RESEARCH ARTICLE

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Association Between Sarcopenia and Fracture Risk in a Population From the UK Biobank Database

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ABSTRACT

Studies on the fracture risk in presarcopenic and sarcopenic patients report contradictory results. The objective was to assess whether presarcopenia and sarcopenia are associated with an increase in fracture risk. We conducted a retrospective study using the UK Biobank cohort and the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) criteria. Muscle strength was evaluated using hand-grip strength (HGS) and muscle mass using the skeletal muscle index (SMI; from bioimpedance analysis). Presarcopenia was defined through the two definitions available in the literature, as low HGS with normal SMI and as normal HGS with low SMI, and sarcopenia as low HGS and low SMI. Fracture events were recorded as "fracture" (location compatible with an osteoporotic origin) and "major osteoporotic fracture" (MOF), as listed in the FRAX tool. Associations were assessed using Cox proportional hazards models, adjusted for sarcopenia and osteoporosis risk factors. Adjusted hazard ratios (HR_a) and their 95% confidence intervals (CI) were reported. A total of 387,025 participants (women 54.4%; median age 58.0 years; interquartile range [IQR] 51.0–63.0 years) were included. At baseline, there were 18,257 (4.7%) presarcopenic participants—subgroup 1 (low HGS only), 7940 (2.1%) presarcopenic participants—subgroup 2 (low SMI only), and 1124 (0.3%) sarcopenic participants. Over a median follow-up of 12.0 years (IQR 11.4–12.6 years), 18,300 (4.7%) participants were diagnosed with at least one incident fracture. Presarcopenic (subgroups 1 and 2) and sarcopenic status were significantly associated with a higher risk of fracture (respectively adjusted HRs: HR = 1.26 [1.19–1.33], HR = 1.20 [1.11–1.30], HR = 1.30 [1.08–1.56]) and with a higher risk of MOF (respectively adjusted HRs: HR = 1.30 [1.21–1.40], HR = 1.19 [1.08–1.72], HR = 1.18 [0.93–1.49]). In a middle-aged population, the fracture and MOF risks were higher in both presarcopenic and sarcopenic participants compared with nonsarcopenic participants. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: SARCOPENIA; MUSCLE STRENGTH; MUSCLE MASS; FRACTURES; UK BIOBANK

Introduction

Sarcopenia has recently been redefined as a progressive loss of muscle strength and muscle mass, associated with adverse consequences for health.[1,2] Based on the definition published by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2),[1] its prevalence is currently around 10% in older adults, and it constitutes a heavy burden for public health systems.[3] Its late recognition as a disease in 2016 by the World Health Organization (WHO) (International Classification of Diseases, ICD-10-CM: M62.84)[4] and a lack of international consensus partly explain the current state of knowledge. Indeed, studies on sarcopenia are not easily comparable[5] as national recommendations use different cut-off points for screening and diagnostic tests.[6]

Over the last 10 years, several scientific societies have published guidelines on defining sarcopenia.[1-3] The EWGSOP2 guidelines[1] are currently the most widely used worldwide and incorporate three muscle parameters (muscle strength, muscle mass, and physical performance tests) in a decision tree.[1]

Although muscle mass can be measured using different methods, the most commonly used method is dual-energy X-ray absorptiometry (DXA). When DXA assessment is impossible, bioelectrical impedance analysis (BIA) can be used to

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calculate an approximation of skeletal muscle mass (SMM) (Sergi or Janssen equation[7,8]) and then the skeletal muscle index (SMI; kg/height(m)^2).

The EWGSOP2[1] recommendations define three thresholds, namely (i) probable sarcopenia, defined as low muscle strength only; (ii) sarcopenia, defined as low muscle strength and muscle mass; and (iii) severe sarcopenia, defined as low muscle strength, muscle mass, and physical performance.

A presarcopenia stage is also used, with various definitions in the literature, including "low muscle mass without impact on muscle strength or physical performance"[3,5] and "low muscle strength with normal muscle mass".[9]

Sarcopenia is directly responsible for negative outcomes. Some of these have been proven (eg, the mortality outcome), whereas others are more debated (eg, the fracture outcome), as reported in the meta-analysis conducted by Beaudart and colleagues,[10] which was based solely on studies using the EWGSOP2 recommendations.[1]

The age-related decline in muscle mass and function also affects mobility, bone mass, and bone microarchitecture.[11] As muscle and bone are highly interconnected, when the aging process affects one of the two, the functionality of the other may be compromised. Consequently, it is widely believed that sarcopenia may increase fracture risk.[12]

Three recent prospective studies[13-15] have assessed fracture risk in sarcopenic patients using the EWGSOP2[1] criteria. In the first study, conducted in 2015 by Cawthon and colleagues,[13] in male older adults aged 65 years and older who answered mailed questionnaires on falls and fractures three times per year, adjusted for femoral neck bone mineral density (BMD), the authors found no evidence of an increase in fracture risk at 9 years. In another study conducted in 2015, in osteosarcopenic male and female older adults aged 65 years and older (low appendicular lean mass plus slowness or weakness and low BMD according to the WHO definition, that is, T-score < -1.0), Chalhoub and colleagues[14] reported an increase in fracture risk at 9 years in women and men with low BMD and sarcopenia, and with low BMD alone, but not with sarcopenia alone, compared with those with normal BMD and no sarcopenia. In the third study, conducted by Schaap and colleagues[15] in 2018, in male and female older adults aged 65 years and older, the authors also failed to find an increase in fracture risk at 10 years in sarcopenic patients. However, in that study, no adjustment was made for BMD values.

In a study on the UK Biobank cohort, also using EWGSOP2 criteria, Petermann-Rocha and colleagues[9] attempted to clarify the association between sarcopenia and incident osteoporosis (defined using ICD-10 codes M80, M81, and M82). In that study, the authors reported that presarcopenia (defined as low hand-grip strength [HGS] and normal SMI) in men and sarcopenia in women were associated with a higher risk of osteoporosis, even after adjusting for a wide range of potential confounding factors.[9]

Finally, sarcopenic people can be divided in subgroups according to their comorbidities, such as obesity, for example. Sarcopenic obesity (SO) is commonly defined as the coexistence of obesity and sarcopenia,[1] but its diagnostic criteria have recently been debated.[16,17] Although it is already known that obesity exacerbates sarcopenia—it increases fat infiltration in muscle, lowers physical function, and increases the risk of mortality[1]—it is still not known whether fracture risk differs in patients with sarcopenic obesity compared with nonobese patients with sarcopenia.

To date, few studies are available on fracture risk in patients with sarcopenia. Among them, comparisons are difficult because they used different diagnostic criteria for sarcopenia, included heterogeneous populations, focused on different outcomes, and not all of them were adjusted for bone density (eg, BMD by DXA or heel quantitative ultrasound [QUS]). As a result, independently of BMD, fracture risk is not clearly identified in presarcopenic and sarcopenic people or in subgroups such as the sarcopenic obese. The main goal of this study was to determine whether sarcopenia is independently associated with an increase in fracture risk in a middle-aged and older, community-dwelling population of women and men from the UK Biobank prospective cohort.

