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ORIGINAL ARTICLE

Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men

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Abstract
Summary The aim of this study was to determine the relationship between reduced muscle mass (sarcopenia) and areal bone mineral density (BMD_a) in middle-aged and elderly community-dwelling European men. Men with sarcopenia had significantly lower BMD_a and were more likely to have osteoporosis compared with men without sarcopenia.
Introduction In men, the relationship between reduced muscle mass (sarcopenia) and BMD_a is unclear. This study aimed to determine this relationship in middle-aged and elderly community-dwelling men.
Methods Men aged 40–79 years from the Manchester (UK) and Leuven (Belgium) cohorts of the European Male Ageing Study were invited to attend for assessment including dual-energy X-ray absorptiometry, from which appendicular lean mass (aLM), fat mass (FM) and whole-body, spine and hip BMD_a were determined. Relative appendicular skeletal muscle mass (RASM) was calculated as aLM/height². Muscle strength was assessed in subjects from Leuven. Sarcopenia was defined by RASM at <7.26 kg/m² and by the recent definition of the European Working Group on Sarcopenia in Older People (RASM at <7.26 kg/m^2 plus low muscle function). Linear regression was used to determine the associations between aLM, FM, muscle strength and BMD_a and logistic regression to determine the association between sarcopenia and osteoporosis.
Results Six hundred seventy-nine men with a mean age of 59.6 (SD=10.7), contributed data to the analysis; 11.9 % were sarcopenic by the conventional definition. After adjustment

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for age and centre, aLM, RASM and FM were positively associated with BMD_a. Men with RASM at <7.26 kg/m² had significantly lower BMD_a compared with those with RASM at ≥7.26 kg/m^2. In a multivariable model, aLM was most consistently associated with BMD_a. Men with sarcopenia were more likely to have osteoporosis compared with those with normal RASM (odds ratio=3.0; 95 % CI=1.6–5.8).

Conclusions Sarcopenia is associated with low BMD_a and osteoporosis in middle-aged and elderly men. Further studies are necessary to assess whether maintaining muscle mass contributes to prevent osteoporosis.

Keywords Areal bone mineral density (BMD_a) · Lean mass · Muscle strength · Osteoporosis · Relative appendicular skeletal muscle mass (RASM), sarcopenia

Introduction

A progressive decline in bone mineral density (BMD), muscle mass and muscle strength are key features of the ageing process. They predispose older individuals to disability, falls, fractures and frailty and so pose a major and increasing clinical and public health burden. There is now considerable evidence that muscle and bone have common genetic, nutritional, lifestyle and hormonal determinants [1–4]. In addition, muscle and bone interact to impact on bone strength [5]. A possible mechanism is the dynamic loading of muscles, to which weight-bearing bones adapt. This dynamic loading arises from muscle contractions as well as from the ground impact during weight-bearing activities [6]. Exploring the relationship between muscle and bone may help in the development of interventions that will benefit musculoskeletal function, with the aim of reducing adverse clinical outcomes such as falls and fractures.

The evidence for this relationship between muscle and bone in ageing individuals comes mostly from observational epidemiological studies in women. In postmenopausal women, almost all studies show that *lean mass* (LM (kg)) is correlated positively with whole-body and/or regional areal bone mineral density (BMD_a (g/cm^2)) [7–10]. Relative appendicular skeletal muscle mass (RASM, appendicular LM divided by height squared (kg/m²)) was also found to contribute significantly to regional BMD_a [11]. In most [7, 9] but not all studies [8, 10], *fat mass* (FM (kg)) was an additional determinant. In some, only FM [12] or body mass index (BMI) [3], and not LM, was linked with BMD_a. There is some evidence that FM may be more important after the menopause [13, 14]. *Muscle strength* was found to be associated with BMD_a in postmenopausal women, independent of weight [15, 16] but dependent on LM [9]. Several authors have assessed the relationship also between *low* muscle mass (sarcopenia) and BMD_a and found lower BMD_a in sarcopenic women [8, 11, 17]. In these studies, sarcopenia in women has been defined as RASM less than 5.45 kg/m^2, according to the approach of Baumgartner et al. [18]. Recently, however, the European Working Group on Sarcopenia in Older People (EWGSOP) suggested restricting the definition of sarcopenia by requiring the presence of an additional criterion besides reduced muscle mass, either low muscle strength or poor physical performance [19].

In men, the available data suggest a different relationship between bone and body composition, although the results are inconsistent. Some studies showed that both LM (absolute or relative) and FM contributed independently to BMD_a, with a positive [7, 20] or a negative [21] correlation between FM and BMD_a. However, in other studies, only absolute LM [22] or RASM [2] remained independently associated with BMD_a, with no influence of FM, contrary to the situation in women. Some studies even showed no relationship between LM and BMD_a after adjusting for BMI [3] or when effects of skeletal size were removed by dividing BMD_a by height [23]. Thus, the relative importance of LM vs. FM on BMD_a remains uncertain in men. As in women, muscle strength was found to be a determinant of BMD_a, independent of weight [16, 24], though not independent of LM [9]. In men, the association between BMD_a and sarcopenia defined as low RASM has not been thoroughly studied, and there are no data exploring the relationship when using the more stringent EWGSOP definition of sarcopenia [19].

The aim of this study was to clarify the relationship between muscle and bone in men. More specifically, we wanted to determine the association between muscle mass, muscle strength and BMD_a, as well as the relationship between sarcopenia and BMD_a in middle-aged and elderly European men. Sarcopenia will be defined by low muscle mass alone as well as by the more stringent EWGSOP definition. To this end, we used cross-sectional data from two centres participating in the European Male Ageing Study (EMAS), a population-based study of ageing in men.

Materials and methods

Subjects

Men aged 40–79 years were recruited from population registers in Manchester (UK) and Leuven (Belgium) for participation in EMAS [25]. Subjects were invited to attend by a letter of invitation which included a short postal questionnaire. Those who agreed to take part were invited to attend a local clinic for an interviewer-assisted questionnaire, assessment of physical function, height, weight and bone densitometry. Subjects in Leuven had also assessment

of muscle strength. Ethical approval for the study was obtained in accordance with local institutional requirements in each centre. All subjects provided written informed consent.

