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Journal

Journal of Bone and Mineral Research, 38(9)

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Publication Date

2023-09-01

DOI

10.1002/jbmr.4874

HHS Public Access

Author manuscript

J Bone Miner Res. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

J Bone Miner Res. 2023 September ; 38(9): 1245–1257. doi:10.1002/jbmr.4874.

Interactions between HR-pQCT bone density and D_3Cr muscle mass (or HR-pQCT bone structure and HR-pQCT muscle density) in predicting fractures: The Osteoporotic Fractures in Men study

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Abstract

We examined if an interaction exists between bone and muscle in predicting fractures in older men. Prospective data from the Osteoporotic Fractures in Men study was used to build Cox proportional hazards models. Predictors included HR-pQCT total volumetric BMD (Tt.BMD), trabecular BMD (Tb.BMD), cortical BMD (Ct.BMD) and cortical area (Ct.Ar) at distal radius/tibia, HR-pQCT muscle volume and density (diaphyseal tibia), D_3-creatine dilution (D_3Cr) muscle mass, and grip strength and leg force, analyzed as continuous variables and as quartiles.

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Conflicts of interest

BK is supported by a research grant from TSI Pharmaceuticals which is unrelated to the content of this manuscript. PMC has grants to her institution from Nestle and Abbott outside of the work of this manuscript. All other authors have no conflicts of interest to declare regarding the content of this manuscript.

Incident fractures were self-reported every 4 months via questionnaires and centrally adjudicated by physician review of radiology reports. Potential confounders (demographics, comorbidities, lifestyle factors, etc.) were considered. 1,353 men (mean age: 84.2 ± 4.0 years, 92.7% white) were followed for 6.03 ± 2.11 years. In the unadjusted (continuous) model, there were no interactions (p>0.05) between any muscle variable (D_3Cr muscle mass, muscle volume, muscle density, grip strength or leg force) and Tt.BMD at distal radius/tibia for fractures (all: n=182–302; nonvertebral: n=149–254; vertebral: n=27–45). No consistent interactions were observed when interchanging Tt.BMD for Tb.BMD/Ct.BMD or for Ct.Ar (bone structure) at the distal radius/tibia in the unadjusted (continuous) models. Compared to men in Quartiles(Q) 2–4 of D_3Cr muscle mass and Q2–4 of distal tibia Tt.BMD, men in Q1 of both had increased risk for all fractures (Hazard Ratio (HR): 2.00; 95% confidence interval [CI], 1.24 –3.23, p= 0.005) and nonvertebral fractures (HR: 2.10; 95% CI, 1.25–3.52, p <0.001) in the multivariable-adjusted model. Confidence intervals overlapped (p >0.05) when visually inspecting other quartile groups in the multivariable-adjusted model. In this prospective cohort study of older men, there was no consistent interactions between bone and muscle variables on fracture risk. Larger sample sizes and longer follow-up may be needed to clarify if there is an interaction between bone and muscle on fracture risk in men.

Keywords

Bone-muscle interactions; Sarcopenia; Osteoporosis; Fracture risk assessment

Introduction

Musculoskeletal health is compromised in old age due to the deterioration of bone density/structure and muscle mass, both of which independently increase the risk of fractures [1,2]. Categorical definitions of osteopenia/osteoporosis and sarcopenia also support the notion that these diseases are risk factors for fractures [3–5]. A recent review of pre-clinical and human work [6] suggests that bone and muscle loss during aging is underpinned by shared mechanisms relating to chemical and mechanical cross-talk. Considering mechanical interactions, a recent study [7] showed strong site-specific associations between grip strength and radial cortical bone and chair stand force and tibial cortical bone, measured by HR-pQCT. Indeed, it has been suggested that the joint loss of bone and muscle during aging, a concept known as osteosarcopenia (see reviews here: [8,9]), may increase fracture risk in older adults.

However, findings from prospective cohort studies examining bone-muscle interactions in fracture risk are mixed. In the MrOS study, older men with combined osteopenia/osteoporosis (defined as T score below −1.0) and sarcopenia (defined as low appendicular lean mass adjusted for height plus slow gait speed and/or low grip strength) (HR: 3.79, 95% CI: 2.65–5.41) and men with osteopenia/osteoporosis only (HR: 1.67, 95% CI: 1.45– 1.93), but not sarcopenia alone (HR: 1.14, 95% CI: 0.62–2.09), had a greater risk of nonvertebral fractures than those with normal bone density and no sarcopenia [10]. Older men enrolled in Concord Health and Ageing project found those with combined osteopenia/osteoporosis (defined as T score below −1.0) and sarcopenia (defined as low appendicular lean mass adjusted for height plus low grip and/or low gait speed) do not have an increased risk of

fractures compared to either osteopenia/osteoporosis or sarcopenia alone [11]. More recent work from MrOS showed that while physical performance measures (chair rise time, gait speed) are predictive of fracture risk, the association between DXA-lean mass and fractures is significantly attenuated following adjustment of bone density [12] and this finding has been reinforced by data from the Women's Health Initiative showing that DXA-lean mass offers poor predictive value for incident fractures [13]. Other studies support these findings [14,15]. A possible explanation for the discrepancy in these findings relates to the poor prognostic value of DXA-lean mass for fractures [13] (commonly used as a surrogate for muscle mass in sarcopenia definitions [3,16]) due to the influence of non-muscle tissues when compared to other muscle measures such as D_3Cr muscle mass [2] or muscle density [17] which predict fractures.

