Does combined osteopenia/osteoporosis and sarcopenia confer greater risk of falls and fracture than either condition alone in older men? The Concord Health and Ageing in Men Project

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Abstract

Background: It is unclear whether older men with osteopenia/osteoporosis and sarcopenia (so called "osteosarcopenia") are at greater risk of falls and fractures than those with either condition alone.

Methods: 1,575 community-dwelling men aged ≥70 years had appendicular lean mass, total hip and lumbar spine bone mineral density (BMD) determined by dual-energy X-ray absorptiometry, and completed hand grip strength and gait speed tests. Osteopenia/osteoporosis was defined as a T-score at any site ≤-1.0SD. Sarcopenia was defined using the European Working Group on Sarcopenia algorithm. Participants were contacted every four months for 6±2 years to ascertain incident fractures (confirmed by radiographic reports) and for two years for incident falls.

Results: Prevalence of osteosarcopenia was 8%, while 34% of participants had osteopenia/osteoporosis alone and 7% had sarcopenia alone. Men with osteosarcopenia had significantly increased fall (incidence rate ratio: 1.41; 95% CI: 1.02-1.95) and fracture risk (hazard ratio: 1.87; 95% CI: 1.07-3.26) compared to men with neither osteopenia/osteoporosis nor sarcopenia. There was no statistical interaction between osteopenia/osteoporosis and sarcopenia, and falls and fracture risk were not different for osteosarcopenia compared to either condition alone (all P>0.05).

Conclusions: Community-dwelling older men with combined osteopenia/osteoporosis and sarcopenia do not have increased falls and fracture risk compared to those with either condition. Further research is required to clarify whether the term "osteosarcopenia" has any meaning above and beyond either term alone and therefore potential clinical utility for falls and fracture prediction.

Keywords: muscle; bone aging; falls; hip fracture; osteosarcopenia

Introduction

It has been proposed that low bone mineral density (BMD; osteopenia/osteoporosis) and low muscle mass and function (sarcopenia) could be combined into a single entity of "osteosarcopenia" as a means to identify older adults with high fracture risk (1,2). Cross-sectional studies have demonstrated osteosarcopenia is associated with increased risk of frailty (3), poor physical performance and increased bone turnover (4), and historical low-trauma fractures (5). In a prospective study, older Chinese men with osteoporosis and sarcopenia demonstrated over three-fold increased hazard for fracture over 11 years compared to those with neither condition (6). Similar findings were reported in the Osteoporotic Fractures in Men Study, where men with sarcopenia and low BMD had over three-fold higher fracture risk compared to controls over nine years (7). However, there is no evidence to support a synergistic effect whereby osteosarcopenia confers greater fracture risk than osteopenia/osteoporosis or sarcopenia alone. Furthermore, there is no prospective data investigating whether older adults with osteosarcopenia experience higher rates of falls.

The primary aim of this secondary analysis of a longitudinal study of community-dwelling older men was to determine whether, compared with assessing sarcopenia and osteopenia/osteoporosis as distinct entities, combining these two risk factors into one entity (osteosarcopenia) provides a better determination of falls and fracture risk.

Methods

Study design and population

The Concord Health and Ageing in Men Project (CHAMP) is an epidemiological study of Australian men aged ≥70 years. The selection of study subjects has been described elsewhere (8). Men living in a defined urban geographical region near Concord Hospital in Sydney, Australia, were recruited. The sampling frame was the New South Wales Electoral Roll, on which registration is compulsory. The only exclusion criterion was living in a residential aged care facility. Eligible men received a letter describing the study and, if they had a listed telephone number, were telephoned about one week later. Of 2,815 eligible men with whom contact was made, 1,511 participated in the study (54%). An additional 194 eligible men learnt about the study through friends or media and were recruited prior to being identified through electoral rolls, yielding a total cohort of 1,705 subjects.