Subjects and Methods

Participants and ethical approval

We conducted a prospective analysis on the UK Biobank database, using outcome data obtained from National Health Service (NHS) records. Approximately 500,000 British community-dwelling volunteers provided their electronic consent for the baseline assessments. Consent was also obtained for follow-up. Details of the UK Biobank methodology have been published previously,[18] and the protocol is publicly available.[19]

Data collection

Data were collected at four measurement intervals: interval 0 (initial assessment visit, between 2006 and 2010), interval 1 (2012–2013), interval 2 (2014 and later), and interval 3 (2019 and later, still ongoing). Participants completed a series of touchscreen computer-based questionnaires, followed by a face-to-face interview.[19] All assessment were performed by trained data collectors, who followed standardized protocols using a Seca (Hamburg, Germany) stadiometer for height measurements, the Tanita (Tokyo, Japan) BC 418ma body fat analyzer for weight and BIA measurements, the Jamar hydraulic hand dynamometer (model J00105) for HGS measurements, and the Sahara clinical sonometer (Hologic, Marlborough, MA, USA) for heel QUS measurements (broadband ultrasound attenuation [BUA] in db/MHz, and speed of sound [SOS] in m/s).

Inclusion and exclusion criteria

Because of the ethnic-specific Janssen equation we used (see below), our study included only White participants. Participants were excluded if (i) they withdrew their consent between data acquisition and the end of the study; (ii) HGS values were unavailable or null; (iii) body composition values (BIA) were unavailable or null; and (iv) ankle spacing width (ASW) and heel BUA values were unavailable or null. Participants with missing values for nonessential covariates were included in the sensitivity analyses.

Main exposure variable

The main exposure variable was participants' sarcopenic status. To define sarcopenic status in accordance with EWGSOP2 recommendations, we needed the HGS and SMI values, which were obtained by feature extraction.

For the HGS value, we used the highest of the right- and left-hand scores.[20] HGS values were considered pathological if they were less than 16 kg in women and 27 kg in men.[1]

The SMI value was obtained in two steps. Using BIA data, we first calculated the whole-body SMM using the Janssen equation.[8] We then calculated the SMI using the following

formula:[1,9,21,22] SMI = SMM/height^2, where SMM is expressed in kg, and height in meters. SMI values were considered pathological if they were less than 5.5 kg/m^2 in women and 7.0 kg/m^2 in men.[1]

We defined four main subgroups according to EWGSOP2 sarcopenia cut-offs[1] (Fig. 1):

- Sarcopenic participants (low HGS, low SMI);
- Presarcopenic participants: subgroup 1 (low HGS, normal SMI), subgroup 2 (normal HGS, low SMI), according to the definitions currently available;[3,5,9]
- Nonsarcopenic participants (normal HGS, normal SMI), referred to as the NonSarc group.

For the secondary analysis on sarcopenic obesity, as sarcopenic participants were few, presarcopenic (subgroups 1 and 2) and sarcopenic participants were merged to form a single group, referred to as the PreSarc group, and also split into "obese" (BMI ≥30 kg/m^2 [23]) and "nonobese" (BMI <30 kg/m^2[23]) (Fig. 1). As such, the following subgroups were available: PreSarcObese, PreSarcNonObese, NonSarcObese, and NonSarcNonObese.

There was no need to match the nonsarcopenic, presarcopenic (subgroups 1 and 2) and sarcopenic subgroups according to inclusion date, as all participants were ambulatory and inclusion was based on voluntary participation.

Covariates

All covariates were collected at baseline. The directly available covariates, which were sometimes categorized, were sex, age at recruitment, Townsend deprivation index, serum 25-OH vitamin D and calcium levels, vitamin D and calcium supplementation, smoking and alcohol status, physical activity level

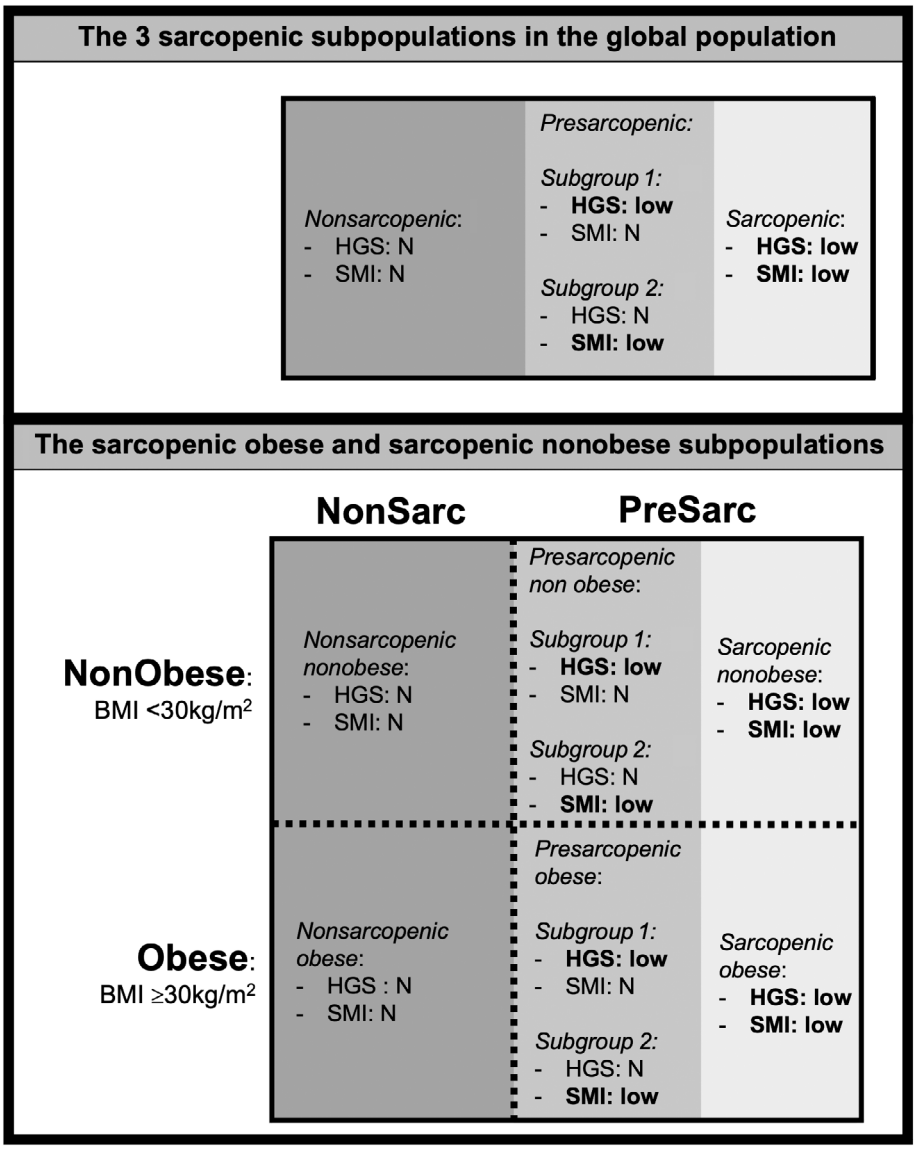


Fig. 1. Subpopulation definitions. HGS = hand-grip strength; N = normal; NonSarc = nonsarcopenic participants; PreSarc = presarcopenic (subgroups 1 and 2) and sarcopenic participants; SMI = skeletal muscle index.

