REVIEW

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Muscle parameters in fragility fracture risk prediction in older adults: A scoping review

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Abstract

Half of osteoporotic fractures occur in patients with normal/osteopenic bone density or at intermediate or low estimated risk. Muscle measures have been shown to contribute to fracture risk independently of bone mineral density. The objectives were to review the measurements of muscle health (muscle mass/quantity/quality, strength and function) and their association with incident fragility fractures and to summarize their use in clinical practice. This scoping review follows the PRISMA-ScR guidelines for reporting. Our search strategy covered the three overreaching concepts of 'fragility fractures', 'muscle health assessment' and 'risk'. We retrieved 14 745 references from Medline Ovid SP, EMBASE, Web of Science Core Collection and Google Scholar. We included original and prospective studies on community-dwelling adults aged over 50 years that analysed an association between at least one muscle parameter and incident fragility fractures. We systematically extracted 17 items from each study, including methodology, general characteristics and results. Data were summarized in tables and graphically presented in adjusted forest plots. Sixty-seven articles fulfilled the inclusion criteria. In total, we studied 60 muscle parameters or indexes and 322 fracture risk ratios over 2.8 million person-years (MPY). The median (interquartile range) sample size was 1642 (921–5756), age 69.2 (63.5–73.6) years, follow-up 10.0 (4.4–12.0) years and number of incident fragility fractures 166 (88–277). A lower muscle mass was positively/not/negatively associated with incident fragility fracture in 28 (2.0), 64 (2.5) and 10 (0.2 MPY) analyses. A lower muscle strength was positively/not/negatively associated with fractures in 53 (1.3), 57 (1.7 MPY) and 0 analyses. A lower muscle function was positively/not/negatively associated in 63 (1.9), 45 (1.0 MPY) and 0 analyses. An in-depth analysis shows how each single muscle parameter was associated with each fragility fractures subtype. This review summarizes markers of muscle health and their association with fragility fractures. Measures of muscle strength and function appeared to perform better for fracture risk prediction. Of these, hand grip strength and gait speed are likely to be the most practical measures for inclusion in clinical practice, as in the evaluation of sarcopenia or in further fracture risk assessment scores. Measures of muscle mass did not appear to predict fragility fractures and might benefit from further research, on D3-creatine dilution test, lean mass indexes and artificial intelligence methods.

Keywords fragility fracture; frailty; muscle; older adults; osteoporosis; risk; sarcopenia

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Introduction

Osteoporosis is characterized by a generalized loss of bone mass and altered microarchitecture, leading to an increased risk of fracture.[1] Over the age of 50, a fifth of men and half women will have a fragility (or osteoporotic) fracture, developed spontaneously or after a minor trauma, such as a fall from a standing height.[1] Major osteoporotic fractures (MOFs) include hip, vertebral, humeral and forearm fractures. Fragility fractures are a major age-related adverse event due to their consequences and high incidence.[2] Osteoporotic fractures account for more days of hospitalization than acute myocardial infarction, chronic obstructive pulmonary disease or breast cancer.[3] In Europe, the direct costs were estimated at 37.4 billion euros in 2010 and 56.9 billion euros in 2019[2] and will continue to increase as the population aged over 65 and over 80 is expected to double and triple respectively between 2020 and 2050.[4] Bone fragility can be prevented and treated. However, the gap in its management consists in the limited capacities to detect and predict fragility fractures.[5]

The gold standard for assessing bone mineral density (BMD) is dual-energy X-ray absorptiometry (DXA). The World Health Organization (WHO) defines osteoporosis as a BMD of 2.5 standard deviations below the mean peak BMD of young female adults.[6] However, half of fractures occurs in individuals with a normal BMD.[7] Risk scores have thus been developed and have improved fracture prediction, by taking into consideration other clinical risk factors for fractures[8]; the most widely used fracture risk score is FRAX® (Fracture Risk Assessment Tool).[8] Although FRAX with BMD performs better than BMD alone in predicting incident fractures, there is still room for improvement in risk prediction, potentially through inclusion of additional measures, such as falls, that are independent of BMD.[9] Muscles lose 40% of their volume between the ages of 20 and 80.[10] Since the first mention of the muscles mass loss as sarcopenia by Rosenberg in 1989,[11] many parameters of muscle health have been studied using a variety of measures such as radiological imaging, strength measurements, functional assessments and blood tests. In parallel, the definition of sarcopenia has evolved to a composite loss of muscle mass, strength and function, and its association with adverse outcomes, including fragility fractures.[12] Sarcopenia and osteoporosis are both associated with ageing and similar risk factors in a close interaction.[13] They increase the risk of falls, fragility fractures, surgery, chronic pain, physical disability, social isolation and death.[14–19] All these negative consequences lead to higher hospital costs and longer hospital stays.[20–22]

A scoping review is a structured approach to summarize and map the evidence and gaps on a topic. This type of knowledge synthesis is particularly useful for planning future research on heterogeneous and broad topics. So far, only one scoping review studied muscle health and its association with adverse outcomes.[23] The authors focused on three definitions of sarcopenia and their ability to predict various adverse outcomes. Of the 11 included studies in this previous review, only one analysed fragility fractures.[24] The currently available studies on muscle health parameters and their association with incident fragility fractures have not been fully reviewed.

The objectives of this scoping review were (1) to review muscle health assessment techniques (muscle mass/quantity/quality, strength and function) and their association with incident fragility fractures and (2) to summarize the clinical use of the parameters associated with fragility fractures risk.

Methodology

This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review (PRISMA-ScR) guidelines for reporting and the JBI methodology for writing.[25,26] The PRISMA-ScR checklist is provided in the supporting information. The study protocol is available online in the OSF (Open Science Framework) registry at https://archive.org/details/osf-registrations-2fmtg-v1 (registration DOI: 10.17605/OSF.IO/2FMTG).

Inclusion criteria

The studies included in this review fulfilled the following criteria: (1) original study; (2) participants over 50 years of age recruited from the general population (community-dwelling) without gender, racial, geographic or cultural restriction. Studies where the participants were recruited on the basis of a medical condition (e.g., frailty, osteoporosis and cancer) were excluded to minimize selection bias; (3) assessment of at least one muscle health parameter; (4) prospective studies; (5) fragility fracture as outcome: a low-trauma fracture at any specific osteoporotic site or a combination of sites; and (6) the association of each muscle health parameter with the fragility fracture incidence was examined. No language restrictions were performed. Meta-analyses, systematic reviews and, text/opinion papers relevant to the current review's question were considered for the qualitative and critical evaluation and interpretation.

Source of evidence and search strategy

A systematic search strategy was developed with a research librarian to cover the three overarching concepts of the research: 'fragility fractures', 'muscle health assessment' and 'risk'. The search syntax contains free and index/mesh terms, a filter to exclude animal studies and a general filter for the study types. Relevant articles were also compared to better define the keywords and index terms of the equations. The search strategy was translated for the following databases:

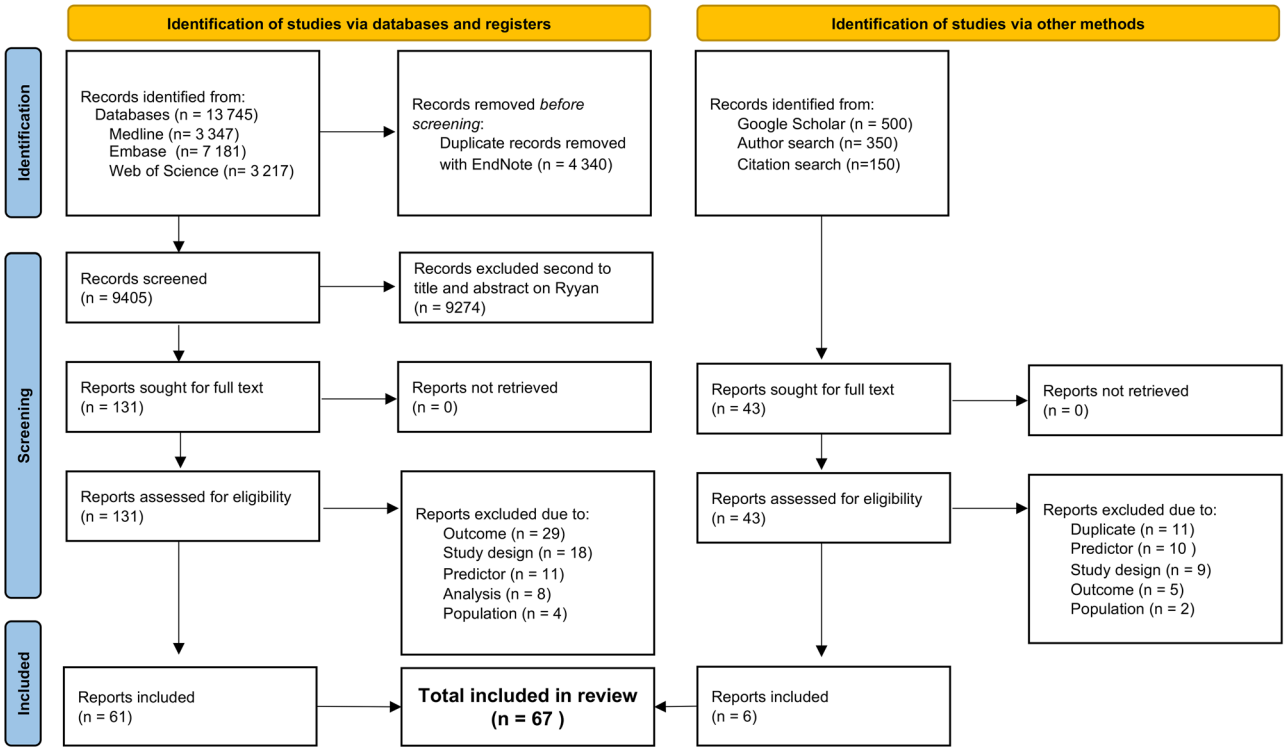
Medline Ovid SP, EMBASE and Web of Science Core Collection. A complementary search equation was developed for Google Scholar. Systematic search syntaxes are available in the supporting information. Unpublished studies and grey literature were not screened. Backward and forward citation chasing of eligible studies was also done. We also undertook hand searching of references within records and on specific authors to identify further eligible studies. The search included article published from inception of the databases to 27 April 2023.