Baseline data were collected between January 2005 and June 2007. Men completed a questionnaire and attended study clinics at Concord Hospital for assessment of body composition, physical performance, and cardiometabolic health. Measurements were repeated at follow-up clinics five years later (January 2012 to October 2013). Trained staff collected data and the same equipment was used for all measurements. All participants gave written informed consent. The study complied with the World Medical Association Declaration of Helsinki and was approved by the Sydney South West Area Health Service Human Research Ethics Committee, Concord Repatriation General Hospital, Sydney, Australia.

Anthropometrics, body composition and BMD

Height was measured using a Harpenden stadiometer and weight using Wedderburn digital scales; BMI was calculated as kg/m^2. Dual-energy X-ray absorptiometry (DXA) scans were performed using a Hologic Discovery-W scanner (Hologic Inc., Bedford, MA, USA).

Quality control scans were conducted daily using the Hologic whole-body phantom and indicated no shifts or drifts. Total hip and lumbar spine BMD (g/cm^2) were estimated. Whole-body DXA also assessed appendicular lean mass (ALM; sum of lean mass of arms and legs) and total body fat percentage. The coefficient of variation for scans duplicated on 30 men from the study cohort was 1.6% for total hip BMD, 1.0% for whole-body lean mass and 2.5%, for whole-body fat mass.

Hand grip strength and gait speed

Hand grip strength (kg) of the dominant hand (best of two trials) was assessed using a Jamar dynamometer (Promedics, Blackburn, UK). Self-selected usual gait speed was measured on a 6-metre course. In order to maintain consistency with current low gait speed cut-points for sarcopenia, 6-metre gait speed was converted to estimate 4-metre gait speed (9).

Sociodemographics

Age, living arrangements (lives alone vs lives with others), income (pension or other source), and smoking status (never smoker, ex-smoker, current smoker) were self-reported. Physical activity was measured using the Physical Activity Scale for the Elderly (PASE) (10). Participants instructed to bring current prescription and non-prescription medications to clinic visits for review. They were also asked whether they had taken any other medications during the past month. Reported medicines were coded using the Iowa Drug Information Service codes (11). Data on medical conditions were obtained from self-report of whether a doctor or a health care provider had told them that they had any of the following diseases: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke, Parkinson's disease, epilepsy, hypertension, heart attack, angina, congestive heart failure, intermittent claudication, chronic

obstructive lung disease, liver disease, cancer (excluding non- melanoma skin cancers), osteoarthritis, and gout. Men also reported whether or not they had sustained a historical fracture. Physical disability was assessed by 7 items from a modified version of the Katz activities of daily living (ADL) scale. ADL disability was defined as needing help with one or more activities (12).

Blood Tests

Blood tests were performed at the Diagnostic Pathology Unit of Concord RG Hospital, which is a NATA (National Australian Testing Authority) accredited pathology service, using a MODULAR Analytics system (Roche Diagnostics, Castle Hill, Australia). Fasting serum 25-hydroxyvitamin D levels (25(OH)D) were measured by RIA (DiaSorin Inc., Stillwater, MN), as described previously (13). The assay for 25(OH)D has a sensitivity of <3.75 nmol/L with an intra-assay precision of 7.6% and an inter-assay precision of 9.0%. Serum albumin level was also measured in the same laboratory at Concord RG Hospital and was used as a continuous measure.

Assessment of incident falls and fracture

Following baseline, men were contacted by telephone every 4 months until January 2014 and administered a questionnaire to determine incidence of falls and fractures. Total number of falls for each four-month period was recorded. If a fracture was reported, radiology reports were obtained either from the participant, or hospital medical records and radiology practices. Additional manual searching for fractures was conducted by accessing medical records within our health district. Only fractures confirmed by radiographic reports were recorded. Pathological fractures and fractures of hands, fingers, feet, toes, and the skull were excluded. Only the first incident fracture that met the inclusion criteria was included,

regardless of trauma level or subsequent fractures reported (14). Fractures were classified as any, non-vertebral, or a hip fracture. Time to censorship was either date of death, date of official withdrawal from the study or date of the last telephone contact. The date of first fracture was the date on the radiology report.

