Sarcopenia and Its Clinical Correlates in the General Population: The Rotterdam Study

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ABSTRACT

Sarcopenia, a complex multifactorial condition, is characterized by loss of muscle mass and function, which increases progressively with age. The existence of different definitions has contributed to the large variation in the prevalence estimates of sarcopenia. We aimed to estimate the prevalence of sarcopenia in the general population using the European Working Group on Sarcopenia in Older People (EWGSOP) proposed definition and compared baseline demographic and clinical characteristics between the nonsarcopenia, presarcopenia, and sarcopenia individuals, with particular emphasis on the overlap with osteoporosis and fracture risk. We studied 5911 subjects at a mean age of 69.2 years (55.8% female) with data on sarcopenia participating in the Rotterdam Study, a prospective population-based cohort study in Rotterdam, the Netherlands. Presarcopenia was defined as having only low muscle mass, whereas sarcopenia was defined based on the presence of low muscle mass, plus either low muscle strength or low physical performance. The prevalence of presarcopenia and sarcopenia was 5.9% and 4.4%, respectively. Individuals with sarcopenia were older, more often males, smokers, with less optimal dietary intake, and more often disabled with lower physical activity. Although the prevalence of fractures was higher in individuals with low lean mass (presarcopenic [16.6%] and sarcopenic [23.5%]) compared with the no sarcopenic group (15.5%), the differences were not present after correcting for age and sex. There were no statistical differences in the prevalence of chronic diseases, with the exception of a higher prevalence of COPD in presarcopenic (29.1%) and sarcopenic (26.9%) individuals compared with nonsarcopenic (13.4%) individuals. Osteoporotic individuals with (odds ratio [OR] = 2.59, 95% confidence interval [CI] 1.4-4.45) and without sarcopenia (OR = 2.75, 95% CI 2.0-3.75) had similar elevated risk of nonvertebral fractures. The presence of sarcopenia appears to be independent of chronic diseases with the exception of COPD and more related to lifestyle factors and disabilities. Sarcopenic individuals in the general population are at no greater risk of fracture than what is determined by their low bone mineral density.

INTRODUCTION

Sarcopenia, the loss of muscle mass with age, has been postulated as one of the most important geriatric syndromes. [1] The prevalence of sarcopenia has been estimated to range from 1% to 33%,[2-6] depending on the population settings and the assessment techniques and cut-offs used. Sarcopenia contributes to functional decline, falls, morbidity, and mortality of elderly people and imposes a high cost to the health care system. [7-9] Furthermore, it is considered to precede physical frailty[10] and, as such, an important pathway through which the adverse associated health outcomes of frailty develop. [11] The increase in life expectancy and growth of the elderly population will likely result in a growing prevalence of the condition and its associated adverse health outcomes.

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) provided a practical clinical and consensus definition, which constitutes the most commonly used diagnostic criteria of sarcopenia.[1] For the diagnosis of sarcopenia, a combination of the presence of low muscle mass and of compromised low muscle function (strength or performance) is required.[1] However, very few studies have applied the EWGSOP criteria in the general population on sufficient scale to obtain stable prevalence estimates. Moreover, little knowledge exists surrounding the relationship between sarcopenia (using the new consensus definition) and its associated factors within large population-based studies. Identifying modifiable risk factors for sarcopenia will help to establish evidence-based interventions to prevent the onset of sarcopenia and associated conditions in order to extend the time free from disability in older adults. Last but not least, sarcopenia has been associated with increased fracture risk. [12] However, sarcopenia may co-occur with osteoporosis, a condition referred to as osteosarcopenia, and it is not clear if the effect of sarcopenia is independent of the bone mineral density (BMD) status. Therefore, our aim was to 1) investigate the prevalence of sarcopenia in the general population using the EWGSOP proposed definition, cut-offs, and measures; 2) identify factors related to sarcopenia by comparing baseline demographic and clinical characteristics between the nonsarcopenia, presarcopenia, and sarcopenia individuals; and 3) estimate if individuals with sarcopenia and osteoporosis have greater risk of fractures compared with individuals with sarcopenia or osteoporosis alone.

MATERIALS AND METHODS

Study Population

Our study included individuals from the Rotterdam Study,[13] an ongoing population-based prospective cohort comprising almost 15,000 Dutch individuals aged 45 years and older. After its start in 1990, a total of 7983 people were included in the initial study wave (RSI). In 2000 and 2006, the cohort was expanded with 3011 (RSII) and 3932 participants (RSIII), respectively. All participants underwent an extensive home interview followed by a visit to the research center where various physical and laboratory examinations took place, all following standardized protocols. Every 2 to 4 years, the participants were invited for follow-up visits. The Rotterdam Study was approved by the medical ethics committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All individuals provided written informed consent to participate in the study and to retrieve information from their treating physicians. The present study used data assessed at the fifth visit of the first Rotterdam Study cohort (RSI-5, 2009–11; n =1521), the third visit of the second cohort (RSII-3, 2011–12; n =1603), and the second visit of the third cohort (RSIII-2, 2012–014; n =2787), for a total of 5911 participants with complete information.