Assessments

Subjects completed a postal questionnaire which included a question about current smoking and subsequently attended a research clinic to complete an interviewer-assisted questionnaire and undergo clinical assessments. The interviewer-assisted questionnaire included the Physical Activity Scale for the Elderly (PASE), which combines information on leisure, household and occupational activity [26]. The questionnaire also included queries about current prescription and non-prescription drugs, by examination of medications and prescriptions brought into the clinic for that purpose. Height and weight were measured in a standardised fashion; height to the nearest 1 mm using a stadiometer (Leicester Height Measure, SECA UK Ltd) and body weight to the nearest 0.1 kg using an electronic scale (SECA, model no. 8801321009, SECA UK Ltd). BMI was calculated as weight in kilogrammes divided by height in square metres. Physical ability/dysfunction was measured by using a component of the Reuben's physical performance test (seconds taken to walk 50 ft) [27] and the Tinetti test for balance and postural stability (seconds taken to go from a sitting to a standing position) [28].

Bone densitometry and assessment of muscle strength

Subjects (N=697) had dual-energy X-ray absorptiometry (DXA) scans performed on QDR 4500A Discovery scanners (Hologic Inc, Bedford, MA, USA), to measure whole-body, femoral neck, total hip and lumbar spine BMD_a, total LM, appendicular LM (aLM) and total FM. All scans and analyses were performed by trained and certified DXA technicians. The Hologic Spine Phantom was scanned daily to monitor the device performance and long-term stability. Devices in Leuven and Manchester were cross-calibrated with the European Spine Phantom.

Muscle strength testing was performed in Leuven only (N=361). *Grip strength* was evaluated with the Jamar 1 hand-held dynamometer (TEC Inc., Clifton, NJ). Three measurements of maximum strength were taken at both sides, and the highest value was recorded as maximal grip strength (in kilogrammes) [29]. *Isometric and isokinetic strength* were evaluated in the knee extensors of the left leg, primarily the quadriceps, to correspond to the side of proximal femur BMD_a measurement. Strength was measured using an isokinetic dynamometer (Cybex II, Lumex Inc., Ronkonkoma, NY) according to the standardised procedures provided by the manufacturer. All tests were demonstrated by the assessor before being performed by the volunteer. Maximum isometric strength was measured at different angles (60° and 90°), the highest value of three measurements taken as maximum isometric strength for each angle. Maximum isokinetic strength was measured at different angular velocities (60°/s and 90°/s) as the highest value of three attempts [30]. To determine the short-term reproducibility, duplicate measurements (with a minimum interval of 1 h) were performed in a random sample of 15 subjects. CV were 10.8, 16.7, 11.3 and 14.6 % for isometric quadriceps strength at 60°, isometric quadriceps strength at 90°, isokinetic quadriceps strength at 60°/s and isokinetic quadriceps strength at 90°/s, respectively.

Diagnosis of osteoporosis and sarcopenia

Osteoporosis was classified as a T-score at the femoral neck, total hip or lumbar spine of at least 2.5 standard deviations (SD) below the peak BMD_a of a young healthy male reference group. The reference population was the Third National Health and Nutrition Examination Survey [31].

Sarcopenia was defined using two approaches. The first was based on the approach of Baumgartner et al. who described sarcopenia as RASM (aLM/height^2) below a threshold of 7.26 kg/m^2 [18]. aLM is the sum of LM of arms and legs, measured by DXA. DXA-measured LM is considered a good indicator of skeletal muscle mass [32]. The second approach was based on the new European consensus definition of the EWGSOP in which a person fulfilling only the criterion of low muscle mass is categorised as having pre-sarcopenia, while a person who also has low muscle strength or low physical performance is categorised as having sarcopenia, and a person with all three criteria as having severe sarcopenia [19]. Low muscle strength was defined as grip strength at ≤29 kg if BMI is ≤24, ≤30 kg if BMI is 24.1–28 and ≤32 kg if BMI is >28 [33], and low physical performance as a walking speed of <1 m/s [34].

Analysis

Subjects taking bone active therapies (corticosteroids, bisphosphonates, calcium and vitamin D, N=39) were excluded from the analysis. No subjects were treated with parathyroid hormone (PTH). Descriptive statistics were used to summarise subject characteristics. The association between RASM, relative FM (total FM/height^2 (in kilogrammes per square metre)) and muscle strength on the one hand and BMD_a (total hip and lumbar spine) on the other hand was assessed visually using scatter plots, superimposing linear lines and also locally weighted scatter plot smooth (LOWESS) curves to examine potential non-linearity. The strength of the associations was assessed using

linear regression (with BMD_a as the dependent variable) and results expressed as β coefficients. In subsequent analyses for ease of interpretation and comparison we standardised the BMD_a measures into Z-scores. Multivariable linear regression was then used to determine the association between the risk factors (anthropometry, physical performance, current smoking, aLM and total FM) and the outcome (whole-body, femoral neck, total hip and lumbar spine BMD_a) with adjustments made for age and centre. Multivariable linear regression was also used to examine the association between muscle strength (quadriceps strength) and BMD_a with adjustments for age (Leuven cohort only). To examine potential non-linear/threshold effects we categorised the risk factors into quintiles. In a final model we used stepwise linear regression including all the potential factors (centre, age, height, time to walk 50 ft, current smoking, aLM, total FM and isometric quadriceps strength at 90°). Both forwards (starting with an empty model) and backwards (starting with the full model) variable selection was employed with no difference in results. Only significant ($p<0.05$) factors were retained in the models. Absolute aLM and not RASM was chosen in these models to allow the influence of height to be independently examined. Isometric quadriceps strength at 90° was chosen to represent muscle strength as it appeared to be the most strongly associated with BMD_a. Similarly, of the physical activity and performance measures, time to walk 50 ft and not PASE score or sit to stand time was chosen as time to walk 50 ft was found to have the most consistent association with BMD_a. For all the stepwise multivariable models, the variance inflation factor was calculated to quantify the severity of any potential multicollinearity and consequently weight/BMI and grip strength were not included due to multicollinearity. The results of all linear regression analyses are expressed as β coefficients or standardised β coefficients and 95 % confidence intervals (CI). Finally, logistic regression was used to examine the association between sarcopenia (using the two operational definitions) and osteoporosis, with results expressed as odds ratios (OR) and 95 % CI. Statistical analysis was performed using STATA version 9.2 (http://www.stata.com).