(in MET-h/wk), history of fracture in the last 5 years, history of fall in the last year, daily dietary energy intake, daily dietary calcium and protein intake, daily processed meat and beef intake, bilateral oophorectomy history, hormone-replacement therapy (HRT) use, and loss to follow-up.

Some covariates were obtained by feature extraction, meaning that they were created from directly available data. Those covariates were BMI (calculated using the directly available values from the directly available "height" and "weight" values), heel BUA and ASW (for each, the mean of the right and left directly available values or the right or left value by default when only one was available), and history of corticosteroid intake (recoded as a binary value, from the "treatment/medication code" directly available data). Medical histories relating to menopausal status, history of diabetes, morbidity score (43 long-term conditions[9]), and history of malignancy or bone diseases were compiled from ICD-9 and ICD-10 directly available data, self-reported directly available data, and OPCS-3 and OPCS-4 directly available data (Classification of Interventions and Procedures 3 and 4, respectively).

Outcomes

A fracture event was defined as a fracture occurring after inclusion, at a location compatible with an osteoporotic origin, that is, all fracture locations except craniofacial, cervical spine, hand, finger, foot, and toe. A major osteoporotic fracture (MOF) event was defined as a fracture occurring at a location compatible with a MOF (ie, clinical spine, proximal femur, proximal humerus. and wrist). Fracture and MOF event data were collected from ICD-10 data and self-reported data (Supplemental Table S1 for code selection). No ICD-9 data were available for fracture or MOF events occurring after inclusion.

Study design

We documented baseline characteristics in the global population and in some subgroups of interest.

We first compared fracture incidence in our four main subgroups (nonsarcopenic participants, versus presarcopenic participants—subgroup 1 versus presarcopenic participants, subgroup 2 versus sarcopenic participants).

We then compared:

- MOF incidence again in our four main subgroups;
- fracture incidence in NonSarcNonObese versus others (Fig. 1).

Finally, for the main objective only, we performed sensitivity analyses:

- in women only, to add adjusting criteria (menopausal status, bilateral oophorectomy, HRT use);
- after excluding participants with a history of (i) bone disease other than osteoporosis (eg, Paget's disease, multiple myeloma) and/or (ii) any cancer history.

When the proportion of missing values was ≥1.5% in the global population, we created a "not available" category. When the proportion of missing values was <1.5%, and/or if data were obviously not missing at random, missing data were imputed based on expert opinion. All reported counts (Table 1 and Supplemental Table S2) are those after imputation.

Participants were followed up until the first fracture event. When no fracture was reported, follow-up was censored at the date of death, the lost-to-follow-up date, or the data extraction date (3/25/2021).

We adjusted the final model by adding an increasing number of covariates, as follows:

- Level 1 (minimally adjusted): sociodemographic covariates (sex, age at recruitment, Townsend deprivation index), BMI, heel QUS-related data (heel BUA and ASW);
- Level 2 (maximally adjusted): same as level 1 but further adjusted for serum vitamin D level, vitamin D and/or calcium supplementation, smoking and alcohol status, history of corticosteroids intake, history of diabetes, morbidity score, incident fracture in the last 5 years, and fall in the last year. Menopausal status, history of bilateral oophorectomy, and history of HRT use were added to level 2 only in the sensitivity analysis in women.

No stepwise procedures were performed as adjusting covariates are scientifically recognized.

Statistical analysis

For univariate analyses, continuous variables were expressed as mean (and standard deviation, [SD]) or as median (and interquartile range [IQR]). Categorical variables were expressed as count (and percentage) for each modality. Bivariate analyses were performed using Student's *t* tests (or Mann–Whitney–Wilcoxon tests) to compare means, and chi-square tests (or Fisher's exact test) to test for independence among qualitative variables. Survival analyses were performed using Cox models. Nonadjusted hazard ratios (HR_{na}) and adjusted hazard ratios (HR_a), along with their 95% confidence intervals (95% CI), are reported. HR_{a1} denotes HR_a derived from minimally adjusted models, whereas HR_{a2} denotes HR_a derived from maximally adjusted models. Quantitative variables were always discretized. The proportional hazards assumption was checked using the Schoenfeld residuals and graphics method.

Statistical analyses were performed using R (version 4.1.2) and RStudio (version 2021.09.0 + 351), and the knitr, dplyr, lubridate, compareGroups, and survival packages. Any p values <0.05 were considered statistically significant. All tests were two-sided. When appropriate, 95% CI were computed.

Results

Study flow chart

After applying the exclusion criteria, our study included 387,025 participants, of which 359,705 (92.9%) were nonsarcopenic participants, 18,257 (4.7%) presarcopenic participants—subgroup 1, 7940 (2.1%) presarcopenic participants—subgroup 2, and 1124 (0.3%) sarcopenic participants. Median follow-up was 12.0 (IQR 11.4–12.6) years (Fig. 2).

Baseline characteristics

Of the included participants, 210,390 (54.4%) were women (Table 1). The median age was 58.0 (51.0–63.0) years, and the median BMI 26.7 (24.2–29.9) kg/m^2. Compared with the nonsarcopenic participants, the presarcopenic participants (subgroups 1 and 2) and the sarcopenic participants were globally older (median age, respectively: 62.0 versus 58.0 years, 63.0 versus 58.0 years, 64.0 versus 58.0 years). Presarcopenic subgroup 2 and sarcopenic participants had a lower BMI (median BMI, respectively: 22.4 versus 26.7 kg/m^2, 22.8 versus 26.7 kg/m^2).