Study selection

The identified citations from the systematic search were de-duplicated (J. E.) in EndNote™ (Clarivate Analytics, Philadelphia, PA, USA) and transferred (C. V.) to Rayyan (*free web application for systematic reviews*[27]). One author (C. V.) screened the titles and abstracts for eligibility and retrieved the full texts of the selected articles. The reasons for exclusion were recorded at full text reading. The study's selection process is fully reported using the PRISMA 2020 flow diagram (cf. *Figure 1*).

Data extraction and qualitative assessment

The data were extracted from the included articles by one author (C. V.) using an Excel table. For each study, qualitative and quantitative data were extracted[25]: first author, year of publication, country, design, duration of follow-up, population, sex, mean age at baseline, sample size, muscle health parameter, fracture type, number of fractures, statistical approach, model adjustments and fracture risk estimates for the muscle parameters studied. When one association had multiple models, we kept the model considering the strongest predictor of fragility fractures including age and/or BMD. Multiple adapted forest plots were used to visually demonstrate the overall trends of associations between each muscle parameter and the fracture risk. The results were grouped by mass/quantity/quality (*Figures 3–5*), strength and function and by fracture type (A–F). The results were ordered by parameter, measure subtype, sex and publication date. The muscle mass mostly refers to lean mass (LM) (or its estimation) while quantity also includes volumes and areas. Muscle quality is a broad terminology and includes muscle density, muscle texture, myosteatosis, muscle fat infiltration and some ultrasound measures.[28] In order to homogenize the reporting and to facilitate the interpretation of the



Legend: This flowchart is based on the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources (Page et al. 2021). The exclusion reasons are: the "outcome" is not a fragility fracture; The "study design" is not a prospective study; the "predictor" does not include a muscle assessment; The "analysis" does not report the association between the outcome and the predictor; The "population" is not representative of the general population over 50 years (eg. hosiptalized).

Figure 1 PRISMA 2020 flow diagram of the study.

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results, we always reported the fracture risk ratios for a lower/slower/deteriorated muscle parameter (e.g., 'the risk ratio for 1 SD decrease in lean mass'). Most of the original articles had reported the fracture risk ratio per unit of deterioration in the muscle parameter studied, and these values were reported identically; if the original article had reported the fracture risk ratios per increase in the muscle parameter studied, we calculated and reported the 1/risk ratio. The rationale is that a worsened/unhealthy muscle parameter is associated with a higher risk of fracture. Finally, the most frequently cited muscle health assessment parameters in the included articles are briefly discussed in terms of their generalizability and availability in clinical practice.[29] Additionally, the best predictors of fragility fractures are reported, including the total person-year.

Results

Characteristics of the included studies

Of the 13 745 studies extracted from the databases and the approximately 1000 studies screened using additional methods (*Figure 1*: PRISMA flow chart), 67 studies were included in this review, comprising 2.8 million person-years: median sample size (1st–3rd quartile) of 1642 (921–5756) participants, follow-up of 10.0 (4.4–12.0) years, age of 69.2 (63.5–73.6) years and number of incident fragility fractures of 166 (88–277).[30–96] The general characteristics of the included studies are summarized in *Table 1* and detailed for each article in *Table 2*. The most cited cohorts were MrOS (USA, China and Sweden; 13 articles), DOES (Australia; 6 articles), SOF (USA; 5 articles), Health ABC (USA; 4 articles) and EPIDOS (France; 4 articles). Within the studies, 37 analysed women, 30 men and 13 both together. All results and references are presented visually and summarized in multiple stacked plots (*Figures 3–5*). The 67 included studies investigated 60 different muscle parameters and were grouped into 6 types of fragility fracture: hip (*Figure 2B*: 126 analyses), all type of fragility fractures (*Figure 2F*: 96 analyses), MOF (*Figure 2A*: 40 analyses), forearm (*Figure 2D*: 25 analyses), vertebral (*Figure 2C*: 20 analyses) and humerus (*Figure 2E*: 15 analyses), for a total of 322 analyses. The studies used different statistical approaches such as logistic, Cox proportional, Poisson or Fine and Gray models and different adjustments (*Table 2* and *Figures 3–5*: 'Model; comparison; adjustment'). The following three sections summarize the main results for each muscle characteristic: mass and quantity (*Figures 3A–E* and *S3f*), strength (*Figures 4A–E* and *S4f*) and function (*Figures 5A–E* and *S5f*).

Muscle mass, quantity and quality

Evaluation of muscle mass and quantity has been performed by very different methods, from radiological images (i.e., DXA and computed tomography [CT]), biological measures (creatine dilution test) or even anthropometric prediction equations. Globally, a lower muscle mass or quantity was associated with risk of incident fragility fracture in 28 (2034 thousand person-years [TPY]) analyses, no risk in 66 (2633 TPY) analyses and lower risk in 10 (230 TPY) analyses (*Figures 2*, *3A–E* and *S3f*). Body composition analysis by DXA was the most used method. Several DXA-derived muscle mass parameters were analysed: appendicular lean mass (ALM), change in ALM, ALM/height, ALM/height^2, change in ALM/height^2, ALM/weight, ALM/body mass index (BMI), total LM, change

Table 1 Summary of the 67 included studies and main characteristics

Most cited first authors (nb. of articles)	Cawthon (5), Nguyen (4), Harvey (3)
Years of publications	From 1989 to 2022, most in 2020
Most cited cohorts (nb. of articles)	MrOS (13), DOES (6), SOF (5), Health ABC (4), EPIDOS (4)
Most represented country (nb. of articles)	USA (22), Australia (8), China (6), Sweden (6), France (6)
Study design	Prospective only
Median follow-up (years)	10.0 (IQR: 4.4–12.0)
Most studied population	Community-dwelling healthy older adults
Sex sub-groups in the analysis (M/W)	Women = 37, men = 30, both (and adjusted for sex) = 13
Median age (years)	69.2 (IQR: 63.5–73.6)
Median sample size	1642 (IQR: 921–5756)
Most analysed parameter (nb. of analysis)	Hand grip strength (76), gait speed (49), DXA–ALMI (28), quadriceps strength (28), chair rising tests (27)
Most studied fragility fractures (nb. of analysis)	Hip (126), all fragility fx (96), MOF (40), forearm (25), vertebral (20), humerus (15), total (322)
Median incident fractures per study	166 (IQR: 88–277)
Most used statistical methods	Hazard ratio and 95% confidence interval, for 1 standard deviation worsening/degradation of the muscle parameter
Most used adjustment factors	Age, weight, height, BMD and sex

Note: Chair rising tests include the timed up and go test and the five-time sit-to-stand test. Abbreviations: BMD, bone mineral density; DXA–ALMI, appendicular lean mass index/height^2 from dual-energy X-ray absorptiometry; IQR, interquartile range; MOF, major osteoporotic fracture.