Definition of osteosarcopenia: There are currently no consensus operational definitions for osteosarcopenia. The accepted definition of osteopenia/osteoporosis is total hip and/or lumbar spine BMD T-score <-1. SD (15). Several consensus definitions exist for sarcopenia including the European Working Group on Sarcopenia in Older People (EWGSOP) definition (16). Combined osteopenia/osteoporosis and EWGSOP-defined sarcopenia has been used to define osteosarcopenia previously (5,7) and we selected this definition to enable comparability with these studies. The EWGSOP defines sarcopenia in men as ALM adjusted for height (in metres squared) <7.25kg/m^2 combined with low hand grip strength (<30kg) and/or low gait speed (≤0.8m/s) (16). Participants were allocated to the following categories: non-osteopenic/osteoporotic non-sarcopenic, osteopenic/osteoporotic alone, sarcopenic alone or osteosarcopenic.

Statistical analyses

Baseline descriptive characteristics were compared across categories of osteosarcopenia using one-way ANOVA for continuous variables and Chi-square tests for categorical variables. Bonferroni post-hoc tests were performed.

Chi-square tests compared proportions of men with falls and fractures across categories of osteosarcopenia. Given falls are relatively common in older age, and sarcopenia is likely to have immediate to short-term effects on falls risk, only falls occurring up to two years after baseline were included in falls analyses, whereas events for the entire follow-up

period were included for fractures. Unadjusted and multivariable negative binomial regression examined two-year incident falls rates for osteopenic/osteoporotic alone, sarcopenic alone and osteosarcopenic men, compared with the non-osteopenic/osteoporotic non-sarcopenic group. These analyses were adjusted for age, income, living alone, number of comorbidities, smoking status, psychotropic and corticosteroid use, history of fracture, physical activity and 25(OH)D. As an aim of this study was to explore differences for osteosarcopenic men compared with those with osteopenia/osteoporosis and sarcopenia alone, these analyses were repeated with the osteosarcopenic group set as the referent.

Kaplan-Meier survival curves were used to compare time to first fracture (any fracture, non-vertebral fracture and hip fracture) across categories of osteosarcopenia. Log-rank tests examined between-group differences in time to first fracture. Unadjusted and adjusted Cox proportional hazards regression models examined associations of osteosarcopenia with incident any, non-vertebral and hip fractures, with adjustment for covariates included in previous multivariable models.

To test for interactions in the relationships of osteopenia/osteoporosis and sarcopenia with incident falls and fractures, multivariable binary logistic regression analyses explored associations of continuous (ALM, hand grip strength, gait speed and total hip BMD) and categorical (osteopenia/osteoporosis and sarcopenia) osteosarcopenia components with likelihood of falls and fractures during follow-up. These analyses were adjusted for variables included in the previous models, and the continuous variable analysis was further adjusted for all other components of osteosarcopenia. Z-scores were obtained for the continuous variable components of osteosarcopenia to allow comparability of effects on falls and fractures. The interaction terms included in these models were, for the categorical variable model: osteopenia/osteoporosis*sarcopenia; and for the continuous variable model: total hip BMD*ALM, total hip BMD*hand grip strength, total hip BMD*gait speed.

Finally, we conducted a sensitivity analysis to explore the associations of different definitions of osteosarcopenia with fractures. Osteosarcopenia was defined in these analyses as osteoporosis (not osteopenia) combined with either pre-sarcopenia (low ALM/height only) or sarcopenia (low ALM/height combined with low grip strength and/or low gait speed) (16). Using these definitions, associations of osteosarcopenia with hazard for any fracture was assessed using Cox proportional hazards regression models, respectively. Few men had osteosarcopenia when defined as osteoporosis, not osteopenia, and so analyses were performed for any fracture only. These models were adjusted for the same covariates as previous analyses, and interaction terms were included.

P values <0.05 or 95% confidence intervals not including the null point were considered statistically significant. Analyses were performed in SPSS Statistics 23 (IBM, NY, USA).