Table 1. Baseline Characteristics in the Global Population

	Global population (n = 387,025)	Nonsarcopenics (n = 359,704, 92.9%)	Presarcopenics—subgroup 1 (n = 18.257, 4.7%)	Presarcopenics—subgroup 2 (n = 7940, 2.1%)	Sarcopenics (n = 1124, 0.3%)
Women, *n* (%)	210,390 (54.4%)	190.492 (53.0%)	11,191 (61.3%)	7653 (96.4%)	1054 (93.8%)
Age at recruitment (years), median [IQR]	58.0 [51.0; 63.0]	58.0 [50.0; 63.0]	62.0 [56.0; 66.0]	63.0 [58.0; 66.0]	64.0 [60.0; 67.0]
BMI (kg/m^2), median [IQR]	26.7 [24.2; 29.9]	26.8 [24.3; 29.9]	27.6 [24.8; 31.3]	22.4 [20.6; 24.4]	22.8 [20.8; 24.9]
BMI category,[23] (kg/m^2), *n* (%)					
Normal weight	126,062 (32.6%)	114,508 (31.8%)	4814 (26.4%)	5967 (75.2%)	773 (68.8%)
Malnutrition and thinness	1867 (0.5%)	1224 (0.4%)	103 (0.6%)	457 (5.8%)	83 (7.4%)
Overweight	165,508 (42.8%)	156,428 (43.5%)	7402 (40.5%)	1422 (17.8%)	256 (22.8%)
Class I and II obesity	86,487 (22.3%)	81,048 (22.5%)	5336 (29.2%)	91 (1.1%)	12 (1.0%)
Class III obesity	7101 (1.8%)	6496 (1.8%)	602 (3.3%)	3 (0.1%)	0 (0.0%)
Townsend deprivation index, *n* (%)					
Least disadvantaged	120,291 (31.1%)	112,985 (31.4%)	4392 (24.1%)	2613 (32.9%)	301 (26.8%)
Intermediate	131,522 (34.0%)	122,636 (34.1%)	5702 (31.2%)	2797 (35.2%)	387 (34.4%)
Most disadvantaged	135,212 (34.9%)	124,083 (34.5%)	8163 (44.7%)	2530 (31.9%)	436 (38.8%)
Smoking status, *n* (%)					
Never	212,089 (54.8%)	197,019 (54.8%)	9718 (53.2%)	4693 (59.1%)	659 (58.6%)
Former	136,276 (35.2%)	126,864 (35.3%)	6636 (36.3%)	2437 (30.7%)	339 (30.2%)
Current	38,660 (10.0%)	35,821 (9.9%)	1903 (10.4%)	810 (10.2%)	126 (11.2%)
Alcohol status, *n* (%)					
Never or rarely	110,060 (28.4%)	99,453 (27.6%)	7447 (40.8%)	2636 (33.2%)	524 (46.6%)
Once or twice a week	102,453 (26.5%)	95,761 (26.6%)	4599 (25.2%)	1852 (23.3%)	241 (21.4%)
Three or four times a week	92,760 (24.0%)	87,653 (24.4%)	3199 (17.5%)	1747 (22.0%)	161 (14.4%)
Daily or almost daily	81,752 (21.1%)	76,837 (21.4%)	3012 (16.5%)	1705 (21.5%)	198 (17.6%)
Serum calcium level (mmol/L), *n* (%)					
Normal	375,123 (96.9%)	348,864 (97.0%)	17,532 (96.0%)	7,41 (96.2%)	1086 (96.6%)
Too low	6247 (1.6%)	5764 (1.6%)	396 (2.2%)	69 (0.9%)	18 (1.6%)
Too high	5655 (1.5%)	5076 (1.4%)	329 (1.8%)	230 (2.9%)	20 (1.8%)
Serum vitamin D level (nmol/L), *n* (%)					
Normal	216,103 (55.8%)	200,976 (55.9%)	10,132 (55.5%)	4,405 (55.5%)	590 (52.5%)
Too low	65,657 (17.0%)	60,711 (16.9%)	3,555 (19.5%)	1,195 (15.0%)	196 (17.4%)
Too high	105,265 (27.2%)	98,017 (27.2%)	4,570 (25.0%)	2,340 (29.5%)	338 (30.1%)
Corticosteroid use, baseline, *n* (%)	3357 (0.9%)	3099 (0.9%)	155 (0.9%)	90 (1.1%)	13 (1.2%)
Hormone-replacement therapy history,[a] *n* (%)	82,765 (39.3%)	71,999 (37.8%)	6213 (55.5%)	3957 (51.7%)	596 (56.5%)
Menopausal status,[a] *n* (%)	7481 (3.6%)	6506 (3.4%)	573 (5.1%)	333 (4.4%)	69 (6.6%)
History of bilateral oophorectomy,[a] *n* (%)	17,135 (8.1%)	15,018 (7.9%)	1321 (11.8%)	676 (8.8%)	120 (11.4%)
Processed meat intake, *n* (%)					
Never or less than once a week	147,764 (38.2%)	136,370 (37.9%)	6859 (37.5%)	4016 (50.6%)	519 (45.2%)

(Continues)

Table 1. Continued

	Global population (n = 387,025)	Nonsarcopenics (n = 359,704, 92.9%)	Presarcopenics—subgroup 1 (n = 18.257, 4.7%)	Presarcopenics—subgroup 2 (n = 7940, 2.1%)	Sarcopenics (n = 1124, 0.3%)
Once a week	115,838 (29.9%)	107,599 (29.9%)	5561 (30.5%)	2335 (29.4%)	343 (30.5%)
2 or more times a week	123,423 (31.9%)	115,735 (32.2%)	5837 (32.0%)	1589 (20.0%)	262 (23.3%)
Beef intake, *n* (%)					
Never or less than once a week	218,675 (56.5%)	202,701 (56.4%)	10,498 (57.5%)	4799 (60.4%)	677 (60.2%)
Once a week	125,810 (32.5%)	117,342 (32.6%)	5831 (31.9%)	2293 (28.9%)	344 (30.6%)
- 2 or more times a week	42,540 (11.0%)	39,661 (11.0%)	1928 (10.6%)	848 (10.7%)	103 (9.2%)
Energy intake[b] (KJ/d), *n* (%)					
0.000–7487.7	27,393 (7.1%)	25,549 (7.1%)	1036 (5.7%)	738 (9.3%)	70 (6.2%)
7487.7–9670.3	27,392 (7.1%)	25,760 (7.2%)	984 (5.4%)	580 (7.3%)	68 (6.1%)
9670.3–47523.8	27,393 (7.1%)	26,106 (7.3%)	904 (5.0%)	352 (4.4%)	31 (2.8%)
Protein intake[b] (g/d), *n* (%)					
0–50	8094 (2.1%)	7543 (2.1%)	323 (1.8%)	206 (2.6%)	22 (2.0%)
50–100	55,393 (14.3%)	52,068 (14.5%)	1976 (10.8%)	1223 (15.4%)	126 (11.2%)
100–640	18,691 (4.8%)	17,804 (4.95%)	625 (3.4%)	241 (3.0%)	21 (1.9%)
Calcium intake[b] (mg/d), *n* (%)					
0–800	28,700 (7.4%)	26,901 (7.5%)	1040 (5.7%)	691 (8.7%)	68 (6.1%)
800–1200	33,474 (8.7%)	31,570 (8.8%)	1173 (6.4%)	654 (8.2%)	77 (6.9%)
1200–7034	20,004 (5.2%)	18,944 (5.3%)	711 (3.9%)	325 (4.1%)	24 (2.1%)
Calcium supplementation, *n* (%)	4898 (1.3%)	4318 (1.2%)	262 (1.4%)	277 (3.5%)	41 (3.7%)
Vitamin D supplementation, *n* (%)	3497 (0.9%)	3176 (0.9%)	150 (0.8%)	154 (1.9%)	17 (1.5%)
Global physical activity (MET, h/wk), *n* (%)					
For walking[c]					
Low (0–6.6)	107,863 (27.9%)	100,331 (27.9%)	5202 (28.5%)	2028 (25.5%)	302 (26.9%)
Moderate (6.6–17.3)	104,191 (26.9%)	97,602 (27.1%)	4277 (23.4%)	2043 (25.7%)	269 (23.9%)
High (17.3–69.4)	101,830 (26.3%)	95,751 (26.6%)	3940 (21.6%)	1908 (24.0%)	231 (20.6%)
For moderate activity[c]					
Low (0–4)	121,495 (31.4%)	112,751 (31.3%)	6079 (33.3%)	2308 (29.1%)	357 (31.8%)
Moderate (4–14)	89,808 (23.2%)	84,556 (23.5%)	3393 (18.6%)	1670 (21.0%)	189 (16.8%)
High (14–84.1)	102,581 (26.5%)	96,377 (26.8%)	3947 (21.6%)	2001 (25.2%)	256 (22.8%)
For vigorous activity[c]					
Low (0–0)	126,578 (32.7%)	115,444 (32.1%)	7575 (41.5%)	3048 (38.4%)	511 (45.5%)
Moderate (0–9.3)	81,516 (21.1%)	77,048 (21.4%)	2771 (15.2%)	1543 (19.4%)	154 (13.7%)
High (9.3–64)	105,790 (27.3%)	101,192 (28.1%)	3073 (16.8%)	1388 (17.5%)	137 (12.2%)
Falls in the last year, *n* (%)					
0	311,836 (80.6%)	292,650 (81.4%)	12,355 (67.7%)	6073 (76.5%)	758 (67.4%)
1	50,809 (13.1%)	46,187 (12.8%)	3022 (16.5%)	1368 (17.2%)	232 (20.7%)
≥2	24,380 (6.3%)	20,867 (5.8%)	2880 (15.8%)	499 (6.3%)	134 (11.9%)
Fractured/broken bones in last 5 years, *n* (%)	36,675 (9.5%)	33,274 (9.6%)	2213 (12.1%)	1010 (12.7%)	178 (15.8%)