Table 2 Characteristics of included studies

Ref Author Date	Study name or city (country)	Follow-up (years)	Population inclusion	Sex	Age (years)	Sample size
[30] Yamada 2022	Maibara city (Japan)	3.0	Community-dwelling over 65 years, recruited through email	♂♀	73.8 ± 6.0	773
[31] Harris 2022	MrOS (USA)	12.0	Ambulatory community-dwelling over 65 years	♂	73.7 ± 5.9	5995
[32] Fujita 2022	FORMEN (Japan)	8.4	Community-dwelling able to walk, consent and self-report information recruited through printed literature	♂	73.1 ± 5.2	1686
[33] Cawthon 2022	MrOS (USA)	4.6	Ambulatory community-dwelling over 65 years	♂	84.2	1363
[41] Alajlouni 2021	MrOS (USA)	12.7	Ambulatory community-dwelling over 65 years	♂	73.5 ± 5.8	5665
[34] Zhong 2021	CHARLS (China)	4.0	Representative sample over 60 years living in households	♂♀	67.5 ± 6.7	5958
[40] Harvey 2021	WHI (USA)	14.1	Postmenopausal women from 50 to 79 years at baseline	♀	63.3 ± 7.4	11 187
[37] Harvey 2021	MrOS (USA, Sweden and China)	7.4	Ambulatory community-dwelling over 65 years	♂	76.0 ± 5.3	3251
[39] Hong 2021	NHIS-HEALS (Korea)	3.0	National representative random sample	♀	60.7 ± 8.4	131 587
				♂	60.2 ± 8.3	158 426
[36] Nordvåg 2021	Tromsø Study (Norway)	14.6	All inhabitant over 50 years that accepted to participate	♀	63.5 ± 6.3	3016
		14.6		♂	62.8 ± 6.5	2836
[38] McGrath 2021	MrOS (USA)	8.7	Ambulatory community-dwelling over 65 years	♂	73.6 ± 5.9	5730
[35] Westbury 2021	Health ABC (USA)	10.0	Random selection of White, and all Black, from 70 to 79 years without physical disability	♂♀	74.0 ± 2.9	2480
[45] Cawthon 2021	SDOC (USA, Sweden, China and Australia)	8.9	Community-dwelling over 65 years	♀	≥65	1745
		10.2		♂		9512
[46] Alajlouni 2020	DOES2 W (Australia)	18.0	Community-dwelling over 60 years	♀	68.6 ± 4.2	811
		18.0		♂	69.2 ± 3.8	440
[43] Leslie 2020	Manitoba (USA)	6.0	DXA record	♂♀	67.0 ± 10.0	9622
[42] Søgaard 2020	Tromsø Study (Norway)	15.0	All inhabitant over 50 years that accepted to participate	♀	61.0 ± 7.4	4002
		15.0		♂	62.9 ± 6.5	2891
[44] Lam 2020	MrOS (China)	10.0	Community-dwelling recruited through notices, stratified by age	♀	72.6 ± 5.4	1518
		10.0		♂	72.4 ± 5.0	1693
[47] Scott 2019	CHAMP (Australia)	6.0	Over 70 years from electoral roll of New South Wales	♂	76.7 ± 5.4	1575
[48] Kamiya 2019	JPOS (Japana)	15.2	Over 50 years randomly selected from resident registration	♀	63.4 ± 8.5	1342
[49] Cronholm 2019	MrOS (Sweden)	9.6	Community-dwelling able to walk, from the register of 3 cities	♂	75.4 ± 3.2	3014
[54] Harvey 2018	MrOS (USA, Sweden and China)	10.0	Ambulatory community-dwelling	♂	73.5 ± 10.9	5660
[51] Schaap 2018	LASA (Netherland)	10.0	Population registries of 11 municipalities, stratified by age (over 65 years) and sex	♂	75.2 ± 6.4	498
[55] Buehring 2018	MrOS (USA)	14.0	Ambulatory community-dwelling	♂	74 ± 6	5834
[53] Kim 2018	Ansung (Korea)	1.0	Community-dwelling	♀	63.3 ± 8.6	1627
				♂	62.9 ± 8.5	1201
[52] McLean 2018	Framingham (USA)	8.3	Over 50 years with DXA	♀♂	66.9	1978
[50] Wright 2018	MrOS (USA)	10.8	Ambulatory community-dwelling	♂	65.0–69.0	5875
[60] Harris 2017	WHI (USA)	15.9	Healthy postmenopausal women from 40 centres	♀	63.3 ± 0.07	10 973
[57] Sornay-Rendu 2017	OFELY (France)	13.1	Volunteers randomly selected from insurance company	♀	66.0 ± 8.0	595
[58] Lundin 2017	PRIMO (Sweden)	10.0	Born in 1920–1930 in Bagarmossen contacted	♀	73.0	351
[59] Lee 2017	KURE (KOREA)	12.0	Over 65 years selected through recruiters, poster promotion, health visit, self-acquaintance	♀	71.0 ± 4.4	1281

Table 2 (continued)

Ref Author Date	Study name or city (country)	Follow-up (years)	Population inclusion	Sex	Age (years)	Sample size
[56] Zaslavsky 2017	WHI (USA)	11.5	Over 65 years with ≥3 Fried's criteria	♀	72.3 ± 4.52	872
[61] Balogun 2017	TASOAC (Australia)	10.0	Over 50 years, sex stratified from an electoral roll	♂♀	63.0 ± 7.5	1041
[63] Hars 2016	GERICO (Switzerland)	3.4	Retirees	♂♀	65.0 ± 1.4	913
[64] Barbour 2016	SOF (USA)	9.0	From US clinics	♀	70.4	6720
[66] Malkov 2015	Health ABC (USA)	13.5	Random White and all Black from 70 to 79 years without physical disability	♀	70.0–79.0	1552
				♂		1459
[62] Pham 2016	DOES (Australia)	11.0	Community-dwelling over 60 years	♀	68.9 ± 5.0	1066
		11.0		♂	69.7 ± 5.0	595
[67] Cawthon 2015	MrOS (USA)	9.8	Community-dwelling over 65 years	♂	73.6 ± 6.0	5934
[65] Wihlborg 2015	OPRA (Sweden)	10.0	Random selection with 75 years	♀	77.7 ± 0.2	1044
[68] Yu 2014	MrOS (China)	11.3	Community-dwelling recruited through notices, stratified by age	♂	65.0	2000
[69] Ryg 2013	SHARE (Europe)	4.0	n.a.	♂♀	63.3	7699
[71] Edwards 2012	Hertfordshire (UK)	5.5	n.a.	♀	66.2 ± 2.8	1418
		5.5		♂		1579
[70] Rouzi 2012	(Saudi Arabia)	5.2	Postmenopausal women over 50 years from multistage random sampling	♀	61.3 ± 7.2	707
[72] Cheung 2012	Hong Kong (China)	2.9	Recruited from public roadshows and health fairs	♂♀	64.1 ± 9.5	1702
[73] Lang 2010	Health ABC (USA)	6.6	Random White and all Black from 70 to 79 years without physical disability	♂♀	73.5 ± 2.8	2914
[74] Sirola 2008	OSTPRE (Finland)	15.0	Random stratified sample from postal enquiry to women	♀	53.3 ± 2.9	971
[75] Kärkkäinen 2008	OSTPRE (Finland)	8.4	Random stratified sample from postal enquiry to women	♀	59.1 ± 2.9	2928
[76] Finigan 2008	Sheffield (UK)	10.0	Random selection from general practitioner list in Sheffield stratified by age	♀	64.6 ± 9.1	367
[77] Cawthon 2008	MrOS (USA)	5.3	Over 65 years	♂	73.4	5902
[78] Nguyen 2007	DOES (Australia)	15.0	Community-dwelling over 60 years	♀	69.0 ± 6.3	924
				♂	69.7 ± 6.0	723
[79] Sipilä 2006	Evergreen Project (Finland)	10.0	All from one city aged 75 years	♀	75.0	187
[80] Shigematsu 2006	Evergreen Project (Finland)	10.0	All participants between 75 and 80 years from one city that accepted	♂♀	78.0 ± 0.1	307
[81] Samelson 2006	Framingham (USA)	25.0	Random selection from Framingham city	♀	54.0	452
				♂		252
[82] Pluijm 2006	LASA (Netherland)	3.0	Stratified sample of 55–85 years from 11 municipalities in Netherland	♂♀	75.3 ± 6.4	1365
[83] Robbins 2005	EPIDOS (France)	3.0	Volunteers selected from voters or health registers from 5 French areas	♀	80.5	7598
[84] Nguyen 2005	DOES (Australia)	12.0	All over 60 years from Dubbo	♂♀	70.6 ± 7.2	1658
[85] Dixon 2005	EPOS (Europe)	3.8	Population registers across Europe	♀	63.6 ± 8.2	1380
[86] Albrand 2003	OFELY (France)	5.3	Postmenopausal women, stratified by age, randomly selected from health insurance company	♀	59.1 ± 9.8	672
[87] Lee 2002	EPIDOS (France)	3.6	Volunteers selected from voters or health registers from 5 French areas	♀	80.5 ± 3.7	6901
[88] Dargent-Molina 1999	EPIDOS (France)	2.8	Volunteers selected from voter or health registers from 5 French areas	♀	80.5 ± 3.8	5895
[90] Dargent-Molina 1996	EPIDOS (France)	1.9	Volunteers selected from voter or health registers from 5 French areas	♀	80.5 ± 3.8	7575

Table 2 (continued)

Ref Author Date	Study name or city (country)	Follow-up (years)	Population inclusion	Sex	Age (years)	Sample size
[89] Nguyen 1996	DOES (Australia)	5.0	Community-dwelling over 65 years	♂	n.a.	820
[91] Cummings 1995	SOF (USA)	4.1	White, over 65 years and able to walk	♀	72.0 ± 5.0	9516
[93] Nevitt 1993	SOF (USA)	4.1	Non-Black, aged over 65 years, living in the community	♀	72.2 ± 5.6	891
[92] Nguyen 1993	DOES (Australia)	3.0	All over 60 years from Dubbo	♀	69.2 ± 6.6	1080
				♂	69.0 ± 6.3	709
[94] Kelsey 1992	SOF (USA)	2.2	White, over 65 years and able to walk	♀	65.0–79.0	9704
[95] Wickham 1989	DHSS (UK)	15.0	Community-dwelling over 65 years	♂♀	65.0–74.0	1419
[96] Farmer 1989	NHANES I (USA)	10	White	♀	40–77	3595

Abbreviations: 5×STS, five-time sit-to-stand test; ALM, appendicular lean mass; BIA, body impedance analysis; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EWGSOP, European Working Group on Sarcopenia in Older People; FRAX®, Fracture Risk Assessment Tool; GS, gait speed; HGS, hand grip strength; HR, hazard ratio; IQR, interquartile range; IWG, International Working Group on Sarcopenia; MOF, major osteoporotic fracture (hip, spine, forearm or humerus); n.a., not applicable; OLST, one-leg standing test; pASMI, predicted appendicular skeletal muscle index; pQCT, peripheral quantitative CT; QS, quadriceps strength; SARC-F, sarcopenia questionnaire; SD, standard deviation; SPPB, Short Physical Performance Battery test; TBLM, total body lean mass; TGUG, timed get up and go test; US, ultrasound. *Source*: Characteristics extraction adapted from Peters et al.[97]

Table 2 (continued)

Ref Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[30] Yamada 2022	US	All fall-related fractures	51	Cox proportional HR	T1 vs. T3 (95% CI)	Age, sex, BMI, cognitive function and polypharmacy
[31] Harris 2022	HGS GS DXA	All fragility MOF Hip	1414	Cox proportional HR	1 SD decrease (95% CI)	BMD T-score, history of diabetes, history of arthritis/gout history of falls, self-reported health rating, depressive feelings, PASE score, smoking status, alcohol per week, living alone, education status, visual acuity, use of benzodiazepines, use of selective serotonin reuptake inhibitors and GS score
[32] Fujita 2022	GS OLST HGS	All fragility MOF Hip	175	Fine and Gray subdistribution HR	Q1 vs. Q4 (95% CI)	Age, BMI, BMD, drinking habits (≥1 day/week), smoking habits, history of type 2 diabetes mellitus, history of prostate cancer with hormone therapy, history of gastrectomy and history of falls at baseline study visit
[33] Cawthon 2022	D3Cr dilution test	MOF Hip	180	Cox proportional HR	1 SD decrease (95% CI)	Age, falls, FRAX® and BMD