Results

After excluding participants with incomplete data for sarcopenia and osteopenia/osteoporosis at baseline, 1575 men were included in the analysis. Included participants were significantly younger (76.7±5.4 vs 79.7±6.5 years; P<0.001), had fewer comorbidities (2.5±1.7 vs 3.2±2.2; P<0.001), and higher ALM (22.1±3.1 vs 19.1±2.9 kg; P<0.001) and total hip BMD (0.94±0.14 vs 0.89±0.20; P=0.032) than excluded participants.

Amongst included participants, 51.5% were non-osteopenic/osteoporotic non-sarcopenic, 33.5% were osteopenic/osteoporotic alone, 6.7% were sarcopenic alone, and 8.3% were osteosarcopenic. Table 1 presents baseline characteristics of participants according to osteosarcopenia categories. Osteosarcopenic men were significantly older, were more likely to live alone and be a current smoker, and had lower physical activity than non-osteopenic/osteoporotic non-sarcopenic and osteopenic/osteoporotic alone men. They also had significantly greater number of comorbidities, and were more likely to report ADL disability and use of corticosteroids and psychotropic medications, compared with non-osteopenic/osteoporotic non-sarcopenic men. Vitamin D levels were significantly lower in osteosarcopenic compared with sarcopenic alone men. As expected, osteosarcopenic and sarcopenic alone men had significantly lower ALM, hand grip strength and gait speed compared to non-osteopenic/osteoporotic non-sarcopenic and osteopenic/osteoporotic alone men. Total hip BMD was significantly lower in osteosarcopenic men compared with all other groups, and lumbar spine BMD was significantly lower for osteosarcopenic and osteopenic/osteoporotic alone men compared with non-osteopenic/osteoporotic non-sarcopenic and sarcopenic alone men. However, osteopenic/osteoporotic alone men had the highest prevalence of history of fracture, and this was significantly different only compared to sarcopenic alone men.

Chi-square tests revealed significant differences in the proportions of fallers (non-osteopenic/osteoporotic non-sarcopenic: 26.1%, osteopenic/osteoporotic alone: 31.5%, sarcopenic alone: 48.1%, osteosarcopenic: 41.2%) and multiple fallers (non-osteopenic/osteoporotic non-sarcopenic: 8.5%, osteopenic/osteoporotic alone: 11.0%, sarcopenic alone: 16.0%, osteosarcopenic: 22.9%) over two years across osteosarcopenia categories (both $P<0.001$). Amongst 1,502 men with complete falls records at the two-year follow-up, unadjusted negative binomial regression models demonstrated that osteopenic/osteoporotic alone had 27% increased rate of falls, while sarcopenic alone and osteosarcopenic men had similar two-fold increased falls rates, compared with non-osteopenic/osteoporotic non-sarcopenic (Table 2). A post-hoc test with the osteosarcopenic group set as referent demonstrated that rate of falls was significantly lower for osteopenic/osteoporotic alone men (incidence rate ratio 0.59; 95% CI 0.44, 0.80), although not after multivariable adjustment. The increase in falls rates for sarcopenic alone and osteosarcopenic men compared with non-osteopenic/osteoporotic non-sarcopenic were substantially reduced, but remained significant after adjustment.

The respective proportions of men with any fracture over a mean follow-up period of 6±2 years were 7.5% for non-osteopenic/osteoporotic non-sarcopenic, 14.0% for osteopenic/osteoporotic alone, 8.5% sarcopenic alone, and 14.5% for osteosarcopenic (Chi-square test: $P=0.001$). Significant differences in the proportions of incident fractures across osteosarcopenia categories were also observed for non-vertebral fractures (non-osteopenic/osteoporotic non-sarcopenic: 6.4%, osteopenic/osteoporotic alone: 11.4%, sarcopenic alone: 5.7%, osteosarcopenic: 10.7%; $P=0.007$) and hip fractures (non-osteopenic/osteoporotic non-sarcopenic: 1.5%, osteopenic/osteoporotic alone: 4.0%, sarcopenic alone: 1.9%, osteosarcopenic: 4.6%; $P=0.017$). Kaplan-Meier survival curves and log-rank tests (Figure 1) demonstrated significantly shorter time to first fracture for the

osteosarcopenic and osteopenic/osteoporotic alone groups compared with the non-osteopenic/osteoporotic non-sarcopenic group, for any fracture, non-vertebral fracture and hip fracture. There were no other significant between-group differences for time to first fracture.