A previous MrOS study showed that low D_3Cr muscle mass is associated with incident fractures after adjusting for confounders, including BMD and FRAX probability [2]. Muscle density (of the calf or gluteal region) has also emerged as a consistent predictor of incident fractures after adjustment for BMD in separate studies using pQCT or HR-pQCT [17,18]. Other MrOS studies using HR-pQCT have demonstrated that volumetric BMD or bone structure (expressed as cortical area) are among the strongest predictors of incident fractures [1]. Yet the interactions between these bone and muscle variables (i.e., volumetric BMD and D_3Cr muscle mass; or cortical bone area and muscle density) in estimating the risk of fractures is currently unknown, as recently highlighted in an editorial [19]. Given that muscle size and strength is suggested to be a determinant of bone density and structure [7,20], this question warrants investigation as it may influence future fracture risk assessments.

Here, we examined if there is an interaction between bone density or structure (measured by HR-pQCT) and muscle mass, volume or density (measured by D_3Cr or HR-pQCT) in estimating the risk of fractures in a prospective cohort study of older men. For instance, we examined whether the association between bone density or structure and fracture risk is the strongest in those with the lowest muscle mass, volume or density. Given the findings of previous studies [7,20], we also examined the interactions between muscle strength (measured by grip strength or leg force) and bone density or structure (measured by HR-pQCT) in predicting fractures. Physical performance measures (such as gait speed or chair rise time) were not considered in the analyses as previous studies have shown no relationship [20] or weak relationships [7] with bone density/structure using pQCT or HR-pQCT.

Methodology

Study design and population

This was a secondary analysis of existing data from the U.S. Osteoporotic Fractures in Men Study (MrOS), a multicenter observational study. MrOS was initially established to identify risk factors for fractures in men (such as bone loss) and has since expanded to identify how changes in other musculoskeletal components (such as muscle mass) contribute to fractures during aging. Between 2000–2002, MrOS enrolled 5994 ambulant men aged ≥65 years who are able to walk independently, free of bilateral hip replacement and able to adhere to study procedures [21]. In 2014–2016, surviving men were recontacted and asked to perform a number of follow-up measures and a number of new measures; including HR-

pQCT evaluation of bone and muscle, D_3Cr muscle mass assessment, and muscle strength evaluation (grip strength and leg force (force plate)). For this secondary analysis, we used the data measured at 2014–2016 visit for the predictor variables of interest (HR-pQCT scans of bone and muscle, D_3Cr muscle mass, and muscle strength measures) and incident fractures reported after 2014–2016 up until early 2023. Covariates used in this analysis were collected at the same time as the predictors during 2014–2016. These variables and time points were chosen as they represented the primary aim of our study. Ethical approval for MrOS was previously received from the Institutional Review Boards for each participating center. Prior to enrolment, all men provided written informed consent. Further information on MrOS, including the study design, access to data, and publications can be found at: https://mrosonline.ucsf.edu/.

Predictor variables: bone and muscle variables

HR-pQCT: scans were performed by trained operators on the non-dominant arm (distal radius) and leg (distal and diaphyseal tibia) using XtremeCT II machines (Scanco Medical AG, Brüttisellen, Switzerland), except in the case where participants had metal artifacts, history of fracture or prolonged unloading (>6weeks) in the limb of interest. In these circumstances, the opposite limb was used. Quality control was performed daily at each center using phantoms. Cross-calibration using a standardized phantom showed excellent precision (coefficient of variation: <0.6%) between study centers. Analysis of imaging data (including the rating of image quality and removal of artifacts and outliers) was performed by a single trained operator to quantify musculoskeletal compartments, including total volumetric BMD (Tt.BMD, mg/cm^3), trabecular BMD (Tb.BMD, mg/cm^3) and cortical BMD (Ct.BMD, mg/cm^3) at the distal metaphysis (radius and tibia) and muscle volume (mm^3) and density (mg/cm^3) at the 30% diaphysis (tibia only). Bone structural parameters included cortical bone area (Ct.Ar, mm^2) at the distal metaphysis (radius and tibia). These procedures in MrOS have been described elsewhere [1,22].