Table 2 (continued)

Ref Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[41] Alajlouni 2021	GS HGS 5×STS	MOF Hip	1014	Cox proportional HR	1 SD decrease (95% CI)	Garvan and FRAX® parameters
[34] Zhong 2021	SPPB	Hip	180	Logistic regression	1 SD decrease (95% CI)	Age, gender, body mass index, education level, falls and chronic diseases (including diabetes, chronic lung diseases, kidney disease, arthritis or rheumatism)
[40] Harvey 2021	ALM ALM/height^2	MOF Hip	1225	Poisson regression	1 SD decrease (95% CI)	Age, follow-up time and FRAX® + BMD
[37] Harvey 2021	pQCT	Hip	112	Poisson regression	1 SD decrease (95% CI)	Falls, FRAX® and femoral neck BMD
[39] Hong 2021	Lee equation (pASMI)	All Vertebral	6175 2350	Cox proportional HR	IQR changes (95% CI)	Age, income, physical activity, smoking, alcohol consumption, systolic blood pressure, fasting serum glucose, total cholesterol, Charlson Comorbidity Index and body mass index
[36] Nordvåg 2021	Creatinine, cystatin, creatinine/cystatin (as eGFR)	Hip Wrist Humerus	761 218	Cox proportional HR	1 SD decrease of creatinine (increase of eGFR) (95% CI)	Age, height, BMI, BMD, smoking, history of previous fracture and diabetes, high-sensitivity C-reactive protein and use of corticosteroid and any blood pressure-lowering drugs Age, height, BMI, BMD, smoking, history of previous fracture, diabetes and cardiovascular disease, and use of any blood pressure-lowering drugs
[38] McGrath 2021	HGS symmetry QS symmetry	MOF Hip Clinical spine	438	Cox proportional HR	Q1 vs. Q4 of asymmetry (95% CI)	Baseline maximum leg extension power or maximum hand grip strength (for the appropriate predictor), age, clinic site, race, alcohol intake, cigarette smoking status, body mass index, cognitive functioning, physical activity participation, morbidities, benzodiazepine usage and femoral neck bone mineral density
[35] Westbury 2021	HGS GS ALM Δ ALM	All	401	Fine and Gray subdistribution HR	1 SD decrease (95% CI)	Height, weight-for-height residual, smoking status (ever vs. never), alcohol consumption, healthy eating index, physical activity, educational attainment, home ownership, cognitive function and number of comorbidities
[45] Cawthon 2021	GS HGS DXA	Hip	166 392	Cox proportional HR	Binary outcomes (95% CI)	Age, self-rated health, pain, use of statins, cognitive function, cancer, congestive heart failure, stroke, chronic obstructive pulmonary disease and diabetes, plus bone mineral density for hip fracture models and competing risk of death

Table 2 (continued)

[Ref] Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[46] Alajlouni 2020	TGUG 5×STS GS HGS QS ALMI	All	224 74	Cox proportional HR	Q1 vs. Q2–Q4 (95% CI)	Age, femoral neck BMD, prior fractures, falls, BMI, smoking, alcohol, physical activity, diabetes, neurological diseases, cardiovascular diseases, cancer, hypertension, respiratory diseases and renal failure
[43] Leslie 2020	TBLM	MOF Hip	692	Cox proportional HR	1 SD decrease (95% CI)	FRAX® with BMD, including competing mortality
[42] Søgaard 2020	HGS	All Hip	868 231	Cox proportional HR	1 SD decrease (95% CI)	Age, height, BMI, marital status, level of education, leisure time physical activity, daily smoking, consumption of alcohol, self-perceived health and self-reported one or more diseases
[44] Lam 2020	SARC-F GS HGS 5×STS ALM + indexes	MOF Hip	236 139	Logistic regression	1 SD decrease (95% CI)	Univariate
[47] Scott 2019	HGS GS ALM/height	All	63	Logistic regression	1 SD decrease (95% CI)	Age, income, living alone, number of comorbidities, smoking status, psychotropic and corticosteroid use, history of fracture, physical activity and 25(OH)D
[48] Kamiya 2019	HGS	All Hip	162	Cox proportional HR	5-kg decrease in HGS (95% CI)	Age, BMD, previous vertebral/hip fracture and BMI
[49] Cronholm 2019	HGS	All	683	Cox proportional HR	1 SD decrease (95% CI)	Univariate
[54] Harvey 2018	ALM/height^2 HGS 5×STS	All MOF Hip fracture	14–35%	Fine and Gray subdistribution HR	1 SD decrease (95% CI)	FRAX® + BMD
[51] Schaap 2018	HGS GS DXA	All	60	Cox proportional HR	Low (EWGSOP1) vs. others (95% CI)	Age, sex and total body fat
[55] Buehring 2018	HGS GS ALM/height^2	MOF Hip	635	Cox proportional HR	Low vs. others (95% CI)	Age, falls, osteoporosis, body fat, muscle mass, grip strength and gait speed
[53] Kim 2018	HGS DXA	All	156 56	Logistic regression	Low AWG1 vs. rest (95% CI)	Age, osteoporosis, total fat mass, current smoking, regular exercise, comorbidity and osteoporosis medication
[52] McLean 2018	DXA leg	Hip	99	Cox proportional HR	1-kg decrease (95% CI)	

(*Continues*)

Table 2 (continued)

Ref Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
	DXA total body					Age, height, study cohort, per cent total body fat, femoral neck BMD, history of hip fracture, smoking, physical activity, oestrogen replacement use and osteoporosis medication use
[50] Wright 2018	HGS 5×STS Leg power Narrow walk GS	Wrist	97	Cox proportional HR	T1 vs. T3 (95% CI)	Age, race/ethnicity and study site
[60] Harris 2017	DXA	All	1648	Cox proportional HR	Low Newman mass vs. others (95% CI)	Age, race, study assignment, physical function, history of fracture, history of self-report falls in the past year, hormone use, physical activity, alcohol consumption, smoking status, corticosteroid use, BMI, dietary calcium intake and dietary vitamin D intake
[57] Sornay-Rendu 2017	DXA	All MOF	138	Cox proportional HR	1 SD decrease (95% CI)	Age, previous fracture, femoral neck BMD, physical activity, incident falls and risk of death
[58] Lundin 2017	GS OLST	MOF Hip	40	Cox proportional HR	1 SD decrease (95% CI)	Age
[59] Lee 2017	BIA Jump power	Vertebral	282	Logistic regression	Q1 vs. Q4 (95% CI)	Age, BMD, serum 25(OH)D level, body fat percentage, previous fracture, parental hip fracture, alcohol, smoking, physical activity, grip strength, cognitive impairment and weight loss over the past year
[56] Zaslavsky 2017	DXA total and regional lean and fat	Hip fracture	49	Cox proportional HR	1 kg/m^2 increase (95% CI)	Age, ethnicity, smoking, history of previous fractures, recurrent falls and several frailty criteria, and BMD
[61] Balogun 2017	HGS DXA Lower limb strength	All		Poisson regression	'Low' vs. others (95% CI)	Age
[63] Hars 2016	DXA	All	40	Logistic regression	Low EWGSOP or IWG vs. others (95% CI)	Gender, age, length of follow-up and FRAX® probability with femoral neck BMD
[64] Barbour 2016	GS 5×STS	Hip	266	Cox proportional HR	Q1 vs. Q2–Q4 (95% CI)	Age at enrolment, interaction between age and PF_age80, physical performance trajectory, interaction between age and physical performance trajectory, BMI, walk for exercise, smoking, alcohol use, calcium use, oestrogen use, health status, falls in the past 12 months, prevalent fracture after age 50 years, stroke, hypertension, diabetes, cognitive function and hip BMD

Table 2 (continued)

Ref Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[66] Malkov 2015	CT DXA	Hip	105 64	Cox proportional HR	1 SD decrease (95% CI)	Age, race, clinical site, BMI, chronic disease, hip BMD, self-reported health, alcohol use, smoking status, education, physical activity and cognitive function
[62] Pham 2016	HGS	All	289 89	Cox proportional HR	1 SD decrease (95% CI)	Femoral neck BMD, age and prior fracture, history of fall and smoking
[67] Cawthon 2015	DXA Newman equation	Hip	207	Cox proportional HR	Change in C-statistic compared with adjusted model only (95% CI)	Age and BMD
[65] Wihlborg 2015	Balance GS QS	Hip Vertebral All	427	Cox proportional HR	1 SD decrease (95% CI)	History of fracture, BMI, smoking habits, bisphosphonate, vitamin D, glucocorticoid and alcohol use
[68] Yu 2014	DXA, GS	All	226	Cox proportional HR	Low AWG1 vs. rest (95% CI)	Age, education levels, socio-economic status ladder, 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 and hip BMD
[69] Ryg 2013	HGS, GS	Hip	216	Logistic regression	Q1 vs. Q4 (95% CI)	Body mass index, country and falls
[71] Edwards 2012	HGS	All	n.a.	Logistic regression	1-kg decrease (95% CI)	Age, height, weight-adjusted-for-height, social class, smoking status, alcohol consumption, activity score and dietary calcium
[70] Rouzi 2012	HGS, TUG, GS, 5×STS	All	148	Logistic regression	Q1 vs. Q4 (95% CI)	Univariate
[72] Cheung 2012	HGS	All (clinical)	43	Cox proportional HR	1 SD decrease (95% CI)	Age, sex, BMI, history of fall, diabetes, current smoking, current drinking, physical activity (exercise $>$ 1 h/week), presence of prevalent fracture and femoral neck BMD T-score
[73] Lang 2010	CT QS SPPB	Hip	63	Cox proportional HR	1 SD decrease (95% CI)	Age, height, BMI, total percentage of fat, race, gender, clinical site and BMD
[74] Sirola 2008	HGS	All	271	Cox proportional HR	Q1 vs. Q4 (95% CI)	Fracture history, body mass index, age, years since menopause, use of hormonal replacement therapy, alcohol intake, smoking, nutritional calcium intake and bone-affecting diseases/medications
[75] Kärkkäinen 2008	HGS QS OLST Squatt	Hip, Vertebral, Forearm	261	Cox proportional HR	10-Nm HGS, 10-kg decrease quadriceps, 10 s. OLST (95% CI)	Age, BMI, current smoking, years since menopause, years of hormonal therapy and history of fracture