Table 3 reports Cox proportional hazards regression models for fracture across categories of osteosarcopenia. In unadjusted models, osteopenic/osteoporotic alone and osteosarcopenic men had approximately two- to three-fold increased hazard for incident any, non-vertebral or hip fractures compared with the non-osteopenic/osteoporotic non-sarcopenic group. After adjustment for confounders, the increase in hazard (85%) for any fracture, but not non-vertebral or hip fracture, remained significant for osteosarcopenic men whereas osteopenic/osteoporotic alone men had significant increased hazard for all fracture types. Age was the primary covariate responsible for the diminished association of osteosarcopenia with hip fracture; the hazard ratio (95% CI) for hip fracture for a one-year increase in age was 1.12 (1.06, 1.19) and adjustment for age reduced the hazard ratio for hip fracture in osteosarcopenic men from 3.9 in the unadjusted model to 2.2. Sarcopenia alone was not associated with increased fracture risk, and no differences for osteosarcopenic men compared with other groups were observed.

Table 4 presents odds ratios for falls and fractures according to components of sarcopenia and low total hip BMD at baseline. After mutual adjustment and further adjustment for potential confounders, only gait speed was significantly associated with reduced likelihood of being a faller. Conversely, only higher total hip BMD predicted lower likelihood of any fracture. There were no significant interactions between total hip BMD and components of sarcopenia for falls and fractures (all $P>0.05$). Similar results were observed for osteosarcopenia/osteoporosis and sarcopenia categories, where only sarcopenia was associated with increased likelihood of a fall and only osteopenia/osteoporosis was

significantly associated with increased likelihood of fracture (Table 4). The interaction between osteopenia/osteoporosis and sarcopenia approached significance for likelihood of falls, but not fractures.

Finally, we conducted a sensitivity analysis to determine associations of different definitions of osteosarcopenia with incident fracture. Relatively few men had osteosarcopenia when defined as osteoporosis, not osteopenia, combined with pre-sarcopenia (N=41) or sarcopenia (N=25). Compared to men with neither osteoporosis nor presarcopenia, adjusted hazard ratios (95% CI) were 2.25 (1.09-4.64) for men with osteoporosis alone, 1.01 (0.69-1.48) for men with presarcopenia alone, and 2.79 (1.37-5.66) for men with both osteoporosis and presarcopenia. Compared to men with neither osteoporosis nor sarcopenia, adjusted hazard ratios were 1.68 (0.85-3.33) for men with osteoporosis alone, 0.85 (0.51-1.42) for men with sarcopenia alone, and 5.00 (2.34-10.64) for men with both osteoporosis and sarcopenia. Significant interactions were observed for osteoporosis with pre-sarcopenia (P=0.024), and for osteoporosis with sarcopenia (P=0.001), for hazard of any fracture.

Discussion

The primary finding from this longitudinal study of Australian community-dwelling older men is that men with "osteosarcopenia" (osteopenia/osteoporosis and EWGSOP-defined sarcopenia) are not at higher risk of falls and fractures than men with only one of these conditions, Sarcopenia, but not osteopenia/osteoporosis, was independently associated with increased likelihood of falls, while osteopenia/osteoporosis, but not sarcopenia, was associated with increased likelihood of fractures.