Results

Subjects

A total of 679 men with a mean age of 59.6 (SD=10.7) years and mean BMI of 27.1 (SD=3.7) kg/m² were included in the analysis. Details of the subject characteristics are shown in Table 1. Mean femoral neck BMD_a was 0.807 (SD=0.128) g/cm² and mean lumbar spine BMD_a 1.049 (SD=0.173) g/cm². Twelve per cent of men were sarcopenic according to the conventional definition of sarcopenia and 3.7 % based on the EWGSOP definition (Leuven cohort only). Nine per cent were classified as being osteoporotic.

Table 1 Subject characteristics

Variable (N=679)	Mean (SD)	Percent
Age at interview (years)	59.6 (10.7)	
Height (cm)	174.5 (7.0)	
Weight (kg)	82.7 (13.1)	
Body mass index (kg/m^2)	27.1 (3.7)	
PASE score (0–1,100)	208.7 (83.8)	
Tinetti: time taken from sitting to standing (s)	12.5 (3.3)	
PPT: time taken to walk 50 ft (s)	13.7 (2.6)	
Whole-body BMD_a (g/cm^2)	1.162 (0.107)	
Femoral neck BMD_a (g/cm^2)	0.807 (0.128)	
Total hip BMD_a (g/cm^2)	1.015 (0.142)	
Lumbar spine BMD_a (g/cm^2)	1.049 (0.173)	
Appendicular lean mass (kg)	25.2 (3.6)	
RASM[a] (kg/m^2)	8.2 (0.9)	
Total fat mass (kg)	19.9 (6.0)	
Relative total fat mass (kg/m^2)	6.5 (1.9)	
Current smoker (yes vs. no)		13.8
Sarcopenia[b]		11.9
Osteoporosis[c]		8.8
Leuven cohort (N=361)		
Isometric quadriceps strength 60° (Nm)	170.8 (50.5)	
Isometric quadriceps strength 90° (Nm)	165.0 (45.3)	
Isokinetic quadriceps strength 60°/s (Nm)	121.2 (44.2)	
Isokinetic quadriceps strength 90°/s (Nm)	105.2 (44.0)	
Grip strength (kg)	41.5 (8.2)	
Sarcopenia[d]		3.7

PPT physical performance test, *BMD_a* areal bone mineral density, *RASM* relative appendicular skeletal muscle mass

[a] Appendicular lean mass divided by height squared

[b] Sarcopenia according to the definition of Baumgartner et al. [18]: RASM at <7.26 kg/m^2

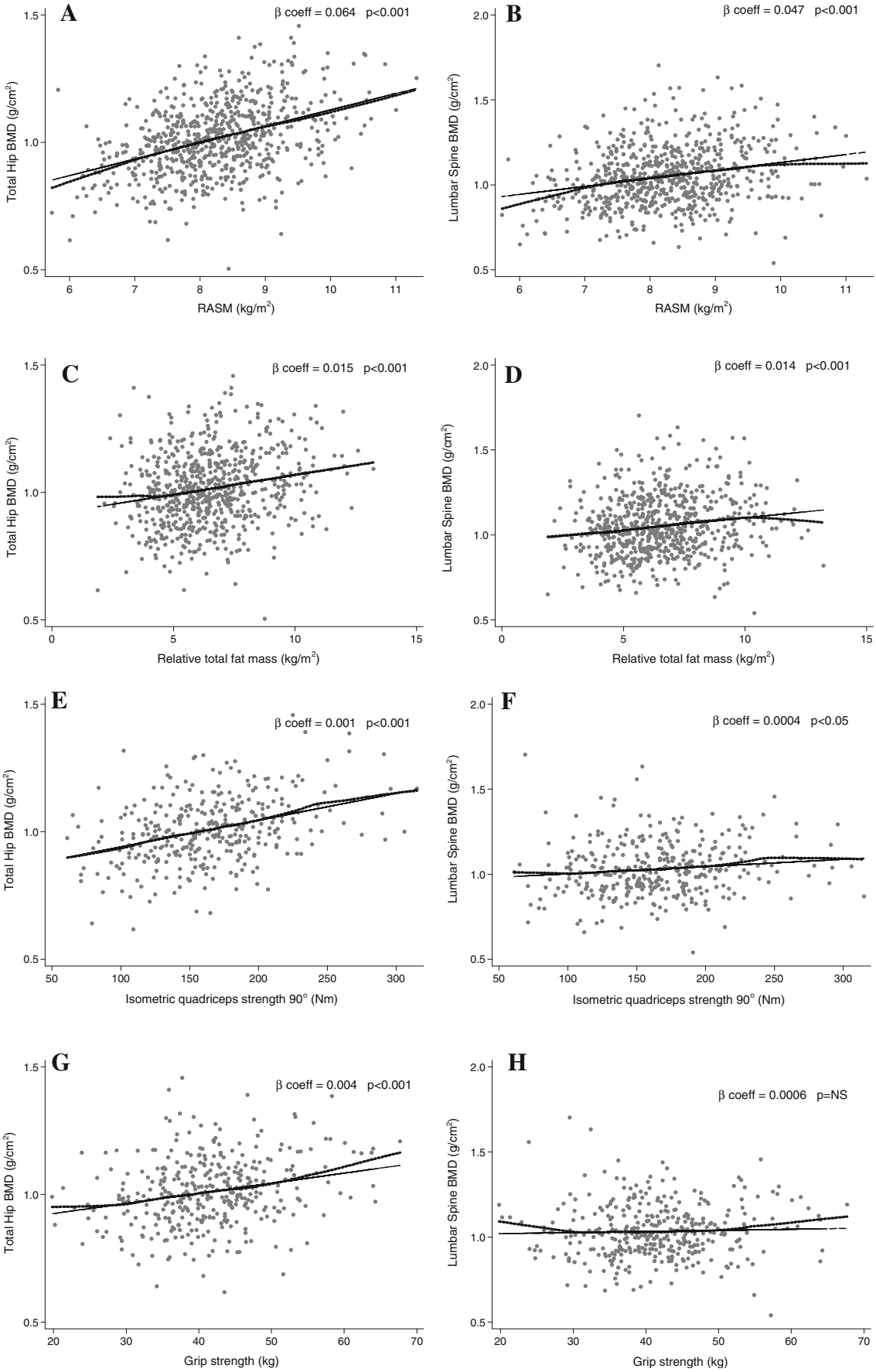
[c] T-score≤−2.5 at femoral neck, total hip, or lumbar spine