Table 2 (continued)

Ref Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[76] Finigan 2008	HGS	Vertebral	99	Cox proportional HR	Q1 vs. Q2–Q4 (95% CI)	Univariate
[77] Cawthon 2008	HGS QS GS Narrow walk 5×STS	Hip	77	Cox proportional HR	1 SD decrease (95% CI)	Age, clinical centre, femoral neck bone mineral density, body mass index, history of heart attack and history of stroke
[78] Nguyen 2007	QS	Hip Clinical vertebral	221 105	Cox proportional HR	10-kg decrease (95% CI)	Univariate
[79] Sipilä 2006	Knee strength Elbow strength	Hip (fall related)	n.a.	Cox proportional HR	n.a. (95% CI)	Height and BMD
[80] Shigematsu 2006	QS Motor speed and reaction	All (fall related)	94	Cox proportional HR	T1 vs. T3 (95% CI)	Age, sex and BMD
[81] Samelson 2006	HGS	Vertebral	110 25	Logistic regression	T1 vs. T3 (95% CI)	Age, height, weight, prevalent vertebral fracture, smoking and alcohol consumption
[82] Pluijm 2006	HGS	All (fall related)	87	Cox proportional HR	Quintile 1 vs. rest (95% CI)	Univariate
[83] Robbins 2005	HGS QS GS 5×STS coordination	Hip	293	Cox proportional HR	1 SD decrease (95% CI)	Age only, but results also stratified by BMD class
[84] Nguyen 2005	QS	Hip	115	Cox proportional HR	1 SD decrease (95% CI)	Gender, age and femoral neck BMD
[85] Dixon 2005	HGS	Vertebral	34	Logistic regression	T1 vs. T3 (95% CI)	Age, BMI, lifetime activity score and current activity
[86] Albrand 2003	Left HGS GS Tandem balance Tandem walking speed Chair stand	All	81	Logistic regression	Group median difference (95% CI)	Univariate, except for grip strength
[87] Lee 2002	HGS Triceps strength 5×STS Static balance	Proximal humerus	165	Cox proportional HR	Low vs. high (95% CI)	Univariate
[88] Dargent-Molina 1999	GS	Hip	170	Cox proportional HR	1 SD decrease (95% CI)	Age, femoral BMD and calcaneal broadband ultrasound attenuation
[90] Dargent-Molina 1996	HGS GS Calf circumference Tandem walk	Hip	154	Cox proportional HR	Q1 vs. Q4 (95% CI)	Age, centre, calf circumference, gait speed, tandem walk score, visual acuity and BMD
[89] Nguyen 1996	QS	All	166	Cox proportional HR	1 SD decrease (95% CI)	BMD
[91] Cummings 1995	GS	Hip	192	Logistic regression	0.22 m/s in gait speed (95% CI)	Age and ability to raise from a chair
[93] Nevitt 1993	Triceps strength GS	Hip Wrist	424	Logistic regression	1 SD decrease (95% CI)	For the other covariates used as predictors, age and radius BMD
[92] Nguyen 1993	QS	All fragility fracture	104 38	Logistic regression	0.45 SD decrease (95% CI)	Univariate

Table 2 (continued)

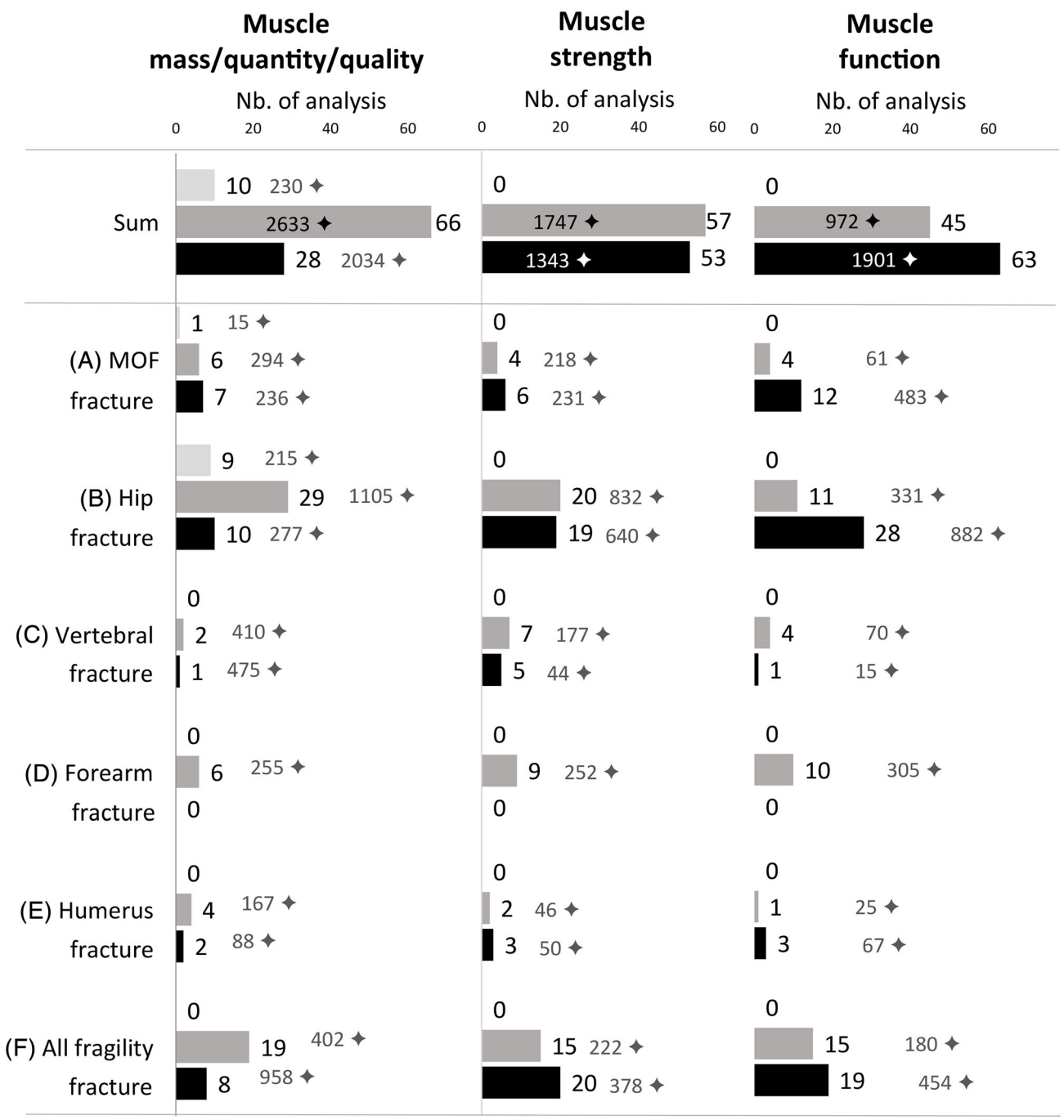
[Ref] Author Date	Predictors	Fragility fracture type	Nb. of fractures	Statistical test	Statistical comparison	Selected adjustments/covariables
[94] Kelsey 1992	Balance GS HGS Triceps strength	Humerus Distal forearm	250	Cox proportional HR	5-kg decrease for HGS and triceps, 0.5 m/s decrease for GS, 1 s for tandem stand (95% CI)	Univariate
[95] Wickham 1989	HGS	Hip	44	Logistic regression	T1 vs. T3 between hip fracture and match (95% CI)	BMI and smoking
[96] Farmer 1989	Arm muscle area	Hip	84	Cox proportional HR	Q1 vs. Q3 (95% CI)	Age, recreational activity, activity apart from recreation, menopausal status, smoking and calcium