Our findings are generally consistent with previous studies investigating associations of combined osteopenia/osteoporosis and sarcopenia with fracture risk in older adults. In 2,000 Chinese older men, osteoporosis combined with sarcopenia (according to the Asian Working Group criteria) was associated with 3.5-fold increased hazard for incident fractures over 11 years compared with men without osteoporosis or sarcopenia (6). Men with osteoporosis alone and sarcopenia alone also had significantly increased risk of fracture compared with controls. A recent analysis of over 10,000 older women followed for 16 years in the Women's Health Initiative reported that participants with osteopenia had increased any and hip fracture risk regardless of sarcopenia status (defined as low lean mass only) (17). A previous cross-sectional study of 680 Australian older adults attending a falls and fracture clinic observed in univariable analyses that osteosarcopenic patients were over two-fold more likely to report a low-trauma fracture in the past five years than non-osteopenic/osteoporotic non-sarcopenic (but not osteopenic or sarcopenic alone) counterparts, but likelihood for past fracture was not increased after adjustment for confounders (5). However, in contrast to our findings, a study among 5,544 older men (mean age=73.7years) from the Osteoporotic Fractures in Men (MrOS) study showed that hazard for fracture compared to healthy controls was substantially greater for men with both low BMD and sarcopenia (3.8-fold) than for men

with only one condition (1.1-1.7-fold) (7). This discrepancy may be explained by differences in the calculation of appendicular lean mass and cut-points.

There is growing discussion regarding whether osteopenia/osteoporosis and sarcopenia should be combined into the single condition of "osteosarcopenia" (1,18). We observed that osteosarcopenia is not infrequent in community-dwelling older men (>8%) and associated with two-fold risk of incident fracture at any site compared with men with neither condition. However, there was no increase in fracture risk for osteosarcopenic men compared with osteopenic/osteoporotic alone, and osteopenia/osteoporosis was the most consistent predictor of fracture at all sites. Similarly, amongst components and categories of osteosarcopenia, only low total hip BMD or osteopenia/osteoporosis, not low ALM, hand grip strength, gait speed or overall sarcopenia, were significantly associated with increased fracture risk. Our study is the first we are aware of to examine prospective falls risk in the context of osteosarcopenia. While a previous study suggested men with osteosarcopenia have reduced past-year falls compared with men with sarcopenia alone (7), our study is the first we are aware of to prospectively examine relationships of osteosarcopenia and incident falls. We observed falls rates for osteosarcopenic men were similar to those for men with sarcopenia alone. We also found that sarcopenia according to the EWGSOP definition increases falls risk independent of low BMD in older men.

However, when osteosarcopenia was defined as osteoporosis, not osteopenia, combined with pre-sarcopenia or sarcopenia, there was evidence for increased risk of any fracture beyond that observed for osteoporosis or sarcopenia alone. Similar to our findings, a previous study reported osteoporosis and pre-sarcopenia was associated with over three-fold increased likelihood of incident fractures compared with neither condition (19). It should be noted that few men in our study had osteoporosis, not osteopenia, combined with pre-sarcopenia or sarcopenia (<3 and <2%, respectively). Nevertheless, it is possible that

sarcopenia assessment improves fracture prediction in those with osteoporosis but not osteopenia. Studies in Chinese older adults reported that sarcopenia according to the Asian Working Group criteria makes incremental improvements to the predictive ability of FRAX® (6,20).

At baseline, total hip BMD was significantly lower for osteosarcopenic men compared with all other groups, including osteopenia/osteoporosis alone. A study of almost 18,000 US and Chinese adults demonstrated that sarcopenia (low muscle mass and hand grip strength) was associated with approximately 80% increased likelihood of osteopenia or osteoporosis (21). In Finnish postmenopausal women, sarcopenia (defined as the lowest quartile of ALM combined with the lowest quartile of muscle strength and/or gait speed) was associated with almost 13-fold increased odds for osteoporosis (22). There are several potential mechanisms by which age-related declines in muscle mass and strength are likely to contribute to bone loss including reduced biomechanical stimuli and growth factors (23). However, our results suggest men with combined osteopenia/osteoporosis and sarcopenia may have lower BMD compared with those with osteopenia/osteoporosis alone, but this does not necessarily increase relative fracture risk. It is notable that osteosarcopenic men had significantly lower physical activity levels than osteopenic/osteoporotic alone. Reduced participation in activities associated with fracture may explain why osteosarcopenic men have similar fracture risk to osteopenic/osteoporotic alone men despite lower BMD.