[d] Sarcopenia according to the definition of EWGSOP [19]: RASM at <7.26 kg/m^2 +low muscle strength (grip strength, ≤29 kg if BMI is ≤24; ≤30 kg if BMI is 24.1–28; and ≤32 kg if BMI is >28 [33]) or low physical performance (walking speed, 1.0 m/s [34]

Association between anthropometry, physical activity/performance, muscle strength and BMD_a

In bivariate unadjusted analysis, height, weight and BMI were positively associated with BMD_a at all sites. Also

Fig. 1 Association between total hip BMD_a and **a** RASM, **c** relative total ▶ fat mass, **e** isometric quadriceps strength 90°, and **g** grip strength. Association between lumbar spine BMD_a and **b** RASM, **d** relative total fat mass, **f** isometric quadriceps strength 90° and **h** grip strength. The *solid lines* represent the linear relationship; the *dashed lines* represent LOWESS


A
β coeff = 0.064 p<0.001
Total Hip BMD (g/cm²)
RASM (kg/m²)
B
β coeff = 0.047 p<0.001
Lumbar Spine BMD (g/cm²)
RASM (kg/m²)
C
β coeff = 0.015 p<0.001
Total Hip BMD (g/cm²)
Relative total fat mass (kg/m²)
D
β coeff = 0.014 p<0.001
Lumbar Spine BMD (g/cm²)
Relative total fat mass (kg/m²)
E
β coeff = 0.001 p<0.001
Total Hip BMD (g/cm²)
Isometric quadriceps strength 90° (Nm)
F
β coeff = 0.0004 p<0.05
Lumbar Spine BMD (g/cm²)
Isometric quadriceps strength 90° (Nm)
G
β coeff = 0.004 p<0.001
Total Hip BMD (g/cm²)
Grip strength (kg)
H
β coeff = 0.0006 p=NS
Lumbar Spine BMD (g/cm²)
Grip strength (kg)

higher aLM (both absolute and relative to height) was associated with higher BMD_a at all sites (data not shown). Total hip BMD_a and lumbar spine BMD_a increased with increasing RASM (β=0.064 and 0.047 g/cm^2 per kg/m² respectively, see Fig. 1a, b). Similarly, higher absolute total FM was associated with higher BMD_a at all sites (data not shown) and increasing relative total FM with increasing total hip and lumbar spine BMD_a (see Fig. 1c, d).

In the *Leuven cohort* only, higher quadriceps strength was associated with higher BMD_a at all sites, and only the association between isometric quadriceps strength measured at 60° and lumbar spine BMD_a was not significant (data not shown). Isometric quadriceps strength measured at 90° was positively associated with BMD_a at the total hip and lumbar spine (see Fig. 1e, f). Higher grip strength was also associated with higher BMD_a at the total hip, but not at the lumbar spine (see Fig. 1g, h). All these associations observed were broadly linear with no evidence of threshold effects.

Physical activity as measured by PASE score was positively associated with BMD_a in the whole body, femoral neck and total hip. Similarly, a longer time taken to walk 50 ft was associated with lower whole-body, femoral neck and total hip BMD_a, while a longer time taken to go from a sitting to a standing position was linked with lower BMD_a at all sites (data not shown). Current smoking was associated with lower BMD_a at the total hip (data not shown).

After adjustment for both age and centre, height, weight and BMI remained positively associated with BMD_a at all sites (see Table 2). Also higher aLM (both absolute and relative) remained associated with higher BMD_a at all sites; compared with those with RASM of ≥7.26 kg/m^2, those with RASM of <7.26 kg/m^2 had significantly lower BMD_a. Higher absolute total FM also remained associated with higher BMD_a at all sites and relative total FM was associated positively with BMD_a at the femoral neck, total hip and lumbar spine (but not whole body). There was no evidence of threshold effects when any of the anthropometric variables were included in the models categorised into quintiles.