Assessment of Sarcopenia

We used the EWGSOP definition to define sarcopenia as the presence of low muscle mass, plus either low muscle strength or low physical performance (**Figure 1**). Presarcopenia was defined as just having low muscle mass without compromising muscle function or physical performance.[1]

Lean mass was measured using dual-energy X-ray absorptiometry (DXA) with an iDXA total body fan-beam densitometer (GE Lunar Corp., Madison, WI, USA). The scans were analyzed using the enCORE software that employs an algorithm, which divides the total body by regions of interest into head, trunk, arms, and legs. Appendicular lean mass (ALM) is the sum of the lean tissue from the arms and legs. Skeletal muscle index (SMI), adjusted for variation in skeletal size, was defined as ALM divided by squared body height (kg/m^2). Low muscle mass was defined as SMI ≤ 7.25kg/m^2 for males and ≤ 5.67 kg/m^2 for females. [14] Muscle strength was assessed using a hydraulic hand dynamometer (Fabrication Enterprises Inc., White Plains, NY, USA) and maximum grip strength was defined as the maximum value (kg) out of the three trials performed in the nondominant hand. [13] Low muscle strength was defined differentially across sexes and according to body mass index (BMI) levels. In men, as a handgrip of ≤ 29kg (if BMI ≤ 24), ≤ 30kg (if BMI ≤ 24.1–28), or 3≤ 2kg (if BMI >28). In women, ≤ 17kg (if BMI ≤ 23), ≤ 17.3kg (if BMI ≤23.1–26), ≤ 18 kg (if BMI ≤ 26.1–29), or ≤ 21kg (if BMI>29).

[15] Physical performance was assessed as gait speed during normal walk using the GAITRite walkway (CIR Systems, Inc., Sparta, NJ, USA), a 5.79-m-long electronical walkway. [16,17] Low physical performance was defined differentially across sexes and according to body height: in men, as a gait speed <0.65 m/s (if height ≤ 173 cm) or <0.76 m/s (if height >173 cm), and in women, as having a gait speed <0.65 m/s (if height ≤ 159 cm) or <0.76 m/s (if height >159 cm).(15) Using these criteria, individuals were classified into one of three groups: 1) sarcopenic; 2) presarcopenic; and 3) non-sarcopenic (**Figure 1**).

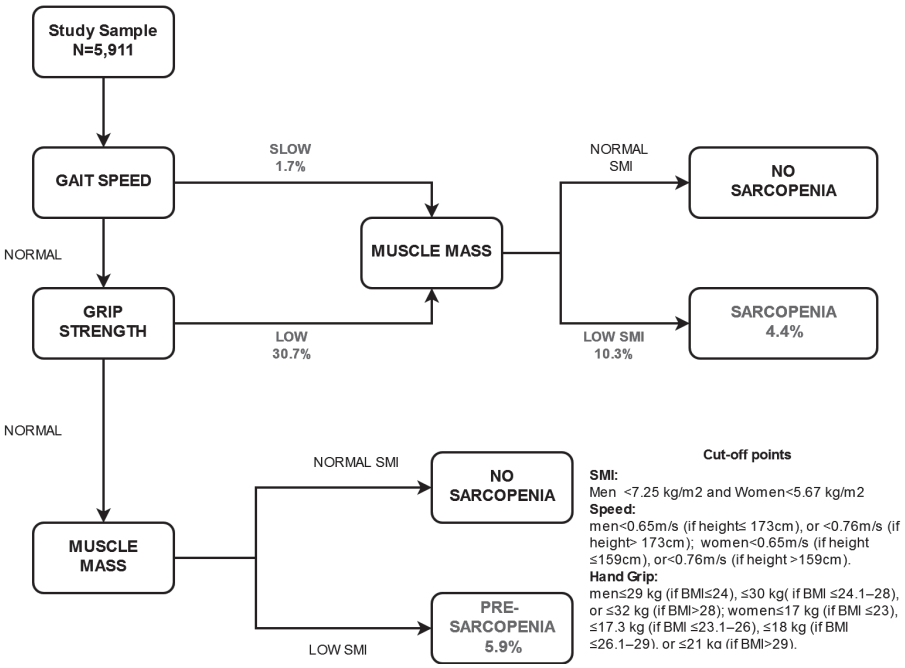

Figure 1 | Application of the European Working Group on Sarcopenia in Older People algorithm

Assessment of Bone Mineral Density

Femoral neck BMD was measured using dual-energy X-ray absorptiometry (DXA) with the same iDXA total body fan-beam densitometer (GE Lunar Corp.). Sex-specific T-scores were calculated using the NHANES III reference population. [18] Osteosarcopenia was defined as sarcopenia plus low BMD (T-score <-1 SD).

Assessment of Associated Factors

Height (cm) and weight (kg) were measured in the research center with the individuals in standing position wearing indoor clothing without shoes. Body mass index was computed as weight in kilograms divided by height in meters squared (kg/m^2). Smok-

ing, education, living status, hospitalization, falls, and pain were collected through self-report. Excessive alcohol consumption was defined as >20 g per day for women and >30 g per day for men. Diet quality was assessed using validated food-frequency questionnaires (FFQ) to assess usual dietary intake in the last month. Next, diet quality was calculated as adherence to the Dutch Dietary Guidelines (2006), as expressed in the Dutch Healthy Diet Index.[19] Physical activity levels were assessed with an adapted version of the LASA Study Physical Activity Questionnaire,[20,21] including questions regarding walking, cycling, sports, gardening, hobbies, and housekeeping. Answers were translated into metabolic equivalent of task (MET) values, and individuals were classified in quartiles. Cognitive function was assessed by the Dutch version of the 30-point Mini-Mental State Examination (MMSE), with a score of 26 or below indicating poor cognition.[22] Disability was assessed using the Stanford Health Assessment Questionnaire (HAQ) that measures disability across eight fields.[23] Mild disability was defined as having difficulties with some of the items and severe as having difficulties with more than half of the items. Prevalent fractures were reported by general practitioners (GPs) in the research area by means of a computerized system or through hospital records. Fracture information from GPs outside the research area was obtained by regular monitoring of the patient record by research physicians. All reported events were verified by a research physician who independently reviewed and coded the information. Metabolic syndrome (MetS) was diagnosed if at least three of the following five traits were present: 1) abdominal obesity, defined as waist circumference >102 cm in men and >88 cm in women; 2) serum triglycerides ≥ 1.7 mmol/L or drug treatment for elevated triglycerides; 3) serum high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L in men and <1.3 mmol/L in women or drug treatment for low HDL-C; 4) blood pressure ≥ 130/85 mmHg or drug treatment for elevated blood pressure; and 5) fasting plasma glucose (FPG) ≥ 100 mg/ dL (5.6 mmol/L) or drug treatment for elevated blood glucose. Coronary heart disease was defined as coronary revascularization or myocardial infarction or death due to coronary heart disease.[24] Diabetes mellitus (DM) was defined from combining information on glucose-lowering medication use, blood glucose levels, and diagnosis in the GP registries. [25] Chronic obstructive pulmonary disease (COPD) was assessed by spirometry (FEV1/ FVC <0.70), performed at the research center or, if not available, confirmed by a physician based on the combination of clinical history, physical examination, and spirometry con outside the research center.[26] Stroke was defined as syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent origin other than vascular.[27] Depression was defined using the CES-D Scale (Center for Epidemiology Studies Depression Scale), with a score of 16 or higher indicating the presence of depressive symptoms.[28] History of neoplasms was collected through self-report.

