]. As lean body mass and strength decrease during aging, it is more common to have sarcopenia in hip fracture patients, as the age of these patients is generally higher than distal radius fracture patients. As physical function is highly related to sarcopenia [44], patients with hip fractures would understandably be less mobile.

The prevalence of sarcopenia after fracture should be analyzed with caution if the time of measurement is much delayed after the fracture. Our review showed that the measurement of sarcopenia before and after surgery differed remarkably, from 12.4–18.3% (pre-surgery) to 34.9–58% (post-surgery) using the ESWSOP criteria [19, 20] and from 44.3–68.2% (pre-surgery) to 67.7–73.6% (post-surgery) using AWGS [22, 23]. It is well known that increased bed rest after lower limb fracture can lead to muscle disuse atrophy. The lean body mass remains stable in the first 10 days, but significantly decreases from 10 days to 2 months after a hip fracture [45]. It is recommended to measure the body lean mass within 10 days after hip fracture to minimize bedrest-induced muscle loss and to avoid overestimating sarcopenia prevalence.

In this review, only 2 studies showed that fracture risk was higher in elderly people with sarcopenia alone [29, 31]. The number of falls was not adjusted for the fracture risk in these 2 papers. On the other hand, hazard ratios were adjusted with the number of falls reported in the studies by Chalhoub et al. [30] and Harris et al. [27], where no increased fracture risk was found. As the majority of fragility fractures are caused by fall incidences, adjusting the number of falls may underestimate the observed fracture risk. The hazard ratio may also be underpowered due to relatively small sample size in the study by Schaap et al. [28]. These are the possible reasons that no significant association between sarcopenia and fragility fracture was found.

It is important to note that men had a much higher fracture risk with both sarcopenia and low BMD. In the study by Chalhoub et al. [30], the fracture risk in men with sarcopenia or osteoporosis alone was 1.20 and 1.82 times, respectively, but the risk was significantly increased to 4.08 times in men with both sarcopenia and osteoporosis. The combined effect of sarcopenia and osteoporosis on fracture risk was greater than the sum of the individual risk. This may be the consequence of the synergistic interaction between low bone mass and low lean body mass on bone quality. Muscles and bones are postulated to closely interact with each other in two ways. In the mechanostat theory, muscle contraction is required to impose mechanical force to the bone structure, thus stimulating the osteogenic effects [46]. In the crosstalk theory, there is a feed-forward loop between bone and skeletal muscle by secreting factors that act on each other and influence metabolism [46, 47]. Studies found that low lean body mass and strength were associated with impaired bone quality in terms of bone geometry and microarchitecture [48–50]. Good bone strength should be comprised of good bone density as well as bone quality [51]. Weak muscle and bone affect each other negatively, and hence contribute to the additive effect of fracture risk. However, despite the theories, there is currently very few clinical data demonstrating a causal relationship between osteoporosis and sarcopenia.

The addition of sarcopenia did not further increase the fracture risk in osteoporotic women [27, 30]. A possible explanation was that muscle loss in women was slower and the severity of sarcopenia in women was not as high as in men. Our current findings support this as there is close relationship observed mainly in males. This is of clinical importance as clinicians should pay extra attention in the screening of sarcopenia in these patients. This also suggests that fractures in women were mainly associated with low BMD. As the number of papers included in this review is limited, further studies are required to confirm the above phenomenon. There has been increasing concern about the combined effect of sarcopenia and osteoporosis on fracture risk. The terms “sarco-osteopenia” and “sarco-osteoporosis” were first coined by Binkley and Buehring [52] to emphasize the weak bones and weak muscles that may contribute to falls and fractures in elderly adults. Recent studies indicated that elder people with sarco-osteoporosis were frailer with higher burden of

comorbidities [53, 54]. However, there is still a knowledge gap in this area and a lack of clinical data. Further research is required for better understanding in the future.