In terms of the physical performance/activity measures, a longer time taken to walk 50 ft remained associated with lower BMD_a at whole body, femoral neck and total hip,

Table 2 Association between anthropometry, physical activity/performance, muscle strength and bone density: adjusted for age and centre

Independent variables	Dependent variable			
	Whole-body BMD_a (per SD)	Femoral neck BMD_a (per SD)	Total hip BMD_a (per SD)	Lumbar spine BMD_a (per SD)
Whole cohort[a]				
Height (cm)	0.043 (0.033, 0.054)***	0.036 (0.025, 0.047)***	0.043 (0.032, 0.054)***	0.036 (0.024, 0.047)***
Weight (kg)	0.024 (0.018, 0.029)***	0.031 (0.026, 0.036)***	0.035 (0.030, 0.040)***	0.026 (0.021, 0.031)***
BMI (kg/m^2)	0.051 (0.032, 0.071)***	0.089 (0.071, 0.108)***	0.098 (0.079, 0.116)***	0.069 (0.050, 0.089)***
Appendicular lean mass (kg)	0.117 (0.096, 0.137)***	0.119 (0.099, 0.139)***	0.139 (0.119, 0.159)***	0.102 (0.080, 0.123)***
RASM (kg/m^2)	0.317 (0.235, 0.398)***	0.373 (0.293, 0.453)***	0.433 (0.353, 0.513)***	0.294 (0.209, 0.379)***
RASM (kg/m^2)				
≥7.26	Referent	Referent	Referent	Referent
<7.26	−0.560 (−0.786, −0.335)***	−0.661 (−0.885, −0.437)***	−0.740 (−0.968, −0.512)***	−0.593 (−0.827, −0.360)***
Total fat mass (kg)	0.020 (0.008, 0.032)**	0.041 (0.030, 0.053)***	0.049 (0.037, 0.061)***	0.034 (0.022, 0.046)***
Relative total fat mass (kg/m^2)	0.028 (−0.010, 0.066)	0.105 (0.068, 0.143)***	0.122 (0.084, 0.160)***	0.081 (0.042, 0.120)***
PASE score/10 units	0.009 (−0.001, 0.019)	0.003 (−0.007, 0.013)	0.004 (−0.007, 0.014)	0.003 (−0.007, 0.014)
Time to walk 50 ft (s)	−0.051 (−0.080, −0.021)**	−0.034 (−0.064, −0.004)*	−0.046 (−0.076, −0.016)**	−0.020 (−0.051, 0.011)
Sit to stand time (s)	−0.029 (−0.052, −0.006)*	−0.015 (−0.039, 0.008)	−0.021 (−0.045, 0.002)	−0.026 (−0.049, −0.002)*
Current smoker (yes vs. no)	−0.253 (−0.464, −0.042)*	−0.252 (−0.464, −0.040)*	−0.307 (−0.523, −0.092)**	−0.185 (−0.403, 0.034)
Leuven cohort only[b]				
Isometric quadriceps strength 60° (per 10 Nm)	0.039 (0.017, 0.060)***	0.046 (0.024, 0.067)***	0.050 (0.028, 0.071)***	0.021 (−0.001, 0.044)
Isometric quadriceps strength 90° (per 10 Nm)	0.060 (0.037, 0.084)***	0.053 (0.029, 0.076)***	0.074 (0.051, 0.096)***	0.041 (0.016, 0.065)**
Isokinetic quadriceps strength 60°/s (per 10 Nm)	0.053 (0.029, 0.077)***	0.035 (0.010, 0.060)**	0.051 (0.027, 0.076)***	0.043 (0.018, 0.068)**
Isokinetic quadriceps strength 90°/s (per 10 Nm)	0.051 (0.027, 0.075)***	0.040 (0.015, 0.064)**	0.048 (0.024, 0.073)***	0.042 (0.018, 0.067)**
Grip strength (kg)	0.024 (0.011, 0.037)***	0.013 (−0.0003, 0.026)	0.024 (0.011, 0.037)***	0.008 (−0.005, 0.021)

Results expressed as β coefficients and 95 % CI

BMD$_a$ areal bone mineral density, *BMI* body mass index, *RASM* relative appendicular skeletal muscle mass, *PASE* Physical Activity Scale for the Elderly, *Nm* Newton meter

*p<0.05; **p<0.01; ***p<0.001

[a] Adjusted for age and centre

[b] Adjusted for age

while a longer time taken to go from a sitting to a standing position remained associated with lower BMD_a in the whole body and lumbar spine. PASE score however was not associated with BMD_a at any site after age and centre adjustment. Current smoking was associated with lower BMD_a at the whole body, femoral neck and total hip.

In the *Leuven cohort*, when examining muscle strength, higher isokinetic quadriceps strength remained associated with higher BMD_a at all sites. Results were comparable for isometric quadriceps strength, though not significant for the 60° measure and lumbar spine BMD_a. In contrast, higher grip strength remained only associated with higher whole-body and total hip BMD_a. Quadriceps strength explained a larger proportion of the variability in BMD_a compared with grip strength (3–10 vs. 0–3 %, respectively; data not shown). There was no evidence of threshold effects when any of the muscle strength measures were included in the models categorised into quintiles.

No difference in results was observed after stratification by age (equal numbers of men in four 10-year age bands—40–49, 50–59, 60–69 and 70–79 years), with broadly similar associations evident above and below the age of 60 years, though the associations between total FM and BMD_a at the femoral neck, total hip and lumbar spine were significantly stronger ($p<0.05$) in those over 60 years of age (data not shown).

In a *stepwise multivariable model* in the Leuven and Manchester cohort which tested centre, age, height, time to walk 50 ft and current smoking as confounding factors, increasing aLM remained associated with higher BMD_a at all sites and total FM was associated with BMD_a at the whole-body and total hip sites (see Table 3). The effect size of total FM on BMD_a was small in comparison with that of aLM and the direction of the effect was not consistent, with total FM being positively linked with total hip BMD_a and negatively with whole-body BMD_a. Age, centre, time to walk 50 ft and current smoking were retained in some of the models. Overall, the significant variables accounted for 12–26 % of the variability in BMD_a.

Similar results were observed in the Leuven and Manchester cohorts individually, though in the Leuven cohort, time to walk 50 ft was not associated with BMD_a at the femoral neck and total FM was not associated with any of the bone measurements (data not shown).