Biochemistry

Serum cholesterol, triglycerides, glucose, insulin, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyltransferase (GGT), alkaline phosphatase, hemoglobulin, and total bilirubin were measured using automatic enzyme procedures. Homeostasis model assessment of insulin resistance (HOMA-IR) was used as proxy for insulin resistance and calculated by multiplying fasting glucose (mmol/L) by fasting insulin (mU/L) divided by 22.5.

STATISTICAL ANALYSES

Characteristics for the population were provided for nonsarcopenic, presarcopenic and sarcopenic individuals. Continuous variables are reported as mean SD unless stated otherwise, and categorical variables were presented as percentages. Differences between the nonsarcopenic and sarcopenic individuals in demographic and clinical characteristics were assessed with crude and age-, sex-, and cohort-adjusted linear and logistic regression models. The same approach was done comparing sarcopenia only, osteoporosis only, and osteosarcopenia. Logistic regression analysis was used to calculate the fracture risk odds ratio (ORs) and 95% confidence intervals (CIs) per group (osteopenia and no [pre] sarcopenia; osteoporosis and no [pre] sarcopenia; normal bone and presarcopenia; osteopenia and presarcopenia; osteoporosis and presarcopenia; normal bone and sarcopenia; osteopenia and sarcopenia; osteoporosis and sarcopenia) using the participants with no low bone mineral density and no sarcopenia as reference. All statistical analyses were performed using R (version 3.3.1). Any p values <0.05 were considered statistically significant.

As sensitivity, we compared the sarcopenia prevalence estimate from the EWGSOP definition with the estimate derived by the Foundation of the National Institutes of Health Sarcopenia Project (FNIH) definition and cut-off points. Moreover, we tested the association of 1-unit increase in T-score (with and without sarcopenia) with fracture.

RESULTS

Individual demographic and clinical variables are summarized in **Table 1**. The majority of the individuals were classified as nonsarcopenic (89.7%). Prevalence of presarcopenia and sarcopenia was 5.9% and 4.4%, respectively. The cases' overlap between the EWGSOP and FNIH definitions was relatively small (**Supplementary Figure 1**). On average, individuals were 69.2 ± 9.1 years old and 56.8% were female. The mean age of individuals with sarcopenia was higher (78.0 ± 8.5 years) than those without

Table 1 | Characteristics of Study Population Participants According to the Presence of Sarcopenia

Study characteristics	No (pre) sarcopenia	Presarcopenia	Sarcopenia	% Missing
Prevalence, n(%)	5,301 (89.7)	350 (5.9)	260 (4.4)	
Age (years), mean ± SD	68.72 ± 8.9	70.42 ± 8.8	77.98 ± 8.5[a]	-
Female,n(%)	3117 (58.8)	146 (41.7)[a]	98 (37.7)[a]	-
Educational level, n (%)				1
Primary	438 (8.4)	30 (8.6)	25 (9.7)	
Intermediate	3661 (69.8)	223 (64.1)	184 (71.3)	
High	1145 (21.8)	95 (27.3)	49 (19.0)	
DHD index score, mean ± SD	56.41 ± 9.9	55.85 ± 9.9	54.37 ± 11.2	17.3
Alcohol ≥20 g/d (women) or ≥30 g/d (men)	350 (7.7)	25 (8.4)	12 (6.0)	15
Smoking, n (%)				0.2
Never	1735 (32.8)	91 (26.0)	68 (26.3)	
Former	2782 (52.6)	176 (50.3)	148 (57.1)	
Current	771 (14.6)	83 (23.7)[a]	43 (16.6)[a]	
Physical activity, median (IQR)	41.5 (17.0–78.9)	31.5 (13.9–75.9)[a]	19.4 (9.0–47.6)[a]	14.2
Height (cm), mean (SD)	168.6 ± 9.5	171.7 ± 9.6[a]	167.8 ± 9.9[a]	-
BMI (kg/m^2), mean (SD)	28.0 ± 4.1	22.8 ± 2.5[a]	23.7 ± 2.9[a]	-
Normal (BMI 18.5–25)	1226 (23.2)	278 (83.5)	178 (70.0)	
Overweight (BMI 25–30)	2680 (50.6)	54 (16.2)	70 (27.6)	
Obese (BMI 30+)	1387 (26.2)	1 (0.3)	6 (2.4)	
WHR, mean (SD)	0.90 ± 0.1	0.88 ± 0.1[a]	0.91 ± 0.1[a]	0.05
Femoral neck BMD (g/m^2), mean ± SD	0.91 ± 0.1	0.86 ± 0.1[a]	0.83 ± 0.2[a]	4.3
Disability index, n (%)				6.2
No disability	3874 (77.6)	276 (83.1)	119 (54.3)	
Mild disability	883 (17.7)	44 (13.3)	68 (31.1)[a]	
Severe disability	234 (4.7)	12 (3.6)	32 (14.6)[a]	
MMSE, n (%)				0.19
Cognitive impairment (<26)	404 (7.3)	74 (13.4)[a]	45 (18.3)	
No cognitive impairment (≥26)	4886 (92.4)	303 (86.6)	215 (82.7)	
Living status, (%)				0.2
Independent	4,929 (93.2)	318 (90.9)	220 (84.9)	
Other	361 (6.8)	32 (9.1)	39 (15.1)	
Hospitalization. yes.n(%)	203 (14.8)	25 (20.8)	33 (21.3)	72.1
Pain, yes, n(%)	1,403 (71.7)	91 (53.8)[a]	111 (63.1)	61.1
Falls, yes, n (%)	505 (25.8)	43 (25.4)	55 (31.2)	61.1