It is important to note that most studies only measure the lean body mass by dual energy X-ray absorptiometry (DXA) scan, which does not have a functional component. Although stating that an established sarcopenia definition was used according to the AWGS, EWGSOP, IWGS, and FNIH, readings of hand grip or gait are often missed. The description as to why these additional assessments was not stated. Following guidelines strictly for the correct diagnosis of sarcopenia is important. It can be assumed that elderlies having fractures would not be able to do gait tests and may decline additional assessments due to pain. Missing values were also identified in the study by Steihaug et al., which was accounted by patients being too ill, refused specific examinations, or discharged before data collection was complete. The study by Schaap et al. had 9 missing falls data but there were no details regarding the cause, but there was complete data on sarcopenic parameters. Furthermore, studies using BIA or triceps skinfold are not the gold standard in diagnosing sarcopenia, which is used by 3 studies. Other confounding factors include the fact that sarcopenia may just be an indicator of frailty in the elderly. Other limitation in this systematic review is that the definitions of sarcopenia still varied in different papers, although more consensus have been reached by several working groups in recent years. This leads to difficult comparison of sarcopenia prevalence among different papers. Secondly, only two databases were used for the electronic search and non-English papers were excluded, which may cause some missing relevant articles. Also, only qualitative review was conducted in this review due to the different nature of papers and data heterogeneity.

Based on current studies, the prevalence of sarcopenia in elderly people with fragility fracture was much higher than non-fracture elderly, especially in men. This is an alarming signal to orthopedic experts, as sarcopenia is under-attention. The combined effect of sarcopenia and low BMD on bone quality in males should be further studied. There is also a pressing need for further research on the fragility fracture associated with sarco-osteoporosis to understand their relationship and mechanism. These can provide more evidence to develop potential interventions to improve clinical outcomes.

Funding information This study was partially supported by General Research Fund (Reference: 14113018).

Compliance with ethical standards

Conflicts of interest None.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Janssen I, Heymsfield SB, Wang ZM, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol 89:81–88
2. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 39:412–423
3. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43:748–759
4. Frisoli A, Chaves PH, Ingham SJM, Fried LP (2011) Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: results from the Women's Health and Aging Study (WHAS) II. Bone 48:952–957
5. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, de Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. J Am Med Dir Assoc 12:249–256
6. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JSW, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H (2014) Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15:95–101
7. Studenski SA, Peters KW, Alley DE et al (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. Journals of Gerontology Series a-Biological Sciences and Medical Sciences 69:547–558
8. Woo J, Leung J, Morley JE (2015) Defining sarcopenia in terms of incident adverse outcomes. J Am Med Dir Assoc 16:247–252
9. Blain H, Jaussent A, Thomas E, Micallef JP, Dupuy AM, Bernard PL, Mariano-Goulart D, Cristol JP, Sultan C, Rossi M (2010) Appendicular skeletal muscle mass is the strongest independent factor associated with femoral neck bone mineral density in adult and older men. Exp Gerontol 45:679–684
10. Verschueren S, Gielen E, O'Neill TW et al (2013) Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men. Osteoporos Int 24:87–98
11. Orsatti FL, Nahas EAP, Nahas-Neto J, Orsatti CL, Marocolo M, Barbosa-Neto O, da Mota GR (2011) Low appendicular muscle mass is correlated with femoral neck bone mineral density loss in postmenopausal women. BMC Musculoskelet Disord 12
12. Szulc P, Beck TJ, Marchand F, Delmas PD (2005) Low skeletal muscle mass is associated with poor structural parameters of bone and impaired balance in elderly men - the MINOS study. J Bone Miner Res 20:721–729
13. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, Bernabei R, Onder G (2012) Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. Clin Nutr 31:652–658
14. Cheung CL, Tan KCB, Bow CH, Soong CSS, Loong CHN, Kung AWC (2012) Low handgrip strength is a predictor of osteoporotic