In a *second stepwise multivariable model* in the Leuven cohort only that also included quadriceps strength, increasing aLM remained associated with higher BMD_a at all sites (see Table 3), and isometric quadriceps strength remained

Table 3 Association between age, lean and fat mass, physical performance and bone density: multivariable model

	Dependent variables			
	Whole-body BMD_a (per SD)	Femoral neck BMD_a (per SD)	Total hip BMD_a (per SD)	Lumbar spine BMD_a (per SD)
Independent variables				
Centre: Manchester	−0.425 (−0.559, −0.291)***	–	–	0.158 (0.014, 301)*
Age (years)	–	–	–	0.018 (0.011, 0.025)***
Height (cm)	–	–	–	–
Time to walk 50 ft (s)	−0.034 (−0.060, −0.007)*	−0.027 (−0.054, −0.001)*	−0.036 (−0.061, −0.008)*	–
Current smoker (yes vs. no)	–	–	−0.210 (−0.398, −0.021)*	–
Appendicular lean mass (kg)	0.130 (0.109, 0.151)***	0.121 (0.102, 0.140)***	0.118 (0.097, 0.139)***	0.100 (0.078, 0.122)***
Total fat mass (kg)	−0.016 (−0.028, −0.003)*	–	0.017 (0.005, 0.029)**	–
R^2 for the model	0.24	0.21	0.26	0.12
Model including quadriceps strength: Leuven cohort only				
Age (years)	–	–	–	0.018 (0.009, 0.028)***
Height (cm)	–	–	–	–
Time to walk 50 ft (s)	–	–	–	–
Current smoker (yes vs. no)	–	–	−0.327 (−0.570, −0.084)**	–
Appendicular lean mass (kg)	0.091 (0.058, 0.124)***	0.119 (0.093, 0.145)***	0.109 (0.078, 0.140)***	0.093 (0.063, 0.122)***
Total fat mass (kg)	–	–	–	–
Isometric quadriceps strength 90° (per 10 Nm)	0.028 (0.003, 0.052)*	–	0.024 (0.001, 0.048)*	–
R^2 for the model	0.18	0.20	0.25	0.10

Results expressed as β coefficients and 95 % CI. Stepwise linear regression including centre, age, height, time to walk 50 ft, current smoking, appendicular lean mass and total fat mass. In the Leuven cohort only, stepwise linear regression also included isometric quadriceps strength 90° and excluded centre. Variables remained in model if $p<0.05$

BMD_a areal bone mineral density, *Nm* Newton meter

*$p<0.05$; **$p<0.01$; ***$p<0.001$

Table 4 The association between sarcopenia and osteoporosis

	Number	Osteoporsis[a] OR (95 % CI)
RASM (per SD)[b]	674	0.7 (0.5, 0.9)**
Sarcopenia[c]		
RASM at ≥7.26 kg/m^2	594	Referent
RASM at <7.26 kg/m^2	80	3.0 (1.6, 5.8)**
Leuven cohort only[d]		
Sarcopenia[e]		
Normal	321	Referent
Pre-sarcopenia	41	3.8 (1.6, 9.1)**
Sarcopenia	14	2.0 (0.4, 10.0)
Severe sarcopenia	0	–

Results expressed as odds ratios (OR) and 95 % CI

RASM relative appendicular skeletal muscle mass

*p<0.05; **p<0.01; ***p<0.001

[a] Osteoporosis: T-score≤−2.5 at femoral neck, total hip or lumbar spine

[b] Adjusted for age and centre

[c] Sarcopenia using definition of Baumgartner et al. [18]: RASM at <7.26 kg/m²

[d] Adjusted for age

[e] Sarcopenia using definition of EWGSOP [19]: presarcopenia—RASM at <7.26 kg/m^2, sarcopenia—RASM at <7.26 kg/m^2 +low muscle strength (grip strength, ≤29 kg if BMI is ≤24; ≤30 kg if BMI is 24.1–28; and ≤32 kg if BMI is >28 [33]) or low physical performance (walking speed <1.0 m/s [34]) and severe sarcopenia—all three criteria

associated with whole-body and total hip BMD_a. In contrast, total FM was not associated with BMD_a, nor was time to walk 50 ft. Current smoking was associated with total hip BMD_a. At the lumbar spine, a positive independent association was present between age and BMD_a, but age was not an independent determinant of BMD_a at the other sites. Overall, these variables accounted for approximately 10–25 % of the variability in BMD_a. aLM explained 20 % of the variability in femoral neck BMD_a.

Association between sarcopenia and osteoporosis

Sarcopenia (RASM at <7.26 kg/m^2) was associated with a 3-fold higher risk of osteoporosis (OR=3.0; 95 % CI=1.6, 5.8) compared with those with normal RASM after adjustment for age and centre (see Table 4). Each SD increase in RASM was associated with a 30 % reduction in the likelihood of osteoporosis (OR=0.7; 95 % CI=0.5, 0.9).

Similarly, in the Leuven cohort, men with EWGSOP-defined *pre-sarcopenia* (RASM at <7.26 kg/m^2) were almost four times more likely to have osteoporosis compared with those with normal RASM after adjustment for age (OR=3.8; 95 % CI=1.6, 9.1). Those with *sarcopenia* according to the EWGSOP definition (low RASM and low grip strength or low physical performance) were twice as likely to have osteoporosis compared with men with normal RASM, although the CI were wide as only 14 men were classified into this group (OR=2.0; 95 % CI=0.4, 10.0). No subjects were classified as having severe sarcopenia (low RASM, low grip strength and low physical performance).

Discussion

In this cross-sectional study, both aLM (absolute and relative) and total FM were associated with BMD_a at all sites, after adjusting for age and centre. Quadriceps strength was linked with BMD_a at all sites, and grip strength was associated with BMD_a at the whole-body and total hip site. In a stepwise multivariable model, aLM was the strongest independent determinant of BMD_a at whole body, femoral neck, total hip and lumbar spine. At the whole-body and total hip sites, there was an additional independent contribution of isometric quadriceps strength, and current smoking contributed independently to total hip BMD_a. Overall, these variables accounted for approximately 10–25 % of the variability in BMD_a. aLM explained 20 % of the variability in femoral neck BMD_a. When isometric quadriceps strength was not included in the model, physical performance (time to walk 50 feet), total FM and current smoking were independently associated with BMD_a in some of the models in the entire investigated cohort, while in the Leuven cohort alone, physical performance and current smoking, but not total FM, contributed independently to BMD_a in some of the models.