The primary limitations of the present study are that the findings are generalisable only to relatively healthy community-dwelling older men, and associations may differ for older men with poorer health and older women. Osteosarcopenia was defined as the presence of osteopenia or osteoporosis combined with sarcopenia according to the EWGSOP definition consistent with previous studies but associations with falls and fracture will differ for studies that define osteosarcopenia using osteoporosis only, or that use different

definitions of sarcopenia. Indeed, we observed differing associations for falls and fractures when osteosarcopenia was defined by pre-sarcopenia or sarcopenia according to the EWGSOP definition.

In conclusion, community-dwelling older men with both osteopenia/osteoporosis and sarcopenia do not have increased rates of falls and fractures compared with those with either condition alone. Further research is required to clarify whether the term "osteosarcopenia" has any meaning above and beyond either term alone and therefore potential clinical utility for falls and fracture prediction.

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Table 1. Baseline characteristics according to osteosarcopenia categories.

	Non-osteopenic/osteoporotic non-sarcopenic (N=811)	Osteopenic/osteoporotic alone (N=527)	Sarcopenic alone (N=106)	Osteosarcopenic (N=131)
Age (years)	75.5±4.5[b,c,d]	76.8±5.3[a,c,d]	80.8±6.2[a,b]	80.3±6.3[a,b]
Lives alone (%)	17.9[d]	16.7[d]	17.3	29.0[a,b]
Pension (%)	39.0[b,d]	49.9[a]	49.0	55.7[a]
Current smoker (%)*	5.0[d]	6.0[d]	3.8	13.1[a,b]
Number of comorbidities	2.4±1.6[d]	2.5±1.8	2.8±1.8	2.9±1.8[a]
ADL disability (%)*	3.5[b,c,d]	6.8[a]	13.2[a]	9.9[a]
Psychotropic medication (%)*	9.3[d]	13.2	14.4	20.2[a]
Corticosteroid medication (%)*	6.2[b,c,d]	10.8[a]	17.9[a]	15.3[a]
History of fracture (%)*	42.2	46.3[c]	30.2[b]	39.7
25(OH)D (nmol/L)	56.9±21.2	55.7±23.2	62.0±22.9[d]	53.7±22.9[c]
Albumin (g/L)	44.1±2.6[c]	44.0±2.6	43.4±2.9[a]	43.5±3.1

PASE score	135.6±59.8[c,d]	128.6±60.2[c,d]	95.4±54.9[a,b]	94.7±60.1[a,b]
BMI (kg/m^2)	29.1±3.8[b,c,d]	27.3±3.5[a,c,d]	25.6±3.1[a,b]	24.4±3.1[a,b]
Total body fat (%)	29.5±5.6[b]	28.1±5.9[a]	29.3±6.3	28.2±7.1
ALM (kg)	23.3±2.8[b,c,d]	21.8±2.7[a,c,d]	19.2±2.1[a,b]	18.3±2.0[a,b]
Total hip BMD (g/cm^2)	1.03±0.10[a,c,d]	0.84±0.09[a,c,d]	0.99±0.09[a,b,d]	0.78±0.10[a,b,c]
Lumbar spine BMD (g/cm^2)	1.21±0.17[b,d]	0.96±0.14[a,c]	1.20±0.17[b,d]	0.98±0.17[a,c]
Hand grip strength (kg)	36.8±6.7[b,c,d]	34.6±6.6[a,c,d]	27.4±6.0[a,b]	27.2±6.6[a,b]
Gait speed m/s)	0.94±0.19[c,d]	0.91±0.20[c,d]	0.73±0.18[a,b]	0.75±0.18[a,b]

Note: ± standard deviation; all tests are one-way ANOVA except *(Chi-square tests). Abbreviations: ADL; activities of daily living, 25(OH)D; 2-hydroxyvitamin D, PASE; Physical Activity Scale for Elderly, BMI; body mass index, ALM; appendicular lean mass, BMD; bone mineral density.