DHD = Dutch health diet; BMI = body mass index; WHR= waist hip ratio; BMD = bone mineral density; MMSE = Mini-Mental State Examination.

a Significant p value <0.05 comparing no (pre) sarcopenia with presarcopenia and sarcopenia groups adjusted for age, sex, and cohort effect. For the group comparison analyses, physical activity was log transformed.

sarcopenia (68.7 ± 8.9 years). In the presarcopenic and sarcopenic groups, there were more men than women (58.3% and 62.3%, respectively). Overall, there was a marked increase in the prevalence of sarcopenia with age, being particularly prominent in men after the age of 70 years, reaching 22.1% after the age of 80 years. In women, the prevalence of sarcopenia was lower than in men, reaching 9.3% after age 80 years (**Figure 2**).

Presarcopenic and sarcopenic individuals were more often smokers, were more often hospitalized, lived independently less often, and were more disabled than non-sarcopenic individuals. Furthermore, they were less active and had lower diet quality. After controlling for age and sex, these differences remained significant only for physical activity, smoking, and disability status. Moreover, the nonsarcopenia group

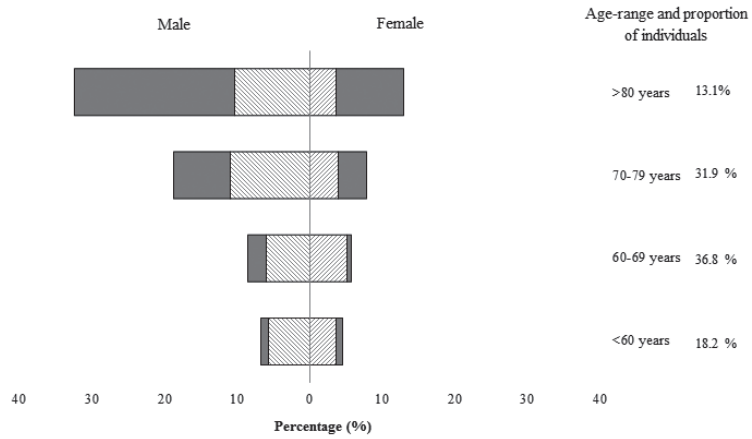

Figure 2 | Prevalence of sarcopenia and presarcopenia by sex and age decades

had higher number of MetS compared with the other groups.

Biochemical characteristics of the study are present in **Table 2**. After age and sex adjustment, the presarcopenia and sarcopenia groups tended to have lower levels of triglycerides, ALT, bilirubin, hemoglobulin, glucose, insulin, and HOMA-IR and higher levels of HDL. Compared with the nonsarcopenic group, individuals with sarcopenia had lower BMD and had higher prevalence of fractures (23.5% versus 15.5%) (**Table 3**). However, the difference in prevalent fractures was driven by age and sex. Furthermore, individuals with sarcopenia had higher prevalence of chronic comorbid conditions, but the differences were not significant with the exception of stroke, coronary heart disease, and COPD. Interestingly, after controlling for age and sex, the prevalence of COPD in the presarcopenia (29.1%) and sarcopenia (26.9%) groups was significantly higher compared with the nonsarcopenia group (13.4%). Notably, the

Table 2 | Biochemical Characteristics of Study Participants According to the Presence of Sarcopenia

Study characteristics	No (pre) sarcopenia	Presarcopenia	Sarcopenia
Cholesterol (mmol/L), mean ± SD	5.5 ± 1.11	5.4 ± 1.04	5.2 ± 1.08
HDL cholesterol (mmol/L), mean ± SD	1.5 ± 0.43	1.6 ± 0.47[a]	1.5 ± 0.43[a]
Triglycerides (mmol/L), mean ± SD	1.5 ± 0.77	1.4 ± 0.73[a]	1.3 ± 0.63[a]
Aspartate transaminase (U/L), median (IQR)	24.0 (21.0–28.0)	24.0 (21.0–28.0)	24.0 (21.0–28.0)
ALT (U/L), median (IQR)	19.0 (15.0–24.0)	17.5 (14.0–23.0)[a]	17.0 (13.0–22.0)[a]
ALP (U/L), median (IQR)	68.0 (58.0–80.0)	68.5 (57.0–83.0)	69.5 (59.0–85.3)[a]
Bilirubin (µmol/L), median (IQR)	8.0 (6.0–11.0)	8.0 (6.0–11.0)	8.0 (6.0–10.3)[a]
GGT (U/L), median (IQR)	24.0 (17.0–35.0)	24.0 (17.0–33.0)	23.0 (17.0–37.0)
Creatinine (µmol/L), median (IQR)	77.0 (67.0–90.0)	77.0 (67.0–90.0)[a]	80.0 (69.0–97.0)
Hemoglobulin (g/dL), mean ± SD	8.8 ± 0.8	8.6 ± 0.8	8.5 ± 0.9[a]
Glucose (mmol/L), median (IQR)	5.5 (5.1–6.1)	5.3 (5.0–5.80)[a]	5.4 (5.10–6.1)[a]
Insulin (pmol/L), median (IQR)	75.0 (53.0–109.0)	55.0 (39.0–80.0)[a]	63.5 (44.00–89.0)[a]
HOMA-IR, median (IQR)	2.7 (1.78–4.17)	1.9 (1.3–2.8)[a]	2.2 (1.47–3.3)[a]

HDL= high-density lipoprotein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; HOMA-IR = homeostatic model assessment-insulin resistance.
a Significant p value (<0.05) comparing no (pre) sarcopenia with presarcopenia and sarcopenia groups adjusted for age, sex, and cohort effect. For the group comparison analyses, the variables presented as median (IQR) were log transformed.