D_3Cr: whole body muscle mass (kg) was estimated using the creatine-(methyl-d3) dilution method [23]. This method assumes that around 98% of creatine is stored in skeletal muscle cells, and that following ingestion of a bolus dose of creatine the intramyocellular creatine is converted to creatinine at a constant rate of around 1.7% per day and excreted in urine [23]. It is assumed that around 1–5% of ingested creatine bypasses the muscle and is directly excreted in urine, termed spillage [23]. In MrOs, men ingested (30-mg) of D3-creatine and then provided a single, fasting morning urine sample 3–6 days (72–144 hours) later. The collection of urine was completed by either the participant returning to the clinic to provide the sample, or by having the participant produce the sample; this sample was then collected by study staff and brought into the clinic (the same day the sample was produced). A combination of high-performance liquid chromatography and tandem mass spectrometry were then used to determine the molecular weight of unlabelled and labelled creatine from the urine sample. These variables, along with a correction factor for spillage, were then used in a validated equation to calculate whole-body creatine pool size (g) and estimate skeletal muscle mass (kg)[23]:

Spillage correction (mg) = (exp((1.2913 × ln(Creatine/Creatinine ratio)) + 0.7783)) × 60; Creatine pool size (grams) = ((0.06—(spillage correction [mg]/1000) × (131.1/134.1))/ percent D_3- Creatinine. Whole body skeletal muscle mass (kg) = Creatine pool size (g)/4.3 (g/kg). The coefficient of variation for this technique is 3.6% as reported by the validation study [23].

Muscle strength: Grip strength (kg) was measured twice on each hand (left/right) using a Jamar handheld dynamometer. The maximum value from two tests was used in the analysis. Leg strength was estimated using a force plate. Men completed 3–5 countermovement jumps with full leg-extension on a force plate. Peak force (Newtons/kg of body-weight) from these attempts was then used in the analysis. These procedures have previously been described [24].

Outcome variable: incident fractures

Participants self-reported fractures every four months (March, July and November) via questionnaires and/or by reporting fractures to study investigators during telephone interviews. The study physician verified fractures through radiology reports/radiographs. For the current analyses, fractures data were classified as any fracture, nonvertebral fracture, and clinical vertebral fracture. Further classification by anatomical site (e.g., hip or wrist) was not included in the present analysis due to the low number of events in these regions. Incident fractures data after 2014–2016 through to February 2023 (when this analysis was completed) were included. This standardized procedure for reporting fractures in MrOs has been published elsewhere [1,2].

Confounding variables

Potential covariates were based on variables known to influence the predictor (bone or muscle variable) and/or the outcome (fractures) in MrOs studies [1,2,24–26]. These covariates were collected between 2014–2016 (at the same time as the predictors) and included participants completing questionnaires on demographic (age, race, clinical center), lifestyle (alcohol use, smoking, education level, physical activity score [PASE survey]) and medical status (number of comorbidities, previous falls, cognition (Modified Mini-Mental State Examination). Other variables included height (cm, stadiometer), limb length (mm), weight (kg, scales), fat mass (%, DXA Hologic 4500), grip strength (kg, Jamar handheld dynamometer, maximum value from two tests on each hand), gait speed (m/s, normal pace over 6 meter track) and time to complete chair-stands (s, using standardized chair). Note, height was used to calculate BMI in baseline characteristics but height was not included in the multivariable-adjusted models due to its strong collinearity with other variables in the model (particularly weight).

Statistical analysis

First, we reported baseline characteristics across quartiles of Tt.BMD at distal tibia and D_3Cr muscle mass as mean (SD) and number (%). To detect if the effect of muscle on these baseline characteristics varied by BMD level, we ran ANOVA tests for continuous variables and chi-square tests for categorical variables. Next, as we hypothesized that there would be a a synergistic effect between bone density (or bone structure) and muscle quantity

(or muscle strength) on fracture risk, we ran Cox proportional hazards models to examine if there was a significant interaction between these continuous variables in estimating the risk of fractures. These models included only main effect estimates and the interaction term, and were unadjusted for covariates. Finally, to observe if the effect of muscle on fracture risk varied by BMD level, combined quartiles of bone and muscle variables (Q1+Q1 [lower+lower], Q1+Q2–4 [lower+not lower], Q2–4-Q1 [not lower+lower], Q2–4+Q2–4 [not lower+not lower] were used as predictors, with quartiles Q2–4+Q2–4 (not lower+not lower) set as the referent group. These multivariate-models were fully adjusted for covariates: age, race, clinical centre, alcohol, smoking, comorbidities, limb length, weight, % fat, physical activity, cognition, fall history, grip strength, chair stands and gait speed. Data are reported as hazard ratios with 95% CIs. Statistical significance was set at p <0.05.

Results

Population characteristics

Table 1 shows the full population characteristics divided into quartiles of distal tibia Tt.BMD (mg/cm^3) and D_3Cr muscle mass (whole body; kg). 1,353 men with a mean age of 84.2 ± 4.0 years (92.7% white) were included. During 6.03 ± 2.11 years of follow-up, the incidence of nonvertebral fractures, clinical vertebral fractures and all fractures was 209 (15.5%), 35 (2.6%) and 244 (18.0%), respectively (Table 1). The incidence of fractures (irrespective of type) appeared higher for men in Q1 of both distal tibia Tt.BMD and D_3Cr muscle mass compared to Q2–4 of both (p<0.05).