(Continues)

Table 1. Continued

	Global population (n = 387,025)	Nonsarcopenics (n = 359,704, 92.9%)	Presarcopenics—subgroup 1 (n = 18.257, 4.7%)	Presarcopenics—subgroup 2 (n = 7940, 2.1%)	Sarcopenics (n = 1124, 0.3%)
If yes, resulting from simple fall, *n* (%)	21,478 (59.3%)	19,024 (57.9%)	1550 (71.6%)	763 (76.1%)	141 (79.7%)
History of neoplasia, at baseline, *n* (%)	33,295 (8.6%)	29,895 (8.3%)	2222 (12.2%)	1003 (12.6%)	175 (15.6%)
History of bone disease, at baseline, *n* (%)	11,936 (3.1%)	10,451 (2.9%)	1229 (6.7%)	182 (2.3%)	74 (6.6%)
History of diabetes, at baseline, *n* (%)	17,268 (4.5%)	15,432 (4.3%)	1729 (9.5%)	88 (1.1%)	19 (1.7%)
Comorbidity at baseline (/43), *n* (%)					
0	205,897 (53.2%)	194,883 (54.2%)	6630 (36.3%)	3978 (50.1%)	406 (36.1%)
1	108,958 (28.2%)	100,873 (28.0%)	5336 (29.2%)	2391 (30.1%)	358 (31.9%)
≥2	72,170 (18.6%)	63,948 (17.8%)	6291 (34.5%)	1571 (19.8%)	360 (32.0%)
Grip strength (highest value; kg), median [IQR]	30.0 [24.0; 40.0]	32.0 [25.0; 42.0]	14.0 [12.0; 22.0]	22.0 [20.0; 26.0]	12.0 [10.0; 14.0]
SMI (BIA) (kg/m^2), median [IQR]	7.6 [6.5; 9.0]	7.7 [6.6; 9.1]	7.2 [6.33; 8.70]	5.34 [5.2; 5.4]	5.3 [5.1; 5.4]
Heel QUS, mean (SD)					
Broadband ultrasound attenuation (dB/MHz)	76.2 [65.3; 88.3]	76.6 [65.7; 88.7]	73.2 [62.1; 85.4]	67.1 [57.0; 77.8]	62.8 [51.0; 74.3]
Ankle spacing width (mm)	43.7 [40.7; 46.9]	43.8 [40.9; 47.0]	43.4 [40.5; 46.7]	39.4 [37.3; 41.7]	39.4 [37.2; 41.8]
Lost to follow-up, *n* (%)	775 (0.2%)	729 (0.2%)	30 (0.16%)	14 (0.2%)	2 (0.18%)
Death during the follow-up period, *n* (%)	24,995 (6.5%)	21,930 (6.1%)	2231 (12.2%)	673 (8.5%)	161 (14.3%)

[a]In women only.
[b]Significant number of missing values (304,847 in the global population, 282,289 in the nonsarcopenics, 15,333 in the presarcopenics subgroup 1, 6270 in the presarcopenics subgroup 2, 955 in the sarcopenics).
[c]Significant number of missing values (73,141 in the global population, 66,020 in the nonsarcopenics, 4838 in the presarcopenics subgroup 1, 1961 in the presarcopenics subgroup 2, 322 in the sarcopenics).

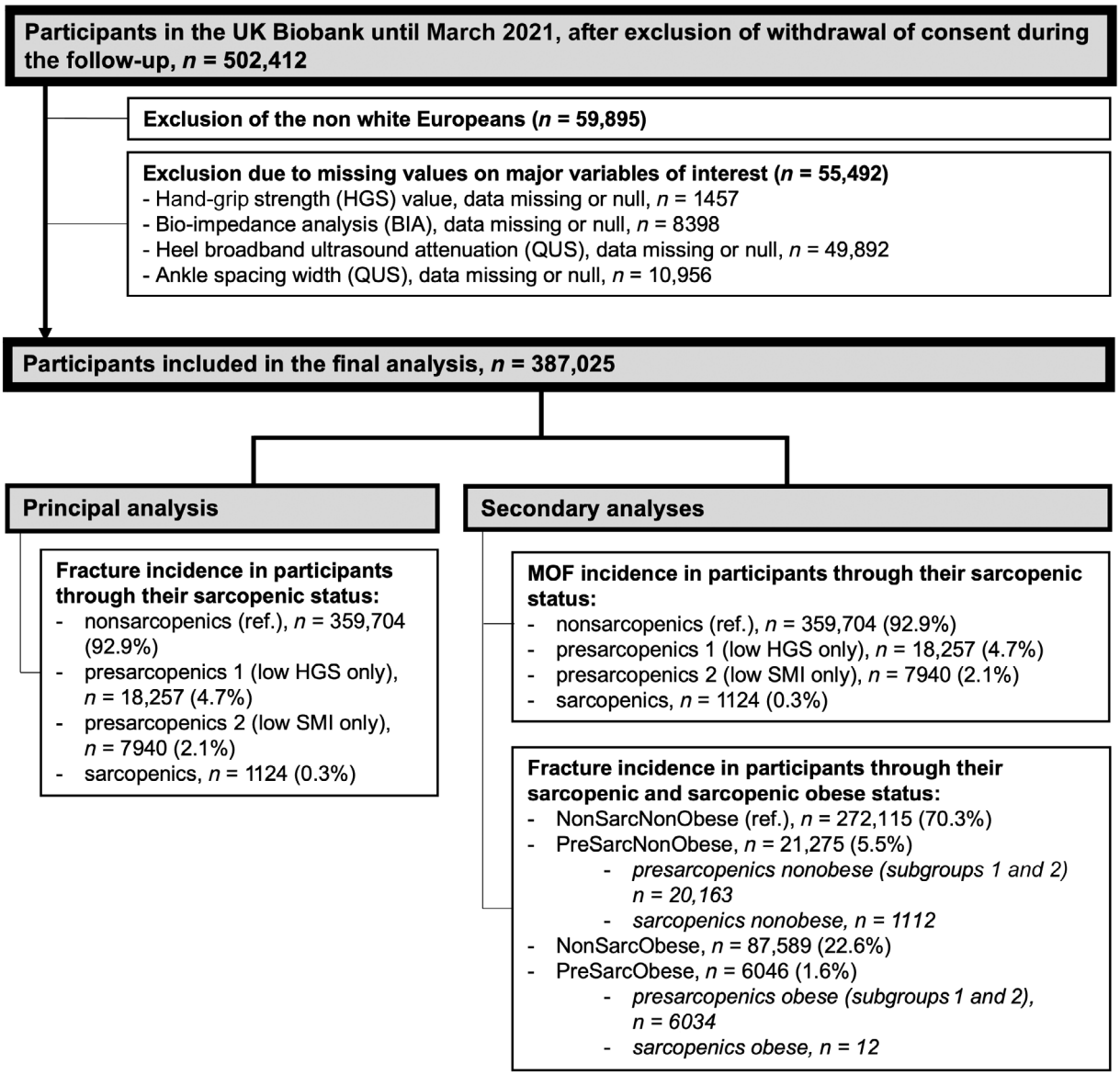


Fig. 2. Flow chart. NonSarcNonObese = nonsarcopenic nonobese participants; NonSarcObese = nonsarcopenic obese participants; PreSarcNonObese = presarcopenic and sarcopenic nonobese participants; PreSarcObese = presarcopenic and sarcopenic obese participants; QUS = quantitative ultrasound; Ref. = reference subgroup for statistical analyses.