Table 3 | Clinical Characteristics of Study Participants According to the Presence of Sarcopenia

Study characteristics	No (pre) sarcopenia	Presarcopenia	Sarcopenia	% Missing
Prevalence, n (%)	5301 (89.7)	350 (5.9)	260 (4.4)	
History of non-vertebral fracture, n (%)	820 (15.5)	58 (16.6)	61 (23.5)	-
Metabolic syndrome, n (%)	1768 (34.0)	50 (14.5)[a]	41 (16.5)[a]	2.1
Blood pressure >130/85 mmHg	3964 (74.9)	246 (70.3)[a]	207 (80.2)[a]	1.9
Coronary heart disease, n (%)	187 (3.6)	11 (3.2)	19 (7.5)	0.7
Diabetes mellitus, n (%)	477 (9.1)	17 (4.9)[a]	28 (11.0)	1.4
COPD, n (%)	710 (13.4)	102 (29.1)[a]	70 (26.9)[a]	2
Stroke, n (%)	184 (3.5)	13 (3.7)	20 (7.7)	-
Neoplasm, n (%)	210 (15.3)	15 (12.4)	31 (20.3)	72.1
Depression, n (%)	405 (8.0)	29 (8.8)	21 (9.1)	4.6

COPD = chronic obstructive pulmonary disease.
a Significant p value (<0.05) comparing no (pre) sarcopenia with presarcopenia and sarcopenia groups adjusted for age, sex, and cohort effect.

association with COPD remained significant after additional controlling for smoking, physical activity, and number of prescribed corticosteroids.

We then moved on to compare sarcopenic individuals according to osteoporosis status. Individuals with sarcopenia only (n = 47) had similar clinical and biochemical characteristics compared with the individuals with osteoporosis only (n = 278) and osteosarcopenia (n = 195) (**Table 4**). Individuals with osteoporosis only had higher

prevalence of fractures (34.5%) compared with individuals with sarcopenia only (17.0%) (**Table 5**). The sarcopenia only group compared with the osteosarcopenia

Table 4 | Comparing Demographic and Clinical Characteristics Between Sarcopenia Only, Osteoporosis Only, and Osteosarcopenia Groups

Study characteristics	Osteoporosis only	Sarcopenia only	Osteosarcopenia
No. of participants	278	47	195
Age (years), mean ± SD	75.15 (9.7)	76.73 (7.2)	77.88 (8.8)
Female,n(%)	224 (80.6)[a]	13 (27.7)	75 (38.5)[c]
Educational level, n (%)			
Primary	32 (11.8)	3 (6.4)	21 (10.9)
Intermediate	204 (75.0)	35 (74.5)	135 (69.9)
High	36 (13.2)	9 (19.1)	37 (19.2)
DHD index score, mean ± SD	55.5 (10.1)	55.7 (10.0)	54.1 (11.7)
Alcohol ≥20 g/d (women) or ≥30 g/d (men)	13 (6.0)	2 (5.1)	9 (6.1)
Smoking, n (%)			
Never	101 (36.3)	15 (31.9)	48 (24.7)
Former	125 (45.0)	29 (61.7)	109 (56.2)
Current	52 (18.7)a	3 (6.4)	37 (19.1)[b]
Physical activity, median (IQR)	31.8 (11.9. 76.6)	21.6 (9.0. 61.2)	19.4 (9.0. 43.8)
Height (cm), mean (SD)	161.97 (8.52)[a]	171.56 (9.45)	167.13 (9.75)[b]
BMI (kg/m^2), mean (SD)	26.40 (4.23)[a]	24.26 (2.57)	23.57 (2.89)[c]
Normal (BMI 18.5–25)	115 (41.4)	31 (66.0)	142 (72.8)
Overweight (BMI 25–30)	114 (41.0)	15 (31.9)	48 (24.6)
Obese (BMI 30+)	49 (17.6)	1 (2.1)	5 (2.6)
WHR, mean (SD)	0.87 (0.10)	0.92 (0.10)	0.91 (0.11)
Femoral neck BMD (g/m^2), mean ± SD	0.66 (0.05)[a]	1.04 (0.09)	0.78 (0.11)[b, c]
Disability index, n (%)			
No disability	158 (67.2)	20 (51.3)	99 (58.2)
Mild disability	54 (23.0)	13 (33.3)	50 (29.4)
Severe disability	23 (9.8)	6 (15.4)	21 (12.4)
MMSE, n (%)			
Cognitive impairment (<26)	40 (14.4)	7 (14.9)	32 (16.4)
No cognitive impairment (≥26)	238 (85.6)	40 (85.1)	163 (83.6)
Living status, n (%)			
Independent	225 (80.9)	44 (93.6)	163 (84.0)
Other	53 (19.1)	3 (6.4)	31 (16.0)
Hospitalization, yes,n(%)	24 (16.9)	7 (25.0)	22 (19.0)
Pain, yes, n(%)	125 (76.7)	21 (65.6)	80 (60.2)
Falls, yes,n(%)	50 (30.7)	13 (40.6)	34 (25.6)

DHD = Dutch health diet; BMI = body mass index; WHR = waist hip ratio; MMSE = Mini-Mental State Examination.

p value <0.05, adjusted for age, sex, and cohort effect:

a sarcopenia only versus osteoporosis only;

b sarcopenia only versus osteosarcopenia;

c osteoporosis only versus osteosarcopenia. For the group comparisons analyses, physical activity was log transformed.