Interaction between bone and muscle variables in estimating the risk of fractures

In the unadjusted (continuous) model, there were no significant interactions (p>0.05) between any muscle variable (D_3Cr muscle mass, muscle volume, muscle density, grip strength or leg force) and Tt.BMD at the distal radius or tibia for fractures (all: n=182–302; nonvertebral: n=149–254; vertebral: n=27–45). There were no significant interactions (p>0.05) between any muscle variable (D_3Cr muscle mass, muscle volume, muscle density, grip strength or leg force) and Tb.BMD at the distal radius or tibia for fractures (all: n=182–302; nonvertebral: n=149–209; vertebral: n=27–45). There was some suggestion of an interaction between muscle density and Ct.BMD at the distal radius (p=0.077) and between leg force and Ct.BMD at the distal radius (p=0.036) for vertebral fractures (n=27–45). However, this finding was not consistent across other skeletal sites (i.e., interactions between muscle density and Ct.BMD at distal tibia (p=0.337) or leg force and Ct.BMD at distal tibia (p=0.244)), and was not significant in the models with a much larger number of events (all fractures, n=182–302, nonvertebral fractures, n=149–254). When considering a bone structural parameter, there were no significant interactions between any muscle variable (D3Cr muscle mass, muscle volume, muscle density, grip strength or leg force) and Ct.Ar at the distal radius or tibia for fractures (p>0.05). Tables 2–5 shows the full results of the continuous interactions models for for nonvertebral fractures, vertebral fractures and all fractures

Synergistic associations between bone and muscle variables in estimating the risk of fractures

Compared to men in Quartiles(Q) 2–4 of D_3Cr muscle mass and Q2–4 of distal tibia Tt.BMD, men in Q1 of both had increased risk for all fractures (Hazard Ratio (HR): 2.00; 95% confidence interval [CI], 1.24 –3.23, p= 0.005) and nonvertebral fractures (HR: 2.10; 95% CI, 1.25–3.52, p <0.001) but the association for clinical vertebral fractures (HR: 1.81; 95% CI, 0.54–6.07, p= 0.340) was not significant in the multivariable-adjusted model. Confidence intervals overlapped (p >0.05) when visually inspecting other quartile groups in the multivariable-adjusted model. Results were similar (overlapping confidence intervals) when looking at the synergistic effects between other muscle variables (D_3Cr muscle mass, muscle volume or muscle density) and Tt.BMD at the distal radius or tibia (p>0.05) as well as when using a bone structural parameter (Ct.Ar at distal tibia) in the models. Figures 1–4 shows the full multivariable-adjusted quartile analyses for nonvertebral fractures, vertebral fractures and all fractures.

Discussion

In this prospective cohort study of older men, we sought to examine if an interaction exists between bone and muscle variables in predicting fractures. Findings revealed no consistent interactions between these measures of musculoskeletal health in predicting these adverse outcomes.

The basis of this analysis was that, 1) both low BMD and low muscle mass or muscle density independently increase the risk of fractures in previous MrOs studies [1,2,17] and thus there may be an synergistic effect on fracture risk and 2), both tissues can impact one another through biomechanical and biochemical mechanisms [6] and thus there may be an interactive effect on fracture risk [e.g., in men with very low BMD the impact of muscle on the risk of fracture may be stronger than in those with higher BMD and vice-versa]. Indeed, evidence (largely from animal work) shows that bone and muscle are influenced by the same factors (such as physical activity, nutrition and disease states) and affected by local crosstalk between bone, muscle and fat cells [6]. Observational work in older adults have also shown that bone resorption markers are associated with poorer muscle function [27]. Strong site-specific associations have also been observed been upper- and lower-limb muscle strength and bone structural parameters [7,20]. Thus, it has been suggested that both bone and muscle loss are biologically linked and the combined losses of these tissues in older adults may increase fracture risk [19].

However, our findings do not support a consistent interaction between bone and muscle on fracture risk. Two reasons may explain our findings. On one hand, it is possible that both lower bone density and lower muscle mass, volume or density (compared to either alone) do not render older men at a higher risk of fractures. On the other hand, it is well-established that a much greater sample size is required to estimate two-way interactions between independent variables compared to main effects in observational studies [28]. Considering this, in addition to the observed interaction between muscle density/leg force and Ct.BMD at the distal radius, a larger sample size and longer-follow up (greater number of events) may

have been needed to clarify if there is a multiplicative or additive effect of bone and muscle on fracture risk.