Abbreviations: 5×STS, five-time sit-to-stand test; ALM, appendicular lean mass; BIA, body impedance analysis; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EWGSOP, European Working Group on Sarcopenia in Older People; FRAX®, Fracture Risk Assessment Tool; GS, gait speed; HGS, hand grip strength; HR, hazard ratio; IQR, interquartile range; IWG, International Working Group on Sarcopenia; MOF, major osteoporotic fracture (hip, spine, forearm or humerus); n.a., not applicable; OLST, one-leg standing test; pASMI, predicted appendicular skeletal muscle index; pQCT, peripheral quantitative CT; QS, quadriceps strength; SARC-F, sarcopenia questionnaire; SD, standard deviation; SPPB, Short Physical Performance Battery test; TBLM, total body lean mass; TGUG, timed get up and go test; US, ultrasound. *Source*: Characteristics extraction adapted from Peters et al.[97]

in total LM, total LM/height^2, regional LM, thigh muscle cross-sectional area and thigh muscle attenuation. A lower DXA-derived muscle mass parameter was associated with a higher, no and a lower fragility fracture risk in 15 (408 TPY), 46 (1609 TPY) and 8 (145 TPY) analyses, respectively. A lower ALM/height^2 was associated with a higher, no and a lower fragility fracture risk in 5 (158 TPY), 22 (997 TPY) and 1 (20 TPY) analyses, respectively. However, when considering MOF only, lower ALM/height^2 was associated with a higher and no fracture risk in three (147 TPY) and one (158 TPY) studies. Of the MOF subtypes, only the hip fractures were studied with DXA-derived parameters; namely, ALM/height^2 was negatively associated in one (20 TPY) study, and there was no association in eight (547 TPY) studies. No study analysed the association between lower ALM/height^2 and incident vertebral, forearm and humeral fracture. The bioelectrical impedance analysis (BIA) was not associated with vertebral fractures in one (15 TPY) analysis using skeletal muscle mass/height^2. The ultrasonography of the quadriceps (US) was not associated with fragility fractures in one (2 TPY) analysis using quadriceps quantity/quality. The parameters derived from the CT scan (lower thigh muscle cross-sectional area representing muscle mass and lower thigh muscle attenuation representing muscle quality) were positively and not associated with fractures in three (63 TPY) and five (105 TPY) analyses, respectively. Muscle mass can also be estimated using anthropometric prediction equations. The Lee equation includes height, weight, waist circumference, serum creatinine level and health behaviour factors.[39] The Heymsfield equation is based on the triceps skinfold thickness and midarm circumference.[96] A lower muscle mass derived from these two equations was positively and not associated with fractures in four (1381 TPY) and one (395 TPY) analyses, respectively. Using the creatine and creatinine-derived parameters (D3-creatine dilution test and estimated glomerular filtration rate [eGFR]), a lower parameter was associated with a higher, no and a lower fracture risk in 4 (170 TPY), 12 (507 TPY) and 2 (88 TPY) analyses, respectively.

Muscle strength

Muscle strength was mostly assessed using the maximum isometric contraction of a specific muscle group. No analysis showed a negative association between muscle strength and fractures. A lower muscle strength was positively associated with incident fragility fractures in 53 (1.3 TPY) analyses and not associated in 57 (1.7 TPY) analyses. Hand grip strength (HGS) was associated with a higher and no fracture risk in 37 (1181 TPY) and 39 (1312 TPY) analyses, respectively. A lower triceps strength was associated with a higher and no fracture risk in two (29 TPY) and three (46 TPY) analyses, respectively. A lower quadriceps



Legend: Lower, no difference, ■ higher risk for a lower/slower/deteriorated muscle assessment, ✦ Thousand person / year. All detailed results are also availible in Figure 3,4,5 - a,b,c,d,e and supplémentary f. MOF = Major osteoporotic fracture.

Figure 2 (A–F) Summary of the 322 analyses for each muscle assessment and each fracture types.

strength (QS) was associated with a higher and no fracture risk in 13 (131 TPY) and 15 (389 TPY) analyses, respectively. One study also analysed a lower arm and leg strength together and found a positive association (2 TPY) with fractures.

Muscle function

Muscle function refers to tests that assess specific tasks, mobility and balance. As for muscle strength, none showed a negative association between muscle function's assessment

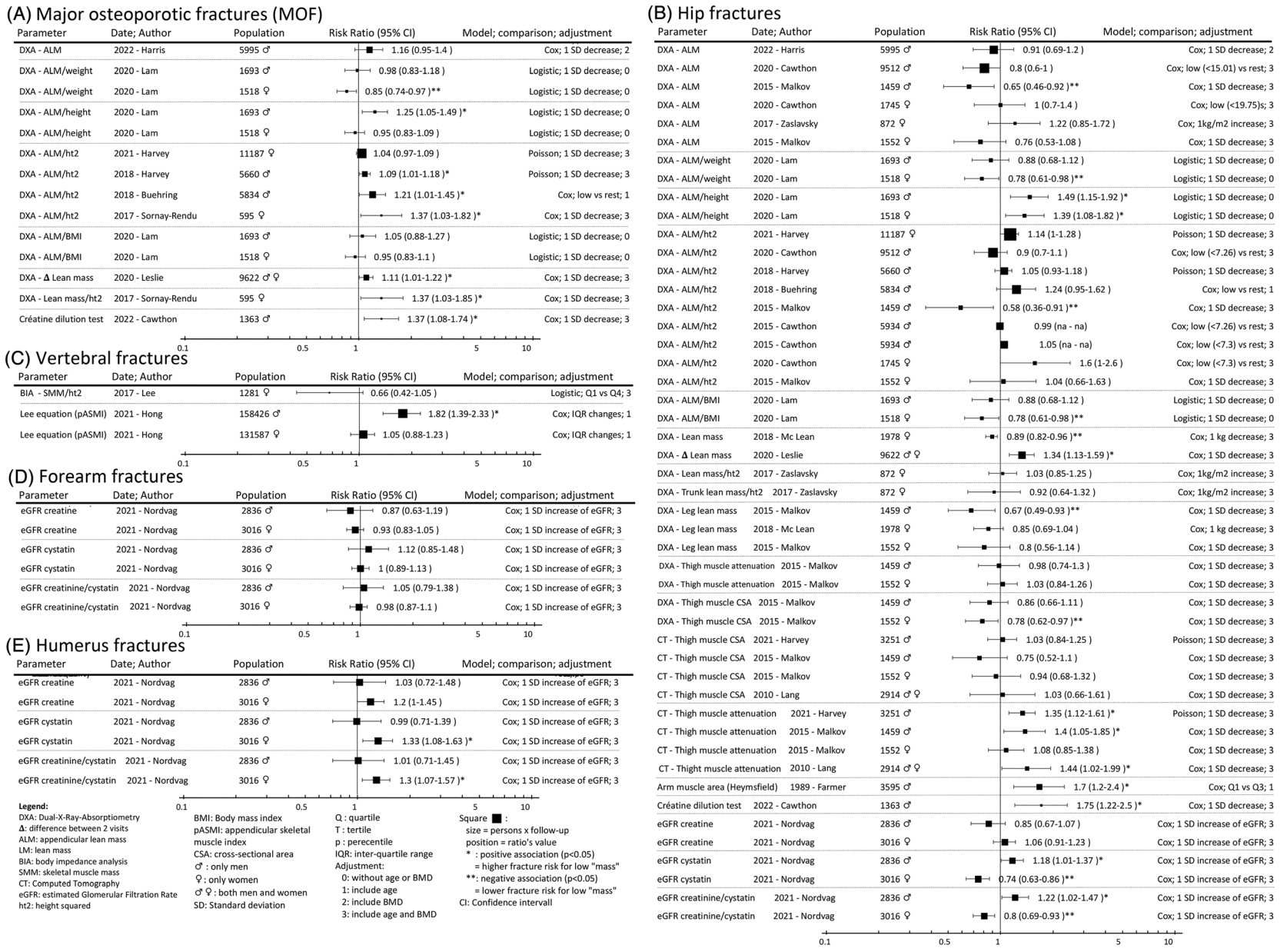


Figure 3 (A–E) Muscle mass/quantity/quality parameters and risk of incident fragility fractures.

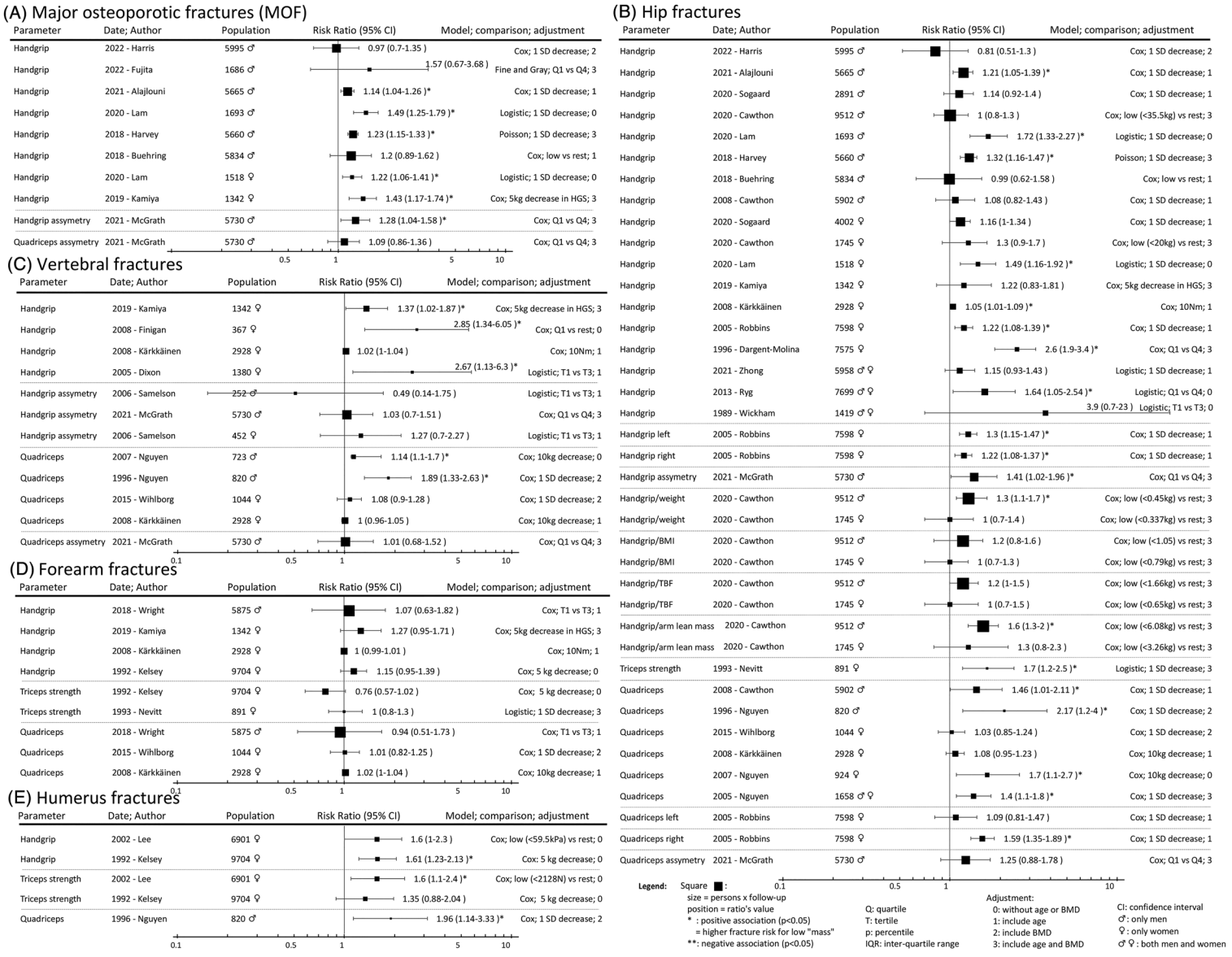


Figure 4 (A–E) Muscle strength parameters and risk of incident fragility fractures.