Table 5 | Comparing Clinical Characteristics Between Sarcopenia Only, Osteoporosis Only, and Osteosarcopenia Groups

Study characteristics	Osteoporosis only	Sarcopenia only	Osteosarcopenia
	278	47	195
History of nonvertebral fracture,n(%)	96 (34.5)a	8 (17.0)	47 (24.1)
Metabolic syndrome,n(%)	64 (24.2)	11 (24.4)	26 (13.9)[c]
Blood pressure >130/85 mmHg	213 (76.6)	37 (80.4)	157 (80.9)
Coronary heart disease,n(%)	6 (2.2)	4 (8.7)	14 (7.3)
Diabetes mellitus,n(%)	20 (7.4)	9 (19.6)	15 (7.9)[b]
COPD,n(%)	57 (20.5)	11 (23.4)	56 (28.7)
Stroke,n(%)	21 (7.6)	6 (12.8)	12 (6.2)
Neoplasm,n(%)	19 (13.4)	6 (21.4)	21 (18.3)
Depression,n(%)	32 (12.9)	3 (7.0)	16 (9.1)

COPD = chronic obstructive pulmonary disease.
p value <0.05, adjusted for age, sex, and cohort effect:
a sarcopenia only versus osteoporosis only;
b sarcopenia only versus osteosarcopenia;
c osteoporosis only versus osteosarcopenia.

Table 6 | Comparing Biochemical Characteristics Between Sarcopenia Only, Osteoporosis Only, and Osteosarcopenia Groups

Study characteristics	Osteoporosis only	Sarcopenia only	Osteosarcopenia
Cholesterol (mmol/L), mean ± SD	5.5 ± 1.05	4.9 ± 1.09	5.2 ± 1.07
HDL cholesterol (mmol/L), mean ± SD	1.6 ± 0.46	1.37 ± 0.42	1.5 ± 0.43
Triglycerides (mmol/L), mean ± SD	1.3 ± 0.55	1.4 ± 0.75	1.3 ± 0.61
Aspartate transaminase (U/L), median (IQR)	24.0 (21.0–27.0)	24.0 (21.0–26.0)	24.0 (22.00–28.0)
ALT (U/L), median (IQR)	16.0 (13.0–21.0)	15.5 (13.0–21.8)	18.0 (14.00–22.0)
ALP (U/L), median (IQR)	72.0 (61.0–84.0)	63.5 (53.3–80.0)	70.0 (61.00–87.0)[b]
Bilirubin (µmol/L), median (IQR)	8.0 (6.0–10.0)	9.00(7.0–13.0)	8.0 (6.00–10.0)[b, c]
GGT (U/L), median (IQR)	21.0 (15.5–30.5)	23.5 (15.5–32.5)	23.0 (17.00–39.5)
Creatinine (µmol/L), median (IQR)	74.0 (65.0–85.0)	86.5 (71.0–108.0)	80.0 (68.00–97.0)
Hemoglobulin (g/dL), mean ± SD	8.4 ± 0.7[a]	8.5 ± 0.9	8.6 ± 0.8
Glucose (mmol/L), median (IQR)	5.3 (5.0–5.8)	5.4 (5.0–6.3)	5.4 (5.10–6.1)
Insulin (pmol/L), median (IQR)	64.0 (43.5–88.0)	61.0 (43.3–78.5)	64.0 (45.00–92.0)
HOMA-IR, median (IQR)	2.2 (1.4–3.3)	2.0 (1.6–3.6)	2.3 (1.46–3.3)

HDL = high-density lipoprotein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; HOMA-IR = homeostatic model assessment-insulin resistance.
p value <0.05, adjusted for age, sex, and cohort effect:
a sarcopenia only versus osteoporosis only;
b sarcopenia only versus osteosarcopenia;
c osteoporosis only versus osteosarcopenia. For the group comparison analyses, the variables presented as median (IQR) were log transformed.

group had higher prevalence of diabetes mellitus (**Table 5**) and higher levels of bilirubin and lower levels of ALP (**Table 6**).

In total 80.4% of the individuals with sarcopenia had low bone mineral density (T-score <–1 SD) (**Figure 3A**). However only 15% of the individuals with osteoporosis were sarcopenic (**Figure 3B**). Being presarcopenic or sarcopenic did not increase the risk of fracture. Individuals with osteoporosis and no (pre) sarcopenia had similar fracture risk (OR: 2.75, 95% CI 2.01-3.75) compared with individuals with osteoporosis and presarcopenia (OR: 3.63, 95% CI 1.83-7.21) or osteoporosis and sarcopenia (OR = 2.59, 95% CI 1.41-4.75) using the individuals with BMD and lean mass in the normal