[a]Significant difference to non-osteopenic/osteoporotic non-sarcopenic

[b]Significant difference to osteopenic/osteoporotic alone

[c]Significant difference to sarcopenic alone

[d]Significant difference to osteosarcopenic (Bonferroni post-hoc tests)

Table 2. Incidence rate ratios (95% CI) for falls two years after baseline, according to osteosarcopenia categories.

	Non-osteopenic/osteoporotic non-sarcopenic (N=778)	Osteopenic/osteoporotic alone (N=498)	Sarcopenic alone (N=101)	Osteosarcopenic (N=125)
Unadjusted	REF	**1.27 (1.04-1.55)#**	**2.15 (1.58-2.94)**	**2.14 (1.61-2.86)**
Adjusted*	REF	1.16 (0.94-1.44)	**1.61 (1.14-2.28)**	**1.41 (1.02-1.95)**

Note: *Adjusted for age, income, living alone, number of comorbidities, smoking status, psychotropic and corticosteroid use, history of fracture, physical activity and 25(OH)D.

#Significantly different to osteosarcopenic ($P<0.05$).

Table 3. Hazards ratios (95% CI) for incident fractures over six years according to osteosarcopenia categories.

	Non-osteopenic/osteoporotic non-sarcopenic (N=811)	Osteopenic/osteoporotic alone (N=527)	Sarcopenic alone (N=106)	Osteosarcopenic (N=131)
Any Fracture				
Unadjusted	REF	**2.03 (1.44-2.85)**	1.29 (0.64-2.59)	**2.54 (1.52-4.25)**
Adjusted*	REF	**1.85 (1.30-2.64)**	1.06 (0.51-2.18)	**1.87 (1.07-3.26)**
Non-vertebral Fracture				
Unadjusted	REF	**1.91 (1.32-2.77)**	0.99 (0.43-2.30)	**2.12 (1.18-3.83)**
Adjusted*	REF	**1.70 (1.15-2.51)**	0.77 (0.32-1.85)	1.49 (0.78-2.82)
Hip Fracture				
Unadjusted	REF	**2.84 (1.40-5.78)**	1.43 (0.32-6.38)	**3.86 (1.45-10.29)**
Adjusted*	REF	**2.58 (1.22-5.45)**	0.78 (0.16-3.73)	1.84 (0.60-5.61)

Note: *Adjusted for age, income, living alone, number of comorbidities, smoking status, psychotropic and corticosteroid use, history of fracture, physical activity and 25(OH)D.

Table 4. Associations of osteosarcopenia and its components with incident falls and fracture.

	Fall at two years		**Any fracture at six years**	
Osteosarcopenia components†*	Odds ratio (95% CI)	Interaction term with total hip BMD (P-value)	Odds ratio (95% CI)	Interaction term with total hip BMD (P-value)
Total hip BMD	0.97 (0.85-1.11)	-	**0.63 (0.52-0.0.77)**	-
Gait speed	**0.84 (0.73-0.97)**	0.901	1.09 (0.89-1.34)	0.512
Hand grip strength	1.02 (0.89-1.18)	0.507	0.97 (0.78-1.20)	0.118
ALM/height	0.95 (0.83-1.08)	0.388	1.05 (0.86-1.29)	0.141
Osteosarcopenia categories	Odds ratio (95% CI)	Interaction term (P-value)	Odds ratio (95% CI)	Interaction term (P-value)
Osteopenia/osteoporosis	1.15 (0.88-1.51)	0.054	**1.81 (1.22-2.69)**	0.970
Sarcopenia	**2.18 (1.36-3.48)**		0.89 (0.39-2.00)	

Note: Adjusted for age, income, living alone, number of comorbidities, smoking status, psychotropic and corticosteroid use, history of fracture, physical activity and 25(OH)D. †Further adjusted for other components of osteosarcopenia at baseline. *Standardised Z-scores.

Figure 1. Survival curves for time to first any (A), non-vertebral (B) and hip (C) fracture according to osteosarcopenic category. Blue (non-osteopenic/osteoporotic non-sarcopenic; NONS), green (osteopenic/osteoporotic alone; OA), yellow (sarcopenic alone; SA), red (osteosarcopenic; OS).