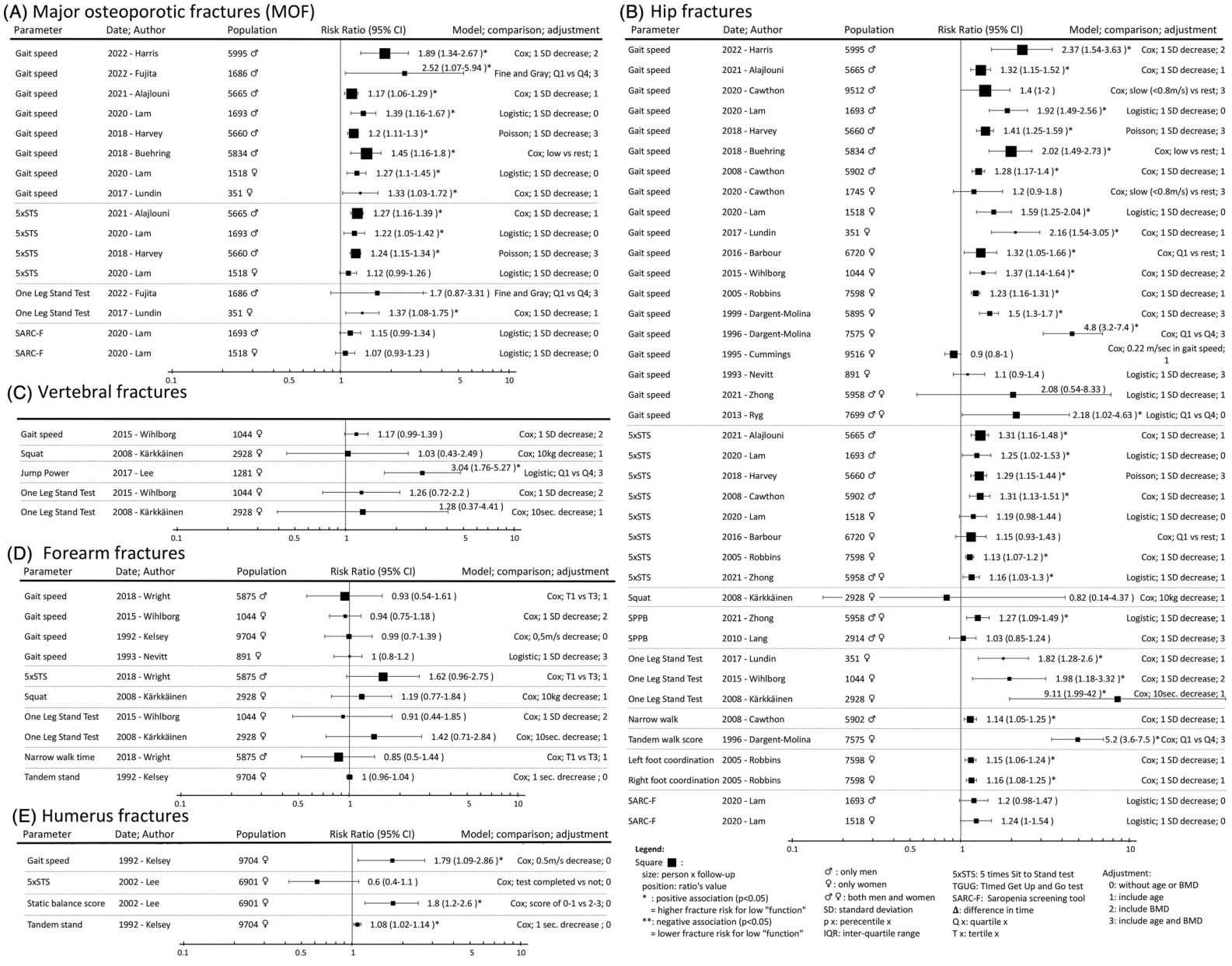


Figure 5 (A–E) Muscle function parameters and risk of incident fragility fractures.

and fractures. A lower muscle function was positively associated with incident fragility fracture in 63 (1901 TPY) analyses, not associated in 45 (972 TPY) analyses and negatively associated in 0 analyses. Gait speed (GS) refers to the usual walking speed over a distance of 4–6 m. A slower GS or loss of GS over time was associated with a higher and no fracture risk in 32 (1121 TPY) and 17 (391 TPY) analyses, respectively; it was positively associated with MOF in all the eight concerned studies (333 TPY).[31,32,41,44,54,55,58] The different walking and chair rising tests were associated with a higher and no fracture risk in 19 (572 TPY) and 12 (299 TPY) analyses, respectively. They included five assessments: timed get up and go test (TGUG), change in TGUG, five-time sit-to-stand test (5×STS), Δ 5×STS and squat/jump. Balance tests were associated with a higher and no fracture risk in 11 (184 TPY) and 10 (196 TPY) analyses, respectively. These included three different assessments: one-leg standing test (OLST), narrow/tandem walk and single-foot coordination. Multi-item tests were associated with a higher and no fracture risk in one (24 TPY) and six (86 TPY) analyses, including three assessments: Short Physical Performance Battery (SPPB) test, sarcopenia screening questionnaire (SARC-F) and a speed/reaction test.

Discussion

In this scoping review, we investigated the association between 60 different muscle parameters with incident fractures risk in 322 separate analyses within 67 studies. Overall, low muscle mass was poorly/not associated with fracture risk, while low muscle strength and low muscle function were associated with higher risk of fracture. The results showed heterogeneity between the studies, in terms of studies' populations, measurement methods and statistical analysis. Our conclusion is a summary of the observed trends in this review and is not comparable to a meta-analysis.

Muscle mass, quantity and quality

Muscle mass, quantity and quality are objective and reproducible assessments of muscle health.[98] The accuracy and the reliability of these assessments mostly depend on the technique used, for which the time available, the radiation dose, the costs and the patient involvement must also be considered. The gold standards are magnetic resonance imaging (MRI) and CT scan, but DXA and BIA remain the most widely used tools due to their easier accessibility.[99–101] In this review, we did not find any studies using MRI. DXA and BIA were more studied as part of the diagnostic criteria of most sarcopenia definitions. The muscle quantity can be estimated from its volume using the muscle length and cross-sectional area. As these two properties are also important components of muscle strength,[102,103] the hypothesis is that a low muscle quantity leads to weaker muscle (dynapaenia), which then lead to disbalance and falls.[104] At the same time, we know that a tailored exercise programme reduces the risk of fall-related fragility fractures.[105] However, the relationship between low muscle mass and fractures has been repeatedly questioned.[12,23,45] The results of our scoping review also suggest that a higher muscle mass, as assessed by different parameters, has little protective effect on the occurrence of fragility fractures. Indeed, seven analyses (within three studies) showed even opposite results with an increased risk of fragility fractures with higher muscle mass[44,52,66]: six (110 TPY) analyses for hip fractures and one (15 TPY) analysis for MOF. Interestingly, the analyses suggest that LM and ALM corrected for weight or BMI are mostly negatively or not associated with fragility fracture, whereas the same parameters corrected for height or height^2 are mostly positively or not associated with fractures (*Figure 3*).[40,44,45,54–57,66,67] The use of LM indexes in fracture prediction models is complex because anthropometric measures are correlated with LM and are associated with fractures. The literature describes weight as a protective factor, height as a risk factor and BMI as having a U-shaped association with fragility fractures.[106] The stratification of LM analyses for body size or shape would enable a better estimation of its association with fragility fracture. Note that these considerations differ between the fragility fracture types and the sex (*Figure 3A–E*). We also know that measures of LM include water, joints and ligaments[107] and may not be specific enough of muscle mass.

Muscle density is a more recent concept. It was first used in CT scans by measuring the X-ray absorption in the different muscle voxels (3D pixels) but is now also available in DXA.[66] It is used as a proxy for intramuscular fat infiltration (as fat absorbs less X-rays than bone or muscle) and has been associated with fragility fractures in this review.[37,66,73] The bottleneck to more widespread use of CT scanning, including in larger studies, is the increased radiation dose and costs.

Muscle mass/quantity has also been investigated using biological tests, with promising results in fracture prediction. Blood creatine, a breakdown product of muscle, is associated with functional and clinical outcomes.[108] Cystatin or its ratio showed a positive association in women with low eGFR and humerus fractures, but it showed conflicting results in men.[36] Using the D3-creatine dilution test, Cawthon et al. found a positive association between low eGFR and hip fractures and MOF.[33] A review summarizes the necessary assumptions of the creatine dilution test, including individual variation (diet, age, activity level and disease state) that lead to underestimation or overestimation of the measurement.[108] As a result, the clinical implementation of blood tests should be further investigated.