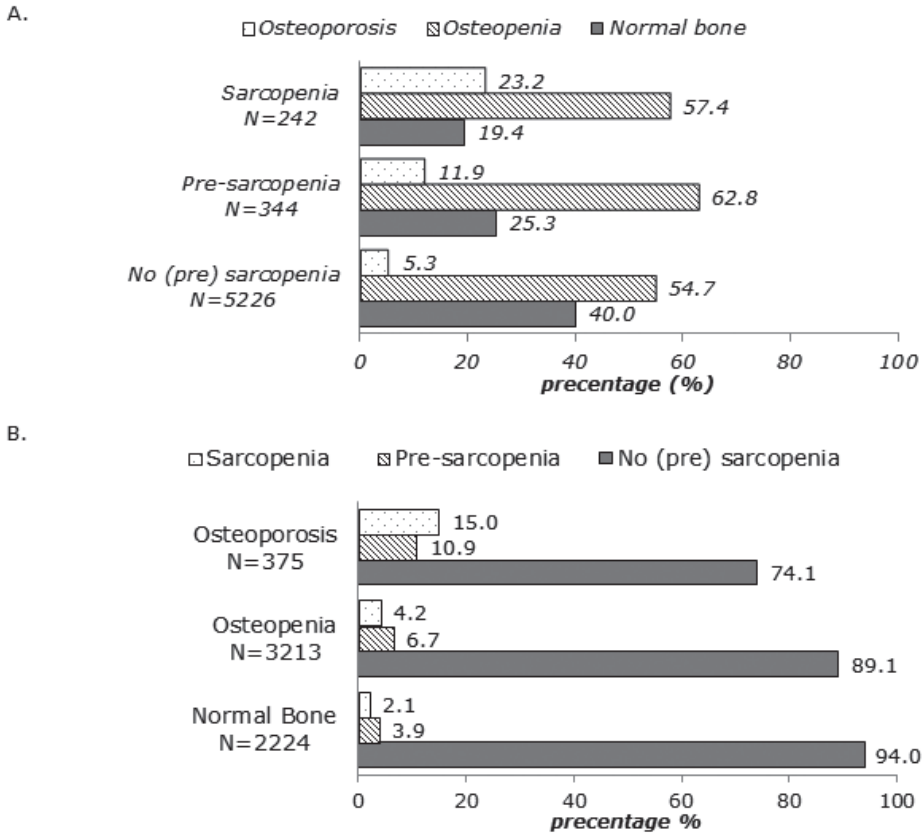

Figure 3 | Bone mineral density status according to the no (pre) sarcopenia, presarcopenia, and sarcopenia groups (A). Sarcopenia status according to the osteoporosis, osteopenia, and normal bone groups (B).

range as reference (**Figure 4**). Furthermore, sarcopenia had no effect even after using T-score in continuous manner (**Supplemental Table 1**).

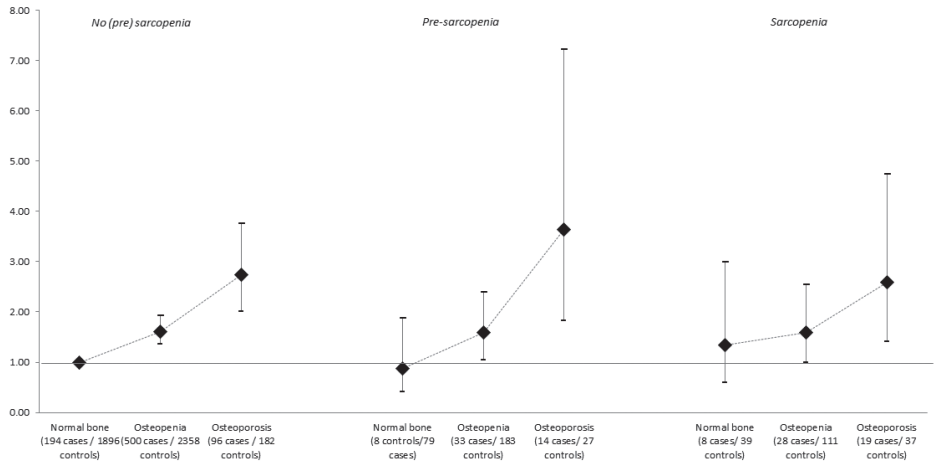

Figure 4 | Fracture risk per different bone mineral density status and sarcopenia status groups compared with individuals with normal bone and no (pre)sarcopenia

DISCUSSION

In this large population-based cohort (n = 5,911), the prevalence of sarcopenia according to the EWGSOP definition was 4.4% (95% CI 3.9-5.0). The prevalence of sarcopenia increased progressively with advancing age and was higher in men than in women. Individuals with sarcopenia were more likely to be smokers and were less physically active. Comorbid conditions were more frequently observed in the sarcopenia group; yet, with the exception of COPD, this finding was mainly explained by age and sex. In total, 80.6% of the sarcopenic individuals had a low bone mineral density. Individuals with osteoporosis, regardless of their sarcopenic status, had greater risk of fracture compared with individuals with normal BMD and normal lean mass.

Previous studies reported substantial differences in prevalence estimates of sarcopenia, fluctuating between 0.9% and 7.5% applying the EWGSOP criteria across population-based studies. Even higher prevalence's of up to 33% were observed in some patient-based settings.[29] These differences in prevalence can be attributed to several reasons, including variation in the instruments used to assess the sarcopenia components; the employed reference population; applied definition and cut-off points; the age range of the included individuals; and regional/ geographical variations. For example, a relatively low prevalence (0.9%) was reported by Patil and colleagues [2] among Finnish community-dwelling women aged 70 to 80 years. This is likely the result of selection bias because women suffering from diverse degenerative conditions were excluded, leaving mostly healthy women in the study. On the contrary, a relatively high prevalence was reported by Volpato and colleagues [4] (7.5%; 95%CI

0.06-0.10) and Patel and colleagues[5] (6.8%; 95%CI 0.03-0.13) among population-based individuals aged 70 to 74 years. However, the CIs of the prevalence's from the previous studies were quite close or overlapped with our Cis, meaning that these differences are not significantly different. However, the higher prevalence in the study by Volpato and colleagues can be caused by the high age of the population and the use of bioelectrical impedance analysis (BIA), which can over/underestimate the lean mass.[30] The equations used to estimate lean mass from BIA differ, leading to varying lean mass estimates depending on the equation used. A prevalence similar to our observation was reported by Kemmler and colleagues[31] (4.6%; 95% CI 0.03–0.06 only in women) and Spira and colleagues[32] (4.1%; 95% CI 0.03-0.05). The latter study population was similar to our population; however, the study population by Kemmler and colleagues was older than ours and used different cut-off points for the sarcopenia components.