fractures: cross-sectional and prospective evidence from the Hong Kong Osteoporosis Study. Age 34:1239–1248
15. Hong W, Cheng Q, Zhu XY, Zhu H, Li H, Zhang X, Zheng S, du Y, Tang W, Xue S, Ye Z (2015) Prevalence of sarcopenia and its relationship with sites of fragility fractures in elderly Chinese men and women. PLoS One 10
16. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB, Study HA (2010) Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and Body Composition Study. J Bone Miner Res 25:513–519
17. Landi F, Calvani R, Ortolani E, Salini S, Martone AM, Santoro L, Santoliquido A, Sisto A, Picca A, Marzetti E (2017) The association between sarcopenia and functional outcomes among older patients with hip fracture undergoing in-hospital rehabilitation. Osteoporos Int 28:1569–1576
18. Roh YH, Do Koh Y, Noh JH, Gong HS, Baek GH (2017) Evaluation of sarcopenia in patients with distal radius fractures. Arch Osteoporos 12
19. Steihaug OM, Gjesdal CG, Bogen B, Kristoffersen MH, Lien G, Ranhoff AH (2017) Sarcopenia in patients with hip fracture: a multicenter cross-sectional study. PLoS One 12
20. Gonzalez-Montalvo JI, Alarcon T, Gotor P, Queipo R, Velasco R, Hoyos R, Pardo A, Otero A (2016) Prevalence of sarcopenia in acute hip fracture patients and its influence on short-term clinical outcome. Geriatr Gerontol Int 16:1021–1027
21. Hida T, Shimokata H, Sakai Y, Ito S, Matsui Y, Takemura M, Kasai T, Ishiguro N, Harada A (2016) Sarcopenia and sarcopenic leg as potential risk factors for acute osteoporotic vertebral fracture among older women. Eur Spine J 25:3424–3431
22. Ho AWH, Lee MML, Chan EWC, Ng HMY, Lee CW, Ng WS, Wong SH (2016) Prevalence of pre-sarcopenia and sarcopenia in Hong Kong Chinese geriatric patients with hip fracture and its correlation with different factors. Hong Kong Med J 22:23–29
23. Yoo JI, Ha YC, Kwon HB, Lee YK, Koo KH, Yoo MJ (2016) High prevalence of sarcopenia in Korean patients after hip fracture: a case-control study. J Korean Med Sci 31:1479–1484
24. Hida T, Ishiguro N, Shimokata H, Sakai Y, Matsui Y, Takemura M, Terabe Y, Harada A (2013) High prevalence of sarcopenia and reduced leg muscle mass in Japanese patients immediately after a hip fracture. Geriatr Gerontol Int 13:413–420
25. Di Monaco M, Castiglioni C, Vallero F, Di Monaco R, Tappero R (2012) Sarcopenia is more prevalent in men than in women after hip fracture: a cross-sectional study of 591 inpatients. Arch Gerontol Geriatr 55:E48–E52
26. Singh MAF, Singh NA, Hansen RD et al (2009) Methodology and baseline characteristics for the sarcopenia and hip fracture study: a 5-year prospective study. Journals of Gerontology Series a-biological Sciences and Medical Sciences 64:568–574
27. Harris R, Chang Y, Beavers K, Laddu-Patel D, Bea J, Johnson K, LeBoff M, Womack C, Wallace R, Li W (2017) Risk of fracture in women with sarcopenia, low bone mass, or both. J Am Geriatr Soc 65:2673–2678
28. Schaap LA, van Schoor NM, Lips P, Visser M (2017) Associations of sarcopenia definitions, and their components, with the incidence of recurrent falling and fractures; the Longitudinal Aging Study Amsterdam. J Gerontol Ser A:glx245
29. Hars M, Biver E, Chevalley T, Herrmann F, Rizzoli R, Ferrari S, Trombetti A (2016) Low lean mass predicts incident fractures independently from FRAX: a prospective cohort study of recent retirees. J Bone Miner Res 31:2048–2056
30. Chalhoub D, Cawthon PM, Ensrud KE, Stefanick ML, Kado DM, Boudreau R, Greenspan S, Newman AB, Zmuda J, Orwoll ES (2015) Risk of nonspine fractures in older adults with sarcopenia, low bone mass, or both. J Am Geriatr Soc 63:1733–1740
31. Yu R, Leung J, Woo J (2014) Incremental predictive value of sarcopenia for incident fracture in an elderly Chinese cohort: results from the Osteoporotic Fractures in Men (MrOs) Study. J Am Med Dir Assoc 15:551–558
32. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25:603–605
33. Carter ND, Khan KM, Mallinson A, Janssen PA, Heinonen A, Petit MA, McKay HA, Grp F-FBR (2002) Knee extension strength is a significant determinant of static and dynamic balance as well as quality of life in older community-dwelling women with osteoporosis. Gerontology 48:360–368
34. Yoshimura N, Muraki S, Oka H, Iidaka T, Kodama R, Horii C, Kawaguchi H, Nakamura K, Akune T, Tanaka S (2018) Do sarcopenia and/or osteoporosis increase the risk of frailty? A 4-year observation of the second and third ROAD study surveys. Osteoporos Int 29:2181–2190
35. Moreland JD, Richardson JA, Goldsmith CH, Clase CM (2004) Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 52:1121–1129
36. Churilov I, Churilov L, MacIsaac RJ, Ekinci EI (2018) Systematic review and meta-analysis of prevalence of sarcopenia in post acute inpatient rehabilitation. Osteoporos Int 29:805–812
37. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB (2002) Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 87:589–598
38. LeBlanc ES, Wang PY, Lee CG, Barrett-Connor E, Cauley JA, Hoffman AR, Laughlin GA, Marshall LM, Orwoll ES (2011) Higher testosterone levels are associated with less loss of lean body mass in older men. J Clin Endocrinol Metab 96:3855–3863
39. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A (1995) Testosterone administration to elderly men increases skeletal-muscle strength and protein-synthesis. Am J Physiol Endocrinol Metab 269:E820–E826
40. van Geel TA, Geusens PP, Winkens B, Sels J-PJ, Dinant G-J (2009) Measures of bioavailable serum testosterone and estradiol and their relationships with muscle mass, muscle strength and bone mineral density in postmenopausal women: a cross-sectional study. Eur J Endocrinol 160:681–687
41. Messier V, Rabasa-Lhoret R, Barbat-Artigas S, Elisha B, Karelis AD, Aubertin-Leheudre M (2011) Menopause and sarcopenia: a potential role for sex hormones. Maturitas 68:331–336
42. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB (2006) The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci 61:1059–1064
43. Yoon BH, Lee JK, Choi DS, Han SH (2018) Prevalence and associated risk factors of sarcopenia in female patients with osteoporotic fracture. J Bone Metab 25:59–62
44. Westbury LD, Dodds RM, Syddall HE, Baczynska AM, Shaw SC, Dennison EM, Roberts HC, Sayer AA, Cooper C, Patel HP (2018) Associations between objectively measured physical activity, body composition and sarcopenia: findings from the Hertfordshire Sarcopenia Study (HSS). Calcif Tissue Int 103:237–245
45. D'Adamo CR, Hawkes WG, Miller RR, Jones M, Hochberg M, Yu-Yahiro J, Hebel JR, Magaziner J (2014) Short-term changes in body composition after surgical repair of hip fracture. Age Ageing 43:275–280
46. Girgis CM (2015) Integrated therapies for osteoporosis and sarcopenia: from signaling pathways to clinical trials. Calcif Tissue Int 96:243–255
47. Karsenty G, Mera P (2017) Molecular bases of the crosstalk between bone and muscle. Bone