Previous work on this topic has involved the use of alternate approaches to examine the combined effects of osteopenia/osteoporosis and sarcopenia (osteosarcopenia) on fracture risk, which makes direct comparisons with our work difficult. In the Tasmanian Older Adult Cohort (TASOAC) study (1032 participants (52% women), 62.9 ± 7.4 years)), the risk of incident fractures over 10 years was not statistically higher is those with both osteopenia/osteoporosis (BMD *T*-score less than 1 SDs) and sarcopenia (low ALM/BMI and low grip strength) compared to either alone. [29] When continuous predictors were used, increasing BMD but not ALM/BMI was associated with a lower fracture risk (interactions between these continuous variables were not reported [29]). In the Concord Health and Ageing project of Australian men (1575 participants, 79.7 ± 6.5 years), the risk of incident fractures with both osteopenia/osteoporosis (BMD *T*-score less than 1 SDs) and sarcopenia (EWGSOP definition: low ALM/height^2, low grip strength and/or slow gait speed) was not higher compared to either condition alone nor were there any interactions between bone and muscle variables in the continuous analysis.[11] Other prospective cohort studies among older adults in North America (The Osteoporotic Fractures in Men study, USA)[10] and South America (Alexandros; Chile)[30], as well as a recent meta-analysis on the topic [31], suggest the risk of incident fractures is not higher when comparing definitions of osteosarcopenia versus osteopenia/osteoporosis or sarcopenia alone. However, a very recent analysis of older outpatients (481 participants (~76% women), median age: 78 years)), showed the odds of recurrent fractures (≥2 vs 0–1) was higher in those with osteosarcopenia (SDOC: OR: 1.63, 95% CI: 1.03, 2.59; EWGSOP2: OR: 1.83, 95% CI: 1.12, 3.01) versus osteopenia/osteoporosis and this was independent of the definition as well as confounders [14]. In the same study, the low prevalence of sarcopenia in those with normal BMD (<10 participants) precluded any statistical comparison with this muscle disease. Lastly, this study showed a significant interaction between hip BMD and gait speed, whereby the effect of gait speed was in the opposite direction when hip BMD was high versus low [14].

Taking the above findings together, it is apparent that further research is needed to clarify if the combined assessment of bone and muscle variables offers additional risk for incident fractures in older adults and if so, which measures best predicts this risk. Elucidating this information is important so appropriate rehabilitation programs for fractures can be initiated in clinical practice to maintain the quality of life of older adults and reduce healthcare costs.

Aside from the comprehensive inclusion of demographic, lifestyle and clinical covariates, the main strength of our paper is the use of accurate imaging techniques to quantify volumetric BMD and bone structure (HR-pQCT), muscle mass (D_3Cr) and muscle density (HR-pQCT), all of which independently predict fractures [1,2,17]. This is in contrast to previous studies [10,11,14,29–31] that used inferior imaging techniques such as DXA-lean mass (a surrogate measure of muscle mass) that show inconsistent associations with fractures [12,13]. A recent study [7] also showed that older women with osteosarcopenia (defined as osteoporosis plus low grip strength and/or chair rise time by EWGSOP2) had significantly lower HR-pQCT cortical bone parameters but similar DXA values when compared to osteoporosis alone. This reiterates the advantage of using HR-pQCT versus DXA to examine

bone-muscle interactions in fracture risk. The main limitation of our analysis is the low number of events, particularly clinical vertebral fractures (n=27–45), which hindered our ability to detect any possible interactions. Our population was also limited to men and therefore our findings cannot be extrapolated to women, who are at higher risk of fractures [32] and have different body composition than men. It is also noteworthy that the prevalence of osteosarcopenia is high in women attending fall and fracture clinics [14,33]. Future research on this topic should consider these factors.

To conclude, in this prospective cohort study of older men, there was no consistent interactions between bone and muscle variables on fracture risk. Larger sample sizes and longer follow-up may be needed to clarify if the assessment of both bone and muscle measures offers additional prognostic value for incident fractures in older adults. Further research should revisit this hypothesis in older people with age-related bone and muscle loss, and in individuals with comorbidities where fracture risk (and post-fracture mortality) may be heightened [34]. In this context, bone-muscle interactions may be informative.

Acknowledgements

The authors would like to thank the MrOS participants for taking part in the research study as well as the MrOS research group for granting access to the data. Finally, the authors would like to thank the Australian Institute for Musculoskeletal Science (AIMSS) for supporting this study.

Funding

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, R01 AG066671, and UL1 TR002369. Funding for the D3Cr muscle mass measure was provided by NIAMS (grant number R01 AR065268 (PMC)). GlaxoSmithKline provided in kind support by providing the D_3Cr dose and analysis of samples.

Data availability

Analysed data is available in this manuscript. Raw data is available on the MrOS website (access is subject to approval): https://mrosonline.ucsf.edu.