Presarcopenic and sarcopenic individuals were more likely to be current smokers (presarcopenia 23.7%; sarcopenia 16.6%; nonsarcopenia 14.6%) and the difference remained significant after adjustment for age and sex. Although several epidemiological studies have shown association between cigarette smoking and increased prevalence of sarcopenia in elderly longtime smokers,[33] a recent meta-analysis showed that the results across studies are largely inconsistent.[34] Previous studies have also reported an inverse association between education level and sarcopenia,[4] but we did not find differences between educational levels. Adequate nutrition and regular physical exercise are the cornerstones of the prevention and treatment of sarcopenia and osteoporosis.[35-37] In line with this, in our study individuals in the sarcopenia group indeed were less physically active, reinforcing its role as an important lifestyle factor in the onset and prevention of sarcopenia. The differences in diet quality in our study were mainly driven by age and sex.

Multiple factors and processes can induce muscle dysfunction leading to the development of sarcopenia. The most prominent ones include physical inactivity, oxidative stress (neuronal degeneration, reduced force generation) and inflammation (elevated interleukin-6 and tumor necrosis factor-alpha). Many diseases can cause muscle dysfunction leading to the development of sarcopenia operating via these mechanisms. With the exception of COPD, we found no significant evidence of sarcopenia being affected or determined by other comorbidities. COPD is a condition presenting with muscle dysfunction and low functional performance. [38] In our study, COPD was more frequently observed in individuals with presarcopenia and sarcopenia, which (unlike other conditions) remained significantly associated after correction for confounding of age and sex. These differences also remained significant after controlling for smoking, physical activity, and number of prescribed corticosteroids (data not shown). These results should be interpreted with caution given that the differences could be affected by other unaccounted confounders. Currently, there

is no clear mechanism underlying the relationship between COPD and sarcopenia. Moreover, a comprehensive summary of the current literature can help us depict the nature of the relationship between COPD and sarcopenia.

Other associations with metabolic factors were significant but not in line with biological expectations, like individuals with sarcopenia holding better lipid profile and less prevalence of metabolic syndrome. These findings make unlikely that other disease processes (with the exception of COPD) are triggered together or by sarcopenia unless supported otherwise by new evidence arising from future well-powered studies. Noteworthy, individuals in the sarcopenia group had a higher prevalence of fractures (sarcopenia 23.5%; nonsarcopenia 15.5%) and presented on average a 0.05 to 0.10 g/cm^2 lower BMD. When we compared fracture risk in sarcopenic and presarcopenic individuals who were in the normal BMD range (T-score >-1SD) with those with osteopenia (T-score >-2.5 and <-1), we identified a trend toward higher risk of fracture in the pre- and sarcopenic groups. The relationship between lean mass and BMD is well established and attributed to mechanical and biochemical interactions.[39,40] Sarcopenia often coexists with osteopenia and/or osteoporosis, and this group of individuals has the highest risk of developing future fractures. [41] Low BMD is associated with fractures, which in turn leads to immobilization and disuse of the lower limbs, resulting in reduced bone and muscle mass. However, we could determine that confounding by age and sex in our study mainly drove the differences in fracture prevalence and fracture risk. In line with a previous study,[42] we showed that sarcopenia does not increase the risk of fracture. Furthermore, 74% of the individuals with osteoporosis did not have low lean mass (11% were presarcopenic and 15% sarcopenic). Interestingly enough, the majority of sarcopenic individuals had low bone mineral density (T-score <-1SD). One theory to explain the latter phenomenon is that low muscle mass cannot exert proper mechanical stimuli on the bone, thus leading to decline in BMD. [43] Yet, the presence of osteosarcopenia is unlikely to exert a higher liability than what low BMD alone exerts on fracture risk. Our study has several strengths as it is performed in a large prospective population-based setting offering the advantage of being able to use standardized methods to define and assess sarcopenia at the population level. Yet, our study is not free of limitations. First, while awaiting follow-up measurements, our study employs a cross-sectional design, which restricts the ability to infer causal relationships between sarcopenia and its clinical correlates. A cross-sectional design can be prone to reverse causation. For example, in our study, we cannot determine if individuals are more disabled because of sarcopenia or if disability leads to sarcopenia. Furthermore, our study setting comprises a follow-up evaluation of the population, which can make it liable to survival bias. Similarly, the measurement of walking speed may present another form of selection bias, as individuals with severe comorbid conditions are not able to walk and be assessed. Therefore, it is possible that

the prevalence of sarcopenia in our study is underestimated. Furthermore, despite our attempts of being as thorough as possible in data acquisition, there was a relatively high percentage of missing data on important covariates like falls and hospitalization. Perhaps this may explain why we do not see significant differences between groups. The dietary intake for RSIII-2 was accessed in the previous visit (RSIII-1), although it has been shown that diet patterns remain relatively constant over time.[44] Yet, there is the possibility that this can have an impact on the comparisons between the groups. Furthermore, in our study, handgrip was measured on the nondominant hand and the cut-off created were based on the dominant hand, which can underestimate the prevalence of low grip strength. In addition, a complete assessment of sarcopenia was only possible during the latest follow-up assessment where total body lean mass and muscle strength/function measurements were both available.

In conclusion, in this population-based cohort, the prevalence of sarcopenia is relatively low but shown to increase markedly with age, where 1 in 5 men and 1 in 10 women are sarcopenic by the age of 80 years. Lifestyle factors seem to play an important role in the prevalence of sarcopenia. COPD was the only clinical risk factor that was more prevalent in individuals with presarcopenia and sarcopenia. Overall, our findings suggest that sarcopenia does not add additional risk for fracture. The majority of individuals with sarcopenia have low bone mineral density, suggesting that co-occurrence of both conditions may follow similar pathways and be responsive to similar interventions.

Detailed acknowledgments and online resources can be found in the published article online

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