Newer methods are being developed such as ultrasound (e.g., with muscle thickness, cross-sectional area, pennation angle and echogenicity)[109] or image analysis (classification, segmentation, texture/pattern analysis and radiomics) using

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artificial intelligence (AI).[110,111] AI models could help us to extract the full information from the DXA scans (or other imaging modalities) and potentially measure new markers of muscle health. Pickhardt et al. analysed low-dose CT scans using deep learning to predict lumbar muscle myosteatosis and cross-sectional area.[112] The prediction of hip fracture at 5 years was similar between their model (area under the curve [AUC] 0.709, 95% confidence interval [CI] 0.639–0.778) and the FRAX® (AUC 0.708, 95% CI 0.629–0.787).[112] AI seems to be a suitable tool to analyse DXA body composition images and to search for unanticipated complex interactions between the available parameters.

The role of muscle mass in fragility fracture remains unclear. The assessment of muscle mass/quantity through the D3-creatine dilution tests and muscle density assessment by DXA and CT imaging seem promising and could be object of further research. Furthermore, AI will undoubtedly influence musculoskeletal imaging and provide novel muscle mass assessments.

Muscle strength

Muscle strength is highly correlated with muscle quantity (length and cross-sectional area), but with greater variability,[102] and is influenced by the conservation of peripheral and central neurological structures.[103] Fifty per cent of the total body muscle mass lies in the lower body, while the upper body represents only 25%.[113] Even if the quadriceps and psoas muscles make standing and walking possible, HGS has been shown to correlate with leg strength and is similarly predictive of low GS.[114] From a clinical perspective, HGS is the most widely used test to assess muscle strength due to its low cost, accessibility, widespread use and reliability, whereas quadriceps testing is more complex and requires more equipment.[45] This is probably the reason why fewer studies analysed QS. In this review, both lower HGS and lower QS were significantly associated with higher fracture risk in 37 and 13 (131 TPY) studies, respectively; 41 analyses showed no association between HGS and fracture risk and 15 (389 TPY) analyses between lower QS and fracture risk.

Muscle strength may be useful in predicting fracture risk using grip strength as a practical and reliable proxy of muscle strength.

Muscle function

Muscle function is the most multifactorial determinant of muscle health. It correlates with both muscle mass and strength and is defined as the ability of the muscle to perform a certain task or movement. The assessment of muscle function, as for muscle strength, also depends on peripheral and central neurological structures. In addition, muscle function is closely linked to the brain (mostly through the cerebellum, motor, pre-motor and supplementary motor cortex) when testing balance, coordination or complex tasks. The reasons for variation in measures of muscle function are similar to those for strength testing and are mainly analytical and/or methodological variations. Based on the observations of this review, GS shows a robust association with fracture risk, as all studies showed a significant association between slow GS and higher risk of MOF. The 5×STS was the second most commonly used muscle function test, with comparable results to QS. The 5×STS is a proxy of the thigh strength in addition to coordination ability. These observations emphasize the importance of assessing muscle function during a clinical consultation. Indeed, physicians are trained to assess the risk of falling (and therefore, to some extent, muscle function) by observing the patient walking around the examination room, sitting in the chair, changing clothes and so forth. For example, the chair stand tests (including 5×STS), the timed up and go test (TUGT), the SPPB and the tandem walk test have been validated to assess the mobility status and fall risk in older adults.[115]

Various muscle functional tests are available and provide an objective assessment of the patient muscle status, and they give an additional information on the patient's risk of fragility fracture. They include more variability than muscle strength or mass assessment but stay reliable overall. These tests were not designed to predict the fracture risk, but as they are associated with multiple medical conditions including neurological and musculoskeletal diseases, their association with fracture is also multifactorial.

Clinical implications

In the field of sarcopenia, the association between muscle parameters and fragility fractures remains subject to debate. In the SDOC sarcopenia definition (2020), the authors argue against the use of muscle mass in further definitions because of insufficient evidence of its association with sarcopenia outcomes (including fractures) and the cost of DXA.[45] Our scoping review similarly suggests that low muscle mass, as currently defined, is not robustly associated with fragility fractures and that an adjustment or stratification for body size is necessary. As we analysed each muscle health component separately and did not assess the other sarcopenia endpoints, our study does not allow us to directly challenge the composite definitions of sarcopenia. On the other hand, the observed association of GS and HGS with fragility fractures supports their use in the diagnostic workflow of current sarcopenia definitions. These muscle parameters provide objective measures of the muscle health and insights on its association with fragility fractures. Ideally, a test or score would be developed to specifically identify the fracture risk associated with sarcopenia, at best independently from the risk of fall.

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In the field of osteoporosis, the relationship between bone and muscle has been studied from various angles. Falls are important risk factors for fracture occurrence. They often, but not always, precede the fracture.[9] In the causal hypothesis linking muscle mass to fragility fractures, falls are more likely to be a mediator in the equation, involving both dependent and independent pathways, rather than just an intermediate factor. In this scoping review, only few studies demonstrated that the relation between muscle mass,[33,37,55,57] strength[69] and function[31,32,34,55,64,69] with incident fracture was positive and independent from falls. At the cellular level, a cross-talk between muscle and bone has been discussed in studies about osteo-sarcopenia.[13] At the organ level, the bone mechanostat hypothesis explains that the properties of load-bearing bones are primarily influenced by their functions, rather than the influence of load and gravitational forces.[116] Our study could support this hypothesis considering that muscle function and strength have an additive discriminative value in fragility fractures prediction models, assuming that bone properties are related in the same way. However, muscle mass and quantity, as it currently stands, do not appear to have an independent effect on fracture susceptibility. Heymsfield et al. insisted on the importance of muscle 'form' (size and shape) and not only muscle function in the pathophysiology of adverse events (cf. OFF hypothesis: Outcome follow function, follow form), based on the axiom that without the physical form of the muscle, there would be no function.[117] The overall lack of association between muscle mass/quantity and fractures that we highlight in this review does not discredit its importance in the pathophysiology of osteoporosis and sarcopenia. Further research is needed on muscle mass, quantity and quality in the prediction of fracture risk, including a judicious use of anthropometric measures. The D3-creatine dilution test and the CT-scan measures showed promising results, while LM, its indexes and the new statistical approaches using AI need to be further investigated.

Muscle health parameters are important in the prevention and diagnostic of sarcopenia and in the assessment of osteoporotic patients. This scoping review highlights the benefits and the gaps of muscle health tests in clinical setting and in community-dwelling older adults.

Strengths and limitations

This study has some limitations. First, a common limitation to scoping reviews is the publication bias. Positive studies are more likely to be published, whereas negative studies may be discontinued. However, most of the results analysed are inconclusive (no association) and some are even negative and contra-intuitive (e.g., the positive association between muscle mass and fragility fracture risk), suggesting that the data observed and discussed here are undistorted. Second, the overall quality and risk of bias of the included studies were not systematically assessed. However, this is not a requirement for conducting a scoping review. As shown in *Tables 1* and *2*, the majority of the included studies have large sample sizes and long follow-up periods and come from recognized and well-conducted national or international cohorts. Finally, although not related to the scoping review itself, the included studies have some limitations that weaken their interpretation, such as the consideration of non-MOF fractures as fragility fractures (*Figures S3f–S5f*); the lack of a clear fragility fracture definition[30,34,41,69,71,78,83,88,90]; and the lack of systematic radiographic assessment for fracture detection, as some incident fractures were only collected based on questionnaires and general practitioners.

To the best of our knowledge, this is the first review, based on a systematic search, that thoroughly reviews studies that investigated the association of incident fracture risk with muscle mass/quantity/quality, strength and/or functional parameters. The rigorous systematic search, under the supervision of medical library experts, adds value to the current study. The inclusion of only prospective studies is a major strength, as prospective studies have a temporal framework to assess causality (outcome occurring after exposure), which positions them as strong scientific evidence. In addition, most of the analyses were performed with the muscle parameter as a continuous variable, assuming that the risk is proportional to the parameter in question. Some studies had previously categorized the variables using percentiles or a specific value (cf. *Figures 3–5*), which lost statistical information but made it easier to use in clinical practice. Furthermore, following the PRISMA checklist for reporting (cf. supporting information) and the JBI methodology for writing improves the transparency, reproducibility and, ultimately, the overall quality of this review. Moreover, we visualize the trend of associations between muscle parameters and fracture risk using adapted forest plots. Finally, our review highlights muscle parameters that could be further analysed in a meta-analysis.

Conclusions

This scoping review gives a broad overview of the gaps and evidences in the relationship between muscle parameters and fragility fractures. Poorer muscle function followed by lower muscle strength were the parameters mostly related to a higher risk of incident fragility fractures. For daily clinical practice, this review suggests that measures of HGS and GS are the most useful methods to assess muscle-dependent fracture risk. This supports their use in the evaluation of sarcopenia. This review also confirms that muscle mass, as currently defined, is a poor independent predictor of fragility fracture. For future research and development of fragility

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fracture prediction models, it will be necessary to determine whether muscle-associated fracture risk is fully independent from other risk factors. In addition, further investigation of DXA images, including body composition, using AI methods may reveal new complex interactions between muscle tissue and fragility fractures.

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Conflict of interest statement

Colin Vendrami, Enisa Shevroja, Guillaume Gatineau, Jolanda Elmers, Elena Gonzalez Rodriguez, Jean-Yves Reginster, Nicholas C. Harvey, Olivier Lamy and Didier Hans declare that they have no conflict of interest related to this manuscript.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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