Nonsarcopenic participants had fewer comorbidities than the presarcopenic participants (subgroups 1 and 2) and sarcopenic (no comorbidity, respectively: 54.2% versus 36.3%, 54.2% versus 50.1%, 54.2% versus 36.1%). Detailed baseline characteristics in NonSarcObese and PreSarcObese are shown in Supplemental Table 2.

Primary outcome: incident fracture in nonsarcopenic participants versus presarcopenic (subgroups 1 and 2) and sarcopenic participants

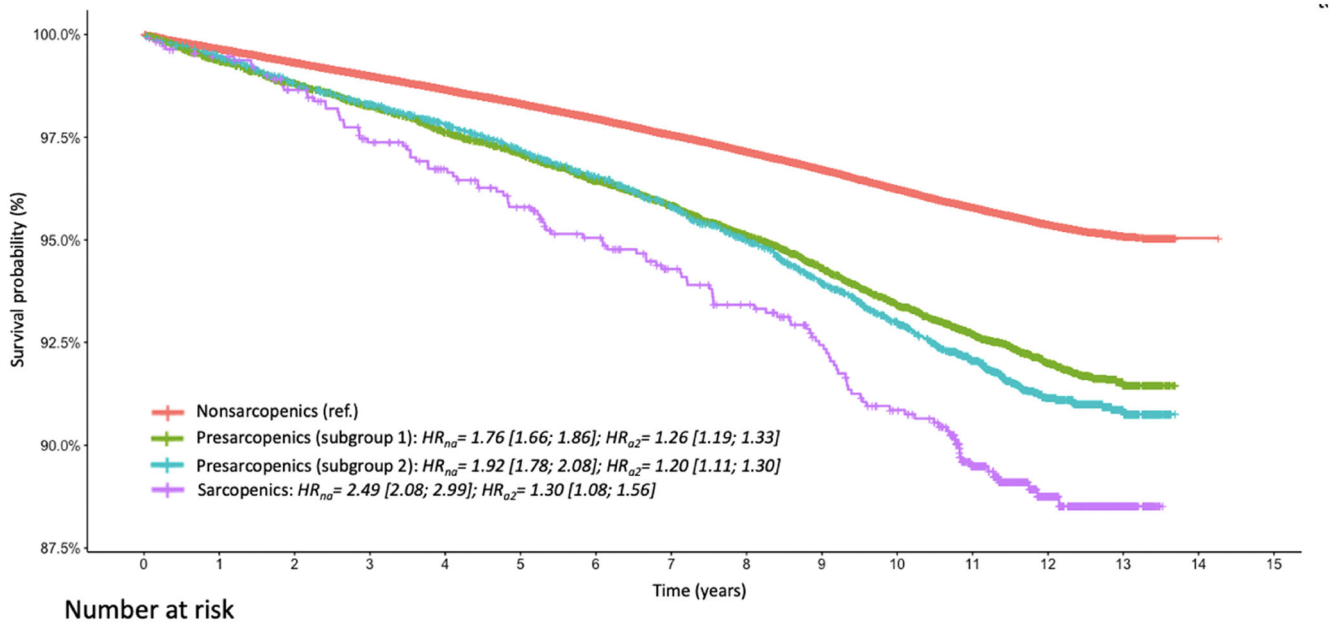
Around 95.0% of the fracture events were collected from the ICD10 classification and the remainder from self-reported histories (Supplemental Table S3). The main analysis was performed on the 387,025 participants in the global population, which comprised 359,705 (92.9%) nonsarcopenic participants, 18,257 (4.7%) presarcopenic participants—subgroup 1, 7940 (2.1%) presarcopenic participants—subgroup 2, and 1124 (0.3%) sarcopenic participants. A total of 18,300 first-time fracture events were recorded. The site-specific descriptive analysis shows that the most common fracture sites were wrist, followed by tibia and fibula, spine, and proximal femur (Table 2).

For the survival analysis, the nonsarcopenic group served as the reference group. The cumulative risk of incident fracture is shown in Figure 3. Where fracture risk was concerned:

- the presarcopenic subgroup 1 was associated with $HR_{na} = 1.76$ (1.66–1.86), $HR_{a1} = 1.43$ (1.35–1.51), and $HR_{a2} = 1.26$ (1.19–1.33);

Table 2. Incident Fracture Events, With Location and Follow-up Duration

	Global population (n = 387,025)	Nonsarcopenics (n = 359,704, 92.9%)	Presarcopenics—subgroup 1 (n = 18,257, 4.7%)	Presarcopenics—subgroup 2 (n = 7940, 2.1%)	Sarcopenics (n = 1124, 0.3%)
At least one incident fracture during follow-up, *n* (%)					
All fractures	18,300 (4.73%)	16,148 (4.49%)	1371 (7.51%)	665 (8.38%)	116 (10.3%)
Major osteoporotic fractures (MOF) only	10,341 (2.67%)	8993 (2.50%)	836 (4.58%)	116 (10.3%)	72 (6.41%)
MOF location, *n* (%)					
Wrist	4710 (1.22%)	4188 (1.16%)	304 (1.67%)	196 (2.47%)	22 (1.96%)
Spine	2380 (0.61%)	2034 (0.57%)	231 (1.27%)	96 (1.21%)	19 (1.69%)
Proximal femur	2370 (0.61%)	1990 (0.55%)	230 (1.26%)	122 (1.54%)	28 (2.49%)
Proximal humerus	1449 (0.37%)	1246 (0.35%)	128 (0.70%)	64 (0.81%)	11 (0.98%)
Non-MOF fracture location, *n* (%)					
Tibia, fibula	2407 (0.62%)	2159 (0.60%)	174 (0.95%)	63 (0.79%)	11 (0.98%)
Upper arm, humerus, elbow	1945 (0.50%)	1681 (0.47%)	170 (0.93%)	79 (0.99%)	15 (1.33%)
Rib	1874 (0.48%)	1694 (0.47%)	128 (0.70%)	45 (0.57%)	7 (0.62%)
Lower leg, ankle	1262 (0.33%)	1152 (0.32%)	79 (0.43%)	28 (0.35%)	3 (0.27%)
Radius, ulna	1242 (0.32%)	1103 (0.31%)	84 (0.46%)	44 (0.55%)	11 (0.98%)
Pelvis	1204 (0.31%)	1013 (0.28%)	114 (0.62%)	63 (0.79%)	14 (1.25%)
Knee, patella	896 (0.23%)	789 (0.22%)	65 (0.36%)	37 (0.47%)	5 (0.44%)
Clavicle, collar bone	772 (0.20%)	708 (0.20%)	37 (0.20%)	23 (0.29%)	4 (0.36%)
Shoulder, scapula	453 (0.12%)	421 (0.12%)	24 (0.13%)	7 (0.09%)	1 (0.09%)
Sternum	251 (0.06%)	219 (0.06%)	18 (0.10%)	12 (0.15%)	2 (0.18%)
Shaft of femur	66 (0.02%)	56 (0.02%)	9 (0.05%)	0 (0.00%)	1 (0.09%)
Follow-up duration before event					
First fracture event, median [IQR]	6.59 [3.40; 9.31]	6.57 [3.39; 9.31]	6.52 [3.29; 9.16]	7,09 [3.87; 9.46]	6.60 [3.32; 9.20]
First MOF event, median [IQR]	6.58 [3.68; 9.51]	6.90 [3.69; 9.52]	6.72 [3.53; 9.34]	7.26 [4.02; 9.60]	6.41 [2.86; 9.32]