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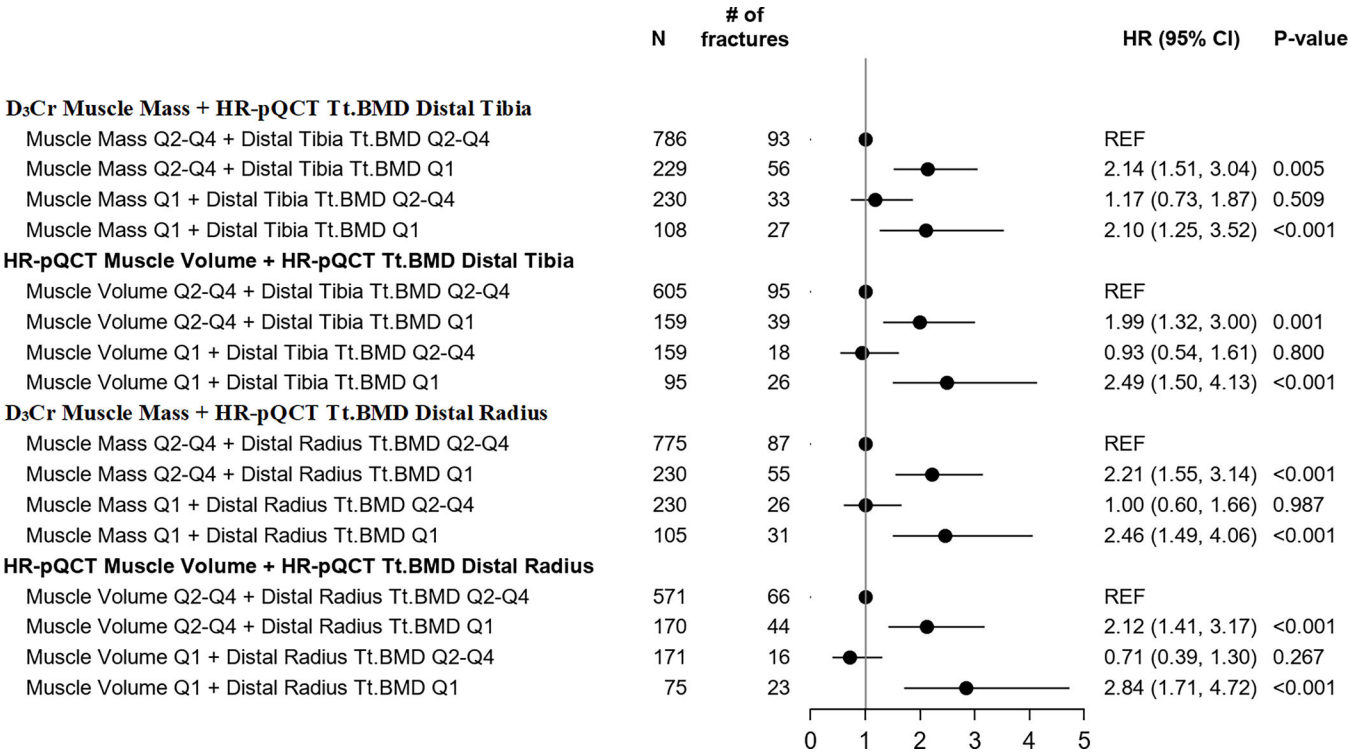

Figure 1.

Multivariable-adjusted hazard ratio (with 95% CI) for nonvertebral fractures across quartiles of Tt.BMD (mg/cm^3) and D_3Cr muscle mass (kg) or Tt.BMD (mg/cm^3) and muscle volume (mm^3). Models are adjusted for age, race, clinical centre, alcohol, smoking, comorbidities, limb length, weight, % fat, physical activity, cognition, fall history, grip strength, chair stands and gait speed.