48. Edwards MH, Ward KA, Ntani G, Parsons C, Thompson J, Sayer AA, Dennison EM, Cooper C (2015) Lean mass and fat mass have differing associations with bone microarchitecture assessed by high resolution peripheral quantitative computed tomography in men and women from the Hertfordshire Cohort Study. Bone 81:145–151
49. LeBrasseur NK, Achenbach SJ, Melton LJ, Amin S, Khosla S (2012) Skeletal muscle mass is associated with bone geometry and microstructure and serum insulin-like growth factor binding protein-2 levels in adult women and men. J Bone Miner Res 27: 2159–2169
50. Szulc P, Blaizot S, Boutroy S, Vilayphiou N, Boonen S, Chapurlat R (2013) Impaired bone microarchitecture at the distal radius in older men with low muscle mass and grip strength: the STRAMBO Study. J Bone Miner Res 28:169–178
51. Carbonare LD, Giannini S (2004) Bone microarchitecture as an important determinant of bone strength. J Endocrinol Investig 27:99–105
52. Binkley N, Buehring B (2009) Beyond FRAX: it's time to consider "sarco-osteopenia". J Clin Densitom 12:413–416
53. Wang YJ, Wang Y, Zhan JK, Tang ZY, He JY, Tan P, Deng HQ, Huang W, Liu YS (2015) Sarco-osteoporosis: prevalence and association with frailty in Chinese community-dwelling older adults. Int J Endocrinol 2015:482940
54. Patel HP, Dawson A, Westbury LD, Hasnaoui G, Syddall HE, Shaw S, Sayer AA, Cooper C, Dennison EM (2018) Muscle mass, muscle morphology and bone health among community-dwelling older men: findings from the Hertfordshire sarcopenia Study (HSS). Calcif Tissue Int 103:35–43