Number at risk

Time (y)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Non-sarcopenics	359,704	357,825	355,622	353,154	350,500	347,663	344,572	341,329	337,977	334,336	330,443	292,035	177,238	38,707	2	0
Presarcopenics n°1	18,257	18,055	17,836	17,605	17,369	17,136	16,838	16,556	16,246	15,920	15,563	13,202	7,355	1,145	0	0
Presarcopenics n°2	7,940	7,879	7,791	7,717	7,630	7,533	7,447	7,348	7,225	7,089	6,940	6,074	3,529	808	0	0
Sarcopenics	1,124	1,109	1,088	1,064	1,045	1,026	1,004	978	961	936	911	781	438	88	0	0

Fig. 3. Nonadjusted fracture-free survival rates (387,025 participants, 18,300 events). HR_{a2} = hazard ratio derived from maximally adjusted model (adjustment on sociodemographic covariates [sex, age at recruitment, Townsend deprivation index], BMI, heel QUS-related data [heel BUA and ASW], serum vitamin D level, vitamin D and/or calcium supplementation, smoking and alcohol status, history of corticosteroids intake, history of diabetes, morbidity score, incident fracture in the last 5 years, and fall in the last year); HR_{na} = nonadjusted hazard ratio; NonSarc = nonsarcopenic participants; PreSarc = presarcopenic and sarcopenic participants; Ref. = Reference subgroup for statistical analyses.

- the presarcopenic subgroup 2 was associated with $HR_{na} = 1.92$ (1.78–2.08), $HR_{a1} = 1.26$ (1.16–1.36), and $HR_{a2} = 1.20$ (1.11–1.30);
- the sarcopenic group was associated with $HR_{na} = 2.49$ (2.08–2.99), $HR_{a1} = 1.48$ (1.23–1.78), and $HR_{a2} = 1.30$ (1.08–1.56).

Secondary outcomes

Incident MOF, in nonsarcopenic participants versus presarcopenic (subgroups 1 and 2) and sarcopenic participants

This secondary analysis was performed on the global population and concerned 10,341 events. For the survival analysis, the nonsarcopenic participants served as the reference group. The cumulative risk of incident fracture is shown in Supplemental Figure S1.

Where fracture risk was concerned:

- the presarcopenic subgroup 1 was associated with $HR_{na} = 1.92$ (1.79–2.06), $HR_{a1} = 1.48$ (1.37–1.59), and $HR_{a2} = 1.30$ (1.21–1.40);
- the presarcopenic subgroup 2 was associated with $HR_{na} = 2.28$ (2.07–2.5), $HR_{a1} = 1.25$ (1.13–1.38), and $HR_{a2} = 1.19$ (1.08–1.72);
- the sarcopenic group was associated with $HR_{na} = 2.76$ (2.19–3.48), $HR_{a1} = 1.36$ (1.08–1.72), and $HR_{a2} = 1.18$ (0.93–1.49).

Incident fracture, NonSarcNonObese versus others

Participants were divided into four subgroups, as follows: NonSarcNonObese = 279,115 (70.3%), PreSarcNonObese = 21,275 (5.5%), NonSarcObese = 87,589 (22.6%), and PreSarcObese = 6046 (1.6%).

For the survival analysis, the NonSarcNonObese served as the reference group, and the analysis was performed on 18,300 events, including 4311 events in obese participants.

Where fracture risk was concerned (Supplemental Figure S2):

- the NonSarcObese group was associated with $HR_{na} = 0.99$ (0.95–1.02), $HR_{a1} = 1.60$ (0.51–4.95), and $HR_{a2} = 1.62$ (0.52–5.03);
- the PreSarcNonObese group was associated with $HR_{na} = 1.86$ (1.77–1.96), $HR_{a1} = 1.36$ (1.29–1.43), and $HR_{a2} = 1.25$ (1.18–1.31);
- the PreSarcObese group was associated with $HR_{na} = 1.72$ (1.57–1.89), $HR_{a1} = 2.27$ (0.73–7.07), and $HR_{a2} = 1.99$ (0.64–6.19).

Sensitivity analysis

In the analysis performed on the 210,390 women in the cohort, where fracture risk was concerned:

- the presarcopenic subgroup 1 was associated with $HR_{na} = 1.65$ (1.55–1.77), $HR_{a1} = 1.38$ (1.29–1.47), and $HR_{a2} = 1.23$ (1.15–1.32);
- the presarcopenic subgroup 2 was associated with $HR_{na} = 1.55$ (1.43–1.68), $HR_{a1} = 1.25$ (1.11–1.31), and $HR_{a2} = 1.16$ (1.07–1.26);
- the sarcopenic group was associated with $HR_{na} = 1.98$ (1.64–2.40), $HR_{a1} = 1.40$ (1.15–1.69), and $HR_{a2} = 1.24$ (1.02–1.5).

After excluding participants with a history of bone diseases and/or any cancer, where fracture risk was concerned:

- the presarcopenic subgroup 1 was associated with $HR_{na} = 1.74$ (1.63–1.85), $HR_{a1} = 1.42$ (1.33–1.51), and $HR_{a2} = 1.26$ (1.19–1.35);
- the presarcopenic subgroup 2 was associated with $HR_{na} = 1.96$ (1.80–2.13), $HR_{a1} = 1.26$ (1.16–1.38), and $HR_{a2} = 1.20$ (1.10–1.32);
- the sarcopenic group was associated with $HR_{na} = 2.61$ (2.12–3.20), $HR_{a1} = 1.54$ (1.25–1.89), and $HR_{a2} = 1.37$ (1.12–1.69).

Finally, when we implemented the same statistical analyses with no imputed data, ie, after exclusion of all the participants with missing data for adjusting covariates, we draw the same conclusions for the primary outcome, the secondary outcomes, and in the sensitive analyses.

Discussion

In this large-scale study of British volunteers, we showed that presarcopenic (whatever the definition used) and sarcopenic participants were independently at higher risk of fractures than nonsarcopenic participants. Furthermore, presarcopenic (whatever the definition used), but not sarcopenic participants, were at higher risk of MOF. The lack of increased risk of MOF in sarcopenic participants is probably due to a lack of power.