Several, though not all [3], studies have suggested that LM [7, 9, 22] or RASM [2, 20] are significantly associated with BMD_a in men. In our analysis, aLM explained 20 % of the variability in BMD_a at the femoral neck in midde-aged and elderly men, which is comparable with a recent study in 160 healthy men aged 20 to 72 years, in whom RASM explained 15 % of the variance in femoral neck BMD_a [2]. Our observation that aLM is an independent contributor to BMD_a may reflect the mechanical loading that muscle contractions and resulting movements place on bone. Alternatively, it could be attributed to the fact that muscle and bone have common genetic, nutritional, lifestyle and hormonal determinants operating mainly during growth.

In a study in men that, in contrast, could *not* identify an independent effect of aLM on femoral neck and total hip BMD_a, the authors surmised that the relationship between aLM and BMD_a was largely mediated by physical activity [3]. This was previously demonstrated by Walsh et al. in women in whom the relationship between RASM and BMD_a disappeared after adjusting for physical activity (assessed using the Baecke Physical Activity Questionnaire) [35]. However, in our study, aLM remained an independent determinant of BMD_a when physical performance (time to walk 50 feet) was included in the multivariate model.

Physical activity (as measured by PASE) was not related with any of the bone measurements. The association between aLM and BMD_a was also independent of current smoking. Other authors have suggested that the positive relationship between LM and BMD_a might be attributed to bone or body size, when this factor is not adjusted for [9, 36]. BMD_a and LM are influenced by bone/body size. Failing to control for height may then overestimate the relationship between LM and BMD_a. Several authors indeed showed that the effect of LM on bone diminished when adjusting BMD_a for body size by dividing it by height or by using bone mineral apparent density [9, 14, 23]. However, in our analysis, the relationship between aLM and BMD_a persisted after adjusting for height (data not shown). Moreover, according to Khosla et al. the attempt to control for body size tends to bias against potential effects of LM on bone [14]. Finally, Baumgartner et al. supposed that the reported association between muscle mass and BMD_a was an artifact related to measuring muscle mass as "fat-free mass" which includes bone, or as "fat-free soft-tissue mass" which includes organ mass. Both are inaccurate parameters of muscle mass and alter therefore the relationship between "mucle mass" and BMD_a: including bone in the measure "fat-free mass" falsely strengthens the relationship with BMD_a, while including organ mass in the measure "fat-free soft-tissue mass" incorrectly attenuates this relationship [36]. However, in our study, LM measured by DXA did not include bone mineral or organ mass but only lean mass of both arms and legs.

In addition to aLM, *age* contributed positively to lumbar spine BMD_a, which is probably an artifact related to the presence of osteophytosis and/or severe aortic calcification [37]. *Smoking* was negatively associated with total hip BMD_a, a relationship that has also been observed by Pluijm et al. [7]. We found no independent contribution of *total FM* to BMD_a in the multivariable model including isometric quadriceps strength. This is consistent with most studies in men, in which only LM or RASM was an independent determinant of BMD_a, with no influence of total FM [2, 22]. This is in contrast to the situation in postmenopausal women, in whom FM usually was an additional independent contributor to BMD_a [7, 9, 11]. However, when quadriceps strength was excluded from the multivariable model, total FM was positively linked with total hip BMD_a and negatively with whole-body BMD_a. This suggests that the effect of FM on total hip BMD_a is mediated by the dynamic loading of muscles on this weight-bearing bone site. Obese people need indeed stronger muscles to move their higher body weight and create higher impacts on bone when moving [6]. The negative link between total FM and whole-body BMD_a has also been observed by other authors [9, 21, 38] and may reflect the increased bone resorption associated with the synthesis of inflammatory cytokines in abdominal (visceral) fat [39]. Thus, an independent contribution of FM to BMD_a was not observed in the multivariable model including isometric quadriceps strength. Yet, FM may contribute to bone mass, secondary to aromatisation of androgens into estrogens, insulin resistance with hyperinsulinemia as well as higher levels of amylin and leptin, all of which are positively associated with obesity [40, 41]. The reason why, despite these obesity-related hormonal changes, we did not observe an independent contribution of FM to BMD_a in this model, might be that testosterone dissociates fat and bone mass in men by respectively decreasing FM and increasing bone mass [42]. The observation that, in contrast with our study in men, the relationship between FM and bone mass is significant in women supports this concept of a potential dissociation of FM and bone mass by testosterone [9, 23].

An additional independent contribution of *isometric quadriceps strength* to the variability of BMD_a was present at whole body and total hip, but not at femoral neck and lumbar spine. In comparison, Taaffe et al. reported that muscle strength contributed independently from LM to limb BMD_a in women, but not to femoral neck or whole-body BMD_a in women and not to any site in men [9]. Thus, our study is in agreement with others that there may be an independent effect of muscle strength on BMD_a over and above that explained by LM. This additional effect of muscle strength may be due to the fact that, although LM and muscle strength are highly correlated, muscle strength does not depend solely on LM. This is illustrated by the observation that, although loss of LM is accompanied by loss of muscle strength, the age-dependent loss of muscle strength is larger than the loss of LM [43]. Yet, as mentioned, the additional effect of muscle strength was not found at the femoral neck and lumbar spine. This may have several explanations. First, finding no additional effect of muscle strength on lumbar spine BMD_a is not surprising, as lumbar spine BMD_a is influenced by multiple other factors, e.g. osteophytosis that may have confounded the effect of muscle strength. Moreover, measuring muscle strength at the quadriceps and not at the trunk may have contributed to the fact that no additional effect of strength was observed at the lumbar spine. An alternative explanation is that most of the effect of muscle strength on BMD_a is explained and expressed by the effect of LM on BMD_a, while the additional contribution of muscle strength to BMD_a, over and above LM, is relatively weak [3, 9].