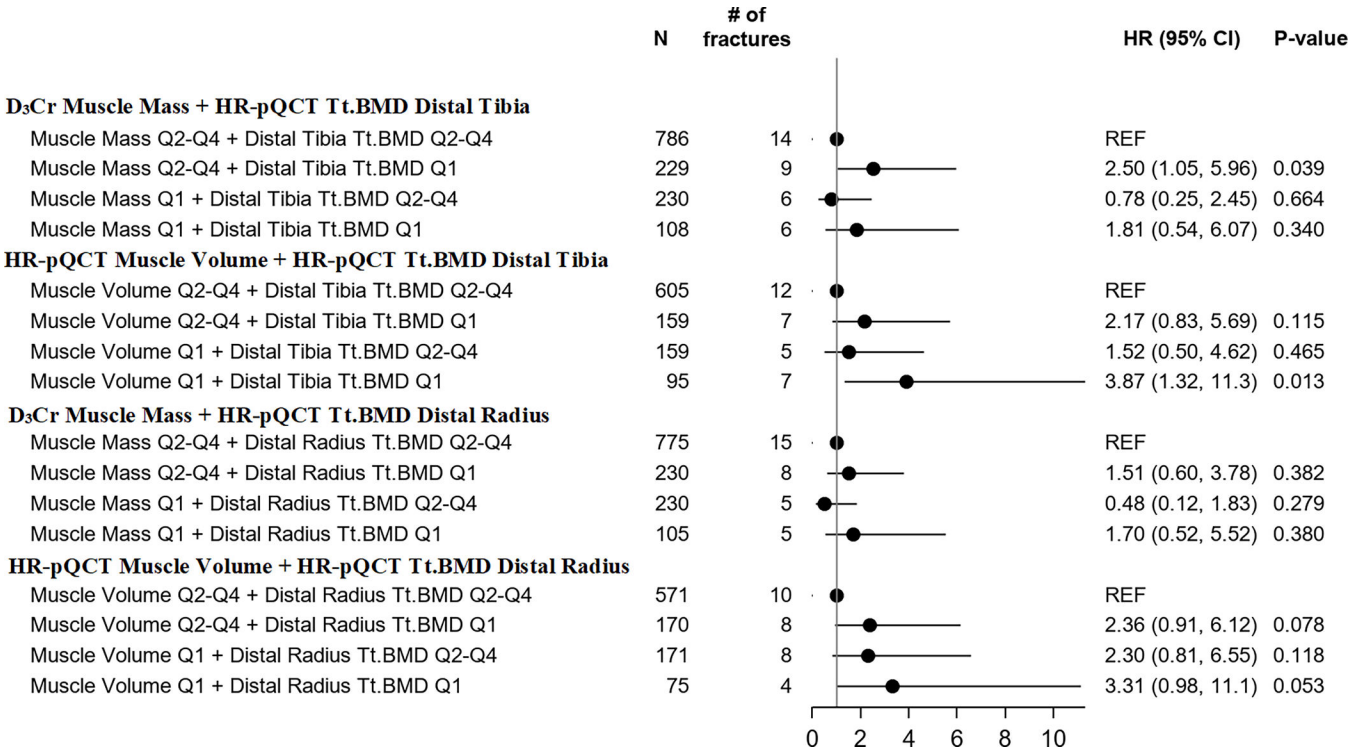

Figure 2.

Multivariable-adjusted hazard ratio (with 95% CI) for vertebral fractures across quartiles of Tt.BMD (mg/cm^3) and D_3Cr muscle mass (kg) or Tt.BMD (mg/cm^3) and muscle volume (mm^3). Models are adjusted for age, race, clinical centre, alcohol, smoking, comorbidities, limb length, weight, % fat, physical activity, cognition, fall history, grip strength, chair stands and gait speed.

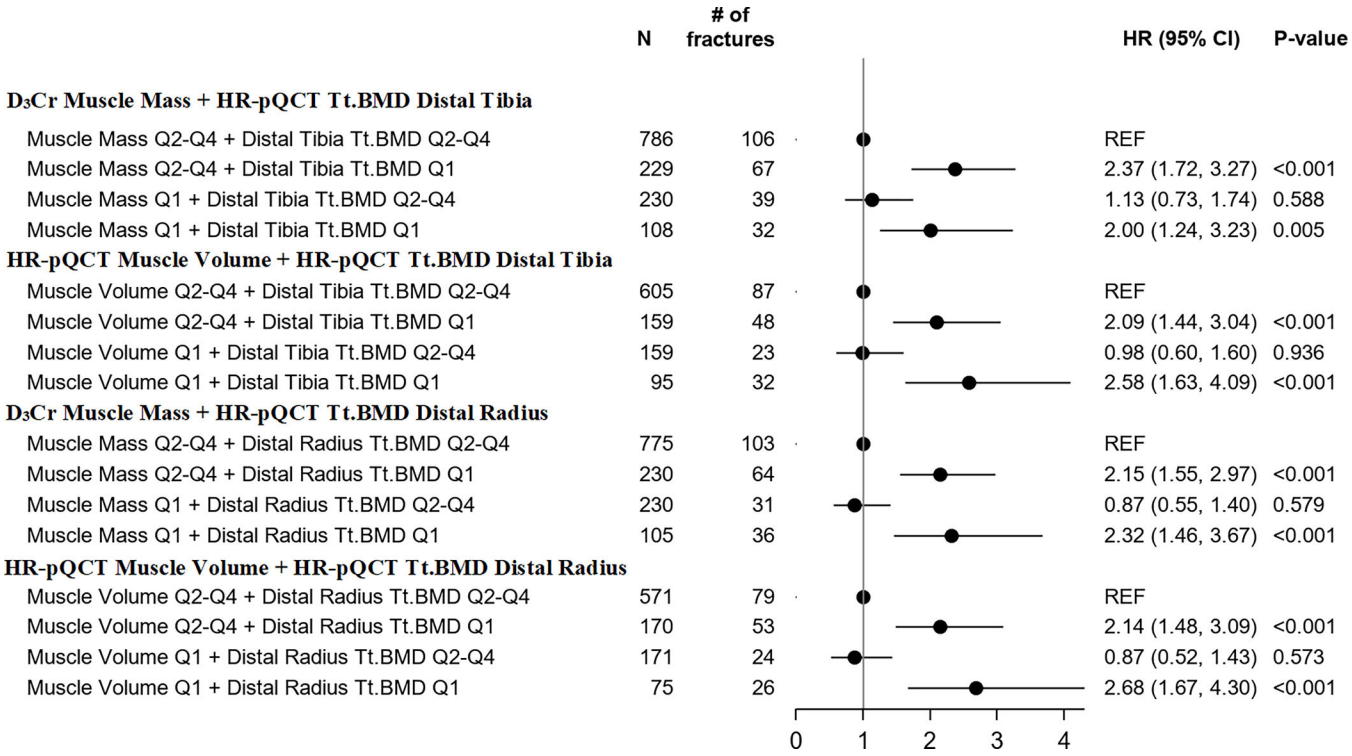

Figure 3.