Our study also suggests that fracture risk is subgroup-specific, with a higher risk of fracture in PreSarcNonObese participants compared with the NonSarcNonObese participants.

Comparison with findings reported in the literature

To the best of our knowledge, this is the first study that investigates independently the fracture risk in presarcopenic and sarcopenic patients compared with nonsarcopenic patients, in a very large cohort, using EWGSOP2 criteria and including the two definitions of presarcopenia.

The number of events we found is consistent with the results that have been previously reported in the literature.[24] The prevalence of sarcopenia was lower in our cohort (1% in participants older than 70 years versus 10% in the literature[1]) than in the global population. This may be because our cohort was a "healthier" community-dwelling population.

Comparing our findings with those in the literature is delicate, as other studies using the EWGSOP[3] or EWGSOP2[1] criteria to define sarcopenic status are few in number. Moreover, in the few studies that have been published, adjusting criteria are variable, the outcome is often not exactly the same,[9] and patients are often older (eg, older than 65 years).[13,14] In the two studies whose findings are closest to ours, the authors investigated fracture risk according to sarcopenic status, with an adjustment for BMD by DXA, but the results of these studies are contradictory.[13,14] Only the study conducted by Chalhoub and colleagues[14] reported an increase in fracture risk after 9 years of follow-up in osteosarcopenic male and female older adults aged 65 years and older but not in sarcopenic patients with normal BMD.

In nonsarcopenic patients with low SMI (ie, normal HGS and low SMI), Tokeshi and colleagues[25] found a significant association between osteoporotic vertebral fractures and sarcopenia (defined as low SMI only, without taking HGS into account). Hong and colleagues[26] investigated the association between body composition and fracture risk in Korean participants aged ≥50 years, with a view to determining the effects of muscle or fat mass on bone health outcomes. The authors reported a significant association between higher lean body mass (or ASMM) and lower risk of total osteoporotic fracture, but their analyses were not adjusted for BMD.

Regarding the PreSarcObese group, it is known whether obesity and sarcopenia potentiate each other for some outcomes (eg, mortality), but the interaction between muscle mass or fat mass and fractures remains unclear.[27] The study conducted by Studenski and colleagues[28] suggests that the coexistence of obesity and sarcopenia (defined using the Foundation for the National Institutes of Health criteria) is associated with a higher fracture risk than obesity alone. In our study, we found no evidence of this.

Study design choices

As our cohort included few sarcopenic patients, we did not differentiate between sarcopenia and severe sarcopenia, and we pooled presarcopenic participants and sarcopenic participants in the secondary analysis on sarcopenic obesity.

To assess HGS, the use of the Jamar hydraulic hand dynamometer (model J00105) seems to be the gold standard, and using the highest of the right-hand and left-hand HGS values seems advisable.[20]

For body-composition measurements, BIA is recognized as a good alternative to DXA.[1] Several population-specific equations exist to calculate an approximation of the SMM from BIA data. Among those validated in the White population, EWGSOP2 recommends prioritizing the Sergi equation.[1] However, since "reactance" data—required in the Sergi equation—was not available in our database, we used the Janssen equation,[8] which is also validated in EWGSOP.[3]

Heel QUS has emerged as a convenient screening tool for osteoporosis.[29] Because DXA data were scarce in our population, we considered that the available heel QUS-related data was the most suitable for adjusting our model. Because the QUS device does not actually measure BMD and since soft tissue thickness may influence heel ultrasound indices, we used heel BUA and ASW.[30]

We included both open fractures and stress fractures, as open fractures can be osteoporotic, and because the most comprehensive description of stress fractures includes both fatigue and insufficiency fractures.[31]

MET scores and dietary intakes were not include in Cox models, as too many values were missing.

Strengths and limitations of the study

The study was conducted on a very large prospective cohort, with good-quality data collection. Because the diagnostic classifications did not specifically mention whether fractures were fragility fractures, we focused only on fractures at locations that were compatible with osteoporotic fractures or MOFs. The 95%

CI for HR were narrow. Compared with the recent prospective study conducted by Petermann Rocha and colleagues[9]:

- we used the highest HGS value (not the average), which is more in keeping with the current recommendations;
- we adjusted our model using a wide range of covariates, including a bone health parameter (heel QUS), whereas they only used the ICD10 codes to define osteoporosis;
- our data were more exhaustive: we used ICD9, ICD10, and self-reported data, whereas they only used ICD10 data.

There was probably no reporting bias as most of the fractures were collected using hospitalization data. We performed sensitivity analyses, considering parameters that could have distorted the fracture's origin. Finally, instead of the Charlson comorbidity index, we used a more up-to-date comorbidity score (43 long-term conditions originally developed for a large epidemiological study in Scotland and subsequently adapted for UK Biobank).[9,32]

The large UK Biobank database is limited by evidence of a "healthy responder" bias. As such, because of the low proportion of sarcopenic participants, presarcopenia (subgroups 1 and 2) and sarcopenia were considered as a single subgroup in our analysis in participants living or not with obesity. Only White European participants were included in our study, which limits the generalizability of our results. Although DXA is recommended as the first-line procedure for assessing bone health, we used QUS data and not DXA data for adjustments, which introduced a bias because of the technique used and the measurement site (heel). We did not assess the risk of fragility fracture directly but an approximation based on fracture location. In including self-reported fracture-history data, we accepted that the broad category "humerus fractures" would be approximate (the most accurate category available in the self-reported fracture history included fractures of the arm, humerus, and elbow).

Perspectives

As several studies on the same subject have reported divergent results, future studies should (i) probably be performed in older prospective cohorts in order to include more sarcopenic participants, and (ii) use the EWGSOP2 diagnostic criteria to facilitate their comparison. However, some modalities of the diagnostic criteria, such as a validated method for measuring HGS and a clear definition of presarcopenia, still need to be specified.

The results of our study demonstrate an increase in the risk of incident fractures in presarcopenic and sarcopenic participants. As such, incorporating sarcopenic status in fracture risk prediction tools (eg, FRAX) may be useful, as has already been suggested.[33]

The increase in fracture risk observed in participants with low SMI only (ie, presarcopenic status for some) and in participants with low HGS only (ie, presarcopenic status for others), compared with the nonsarcopenic participants, suggests that it may be useful to assess muscle strength as well as muscle mass in all participants identified at risk of sarcopenia. Thus, the advisability of routinely measuring muscle mass in all at-risk patients with normal muscle strength should be discussed. This is currently not implied in the EWGSOP2 recommendations.

Author Contributions

Charlotte Jauffret: Conceptualization; writing – original draft; methodology; writing – review and editing; formal analysis; supervision. **Renaud Périchon:** Formal analysis; writing – review and editing; methodology. **Antoine Lamer:** Methodology; formal analysis; writing – review and editing. **Bernard Cortet:** Writing – review and editing; supervision. **Emmanuel Chazard:** Supervision; conceptualization; methodology; writing – review and editing; writing – original draft. **Julien Paccou:** Methodology; writing – original draft; writing – review and editing; supervision; conceptualization.

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Disclosures

All authors state that they have no competing interests in connection with this study.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/jbmr.4884.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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