Compared with grip strength, quadriceps strength might be the stronger predictor of BMD_a since quadriceps strength was more consistently associated with all BMD_a sites and explained a larger proportion of the variation in BMD_a. However, since these results are based on cross-sectional data, more research is needed to understand the relative contribution of grip strength and quadriceps strength to bone health.

Based on the definition of sarcopenia of Baumgartner et al. (RASM at <7.26 kg/m²), 12 % of our random sample of European men between 40 and 79 years were sarcopenic. This prevalence is similar to that reported by Baumgartner et al. (13 %) in non-Hispanic US Caucasian men aged under 70 years [18]. Kyle et al. using a slightly lower cut-off of 7.06 kg/m² for the definition of sarcopenia, reported a prevalence of 11 % in healthy Swiss men aged 60 years and older [44]. With the stricter EWGSOP definition that requires an additional criterion beside low muscle mass, the prevalence of sarcopenia decreased to 3.7 % in the Leuven cohort. In literature, the prevalence of sarcopenia varies widely, from 0 % in Germans between 61 and 83 years [45] to 57.6 % in Hispanic US Caucasian men older than 80 years [18]. It is likely this is due to differences in the study population, the reference group, the technique used to measure muscle mass and the definition of sarcopenia. For example, in the same German population, the prevalence of sarcopenia increased up to 21.8 % when sarcopenia was defined by another measure of muscle mass [45].

We found that men with sarcopenia (RASM at <7.26 kg/m²) had significantly lower BMD_a at all measured sites compared with those without sarcopenia. The same has been previously shown in sarcopenic women, with sarcopenia defined as RASM at <5.45 kg/m^2 according to Baumgartner et al. [8, 11, 17, 18]. We also observed that men with sarcopenia were more likely to have osteoporosis compared with men with normal RASM. EWGSOP-defined pre-sarcopenia in the Leuven cohort (RASM at <7.26 kg/m^2 [19]) was also associated with a higher risk of osteoporosis. A similar association between low RASM and osteoporosis was found by Di Monaco et al. in sarcopenic women with hip fracture, in an analysis corrected for time between fracture and DXA, as a decrease in both LM and BMD_a has been observed after fracture [46]. Men with EWGSOP-defined sarcopenia (RASM at <7.26 kg/m^2 and low grip strength or physical performance) were twice as likely to have osteoporosis compared with non-sarcopenic men, although this result was not significant due to lack of power. To our knowledge, there are no other studies that have examined the relationship between sarcopenia defined by the EWGSOP definition and BMD_a or osteoporosis in men.

Our observation that aLM determines up to 20 % of the variance in BMD_a and that RASM at <7.26 kg/m² is associated with a higher prevalence of osteoporosis, suggests that an interventional approach with physical training programs aimed at improving muscle mass may be important to optimise bone health in middle-aged and elderly men.

Numerous studies and meta-analyses have provided evidence that, even in the elderly, *progressive resistance training* is an effective intervention for sarcopenia [47–49]. With a 10-week training schedule that existed of three times a week three series of eight repetitions with a resistance around 80 % of 1 repetition maximum (RM, the maximum weight that can be lifted), frail elderly with a mean age of 87 years obtained a significant increase in muscle strength, physical activity and physical performance [50]. Also muscle mass improved with resistance training in older adults [49]. An alternative to resistance training is *whole-body vibration training*. With this therapy, the patient stands on a platform that generates vertical sinusoidal vibrations. These mechanical stimuli activate the muscle spindles, resulting in the activation of alpha motor neurons and initiate muscle contraction [51]. Similar to resistance training, vibration training has been shown to increase muscle mass and muscle strength in elderly subjects [52].

At this stage, evidence regarding the efficacy of training on bone loss is inconsistent and further studies are needed. A recent Cochrane review about the effectiveness of exercise in postmenopausal women showed a relatively small, but statistically significant effect of physical activity on BMD [53]. Non-weight bearing high force activity such as progressive resistance training was the most effective intervention for femoral neck BMD, while an exercise program combining weight bearing exercises and progressive resistance training was most effective for lumbar spine BMD [53, 54]. Progressive resistance training was generally ineffective for bone adaptations with a load <80 % of 1 RM [55]. Also in older men, progressive resistance training increased BMD at the hip, but was, contrary to previous studies in women, not better than walking 30 min three times a week [56]. Whole-body vibration had positive effects on BMD in some studies in both genders [52, 54], but a recent meta-analysis failed to observe an important effect, hereby taking into account that the design of whole-body vibration platforms and protocols for their use vary widely [57]. Thus, exercise programs combining strength and weight bearing training, as well as whole-body vibration alone or in combination with exercise, may help to increase or at least prevent declines in BMD, especially in postmenopausal women, while more research is needed in men [54].

Our study had several limitations. This was a cross-sectional study and so it was not possible to determine the temporal nature of the observed associations for which prospective data are needed. The response rate for participation in the study in these two centres was 39 %. It is possible that those invited, but declined to take part, may have differed from those who participated so that the assessments may be an over- or underestimate of the results from the total population. So caution is needed in interpretation of the data. However, any such non-response bias would be unlikely to have influenced the association between bone and muscle parameters. We used LM derived from DXA as our estimate of muscle mass. Although DXA-measured LM, that consists of muscle mass, skin, blood and interstitial fluid, is assumed to be a good indicator of muscle mass [32], the evaluation of LM by DXA might underestimate the

age-related decrease in muscle mass, due to the increase in total body water with ageing [2, 20]. Finally, our results relate to a group of predominantly Caucasian European men and cannot be extrapolated beyond this group. However, in a study of Taaffe et al. LM was independently associated with BMD_a and this relationship was not altered by race [9].

In summary, in this analysis of middle-aged and elderly European men, after adjustment for potential confounders, aLM was strongly correlated with BMD_a at all sites, with an additional independent contribution of muscle strength to whole-body and total hip BMD_a. Men with low muscle mass (RASM at <7.26 kg/m²) had lower BMD_a and were more likely to have osteoporosis compared with non-sarcopenic men.

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