Multivariable-adjusted hazard ratio (with 95% CI) for all fractures across quartiles of Tt.BMD (mg/cm^3) and D_3Cr muscle mass (kg) or Tt.BMD (mg/cm^3) and muscle volume (mm^3). Models are adjusted for age, race, clinical centre, alcohol, smoking, comorbidities, limb length, weight, % fat, physical activity, cognition, fall history, grip strength, chair stands and gait speed.

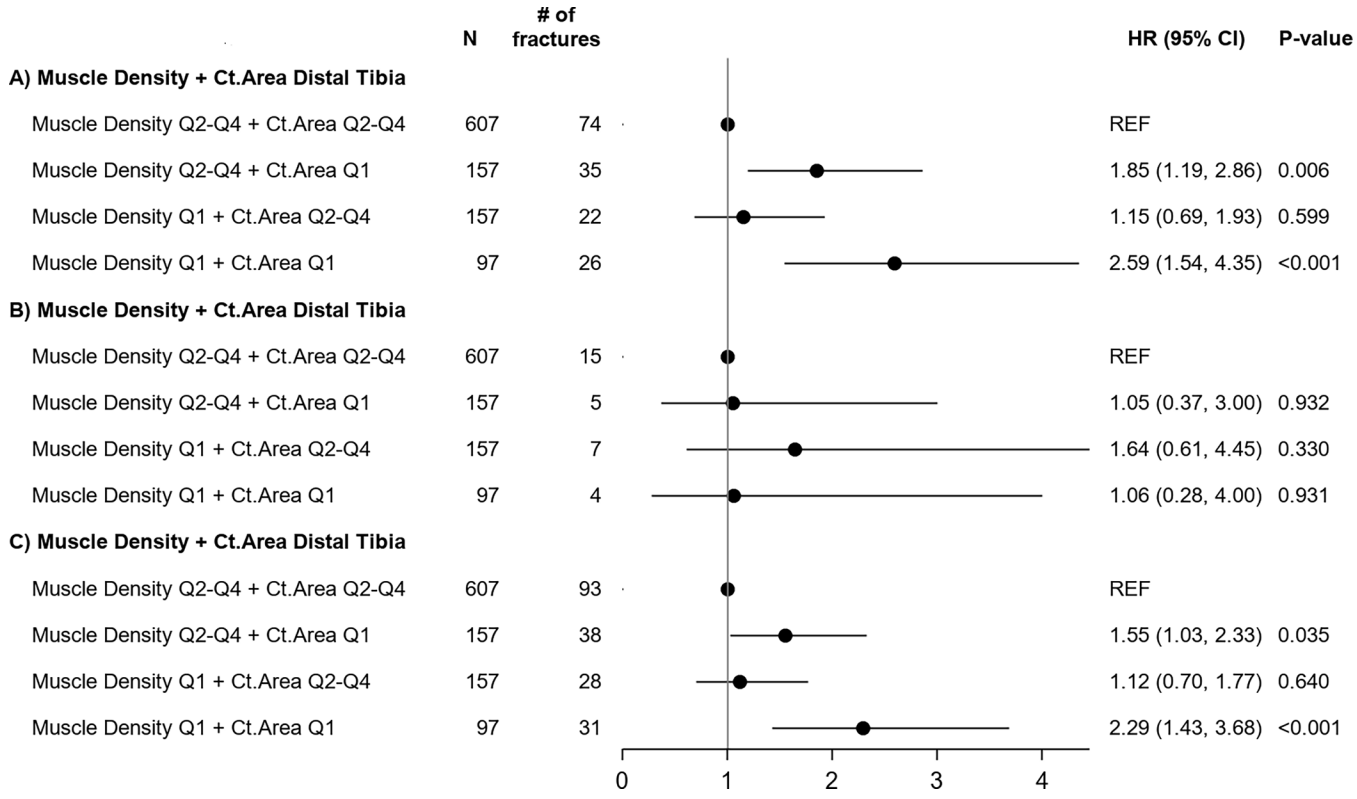

Figure 4.

Multivariable-adjusted hazard ratio (with 95% CI) for A) nonvertebral, B) vertebral and C) all fractures across quartiles of HR-pQCT distal tibia Ct.Ar (mm^2) and HR-pQCT muscle density (diaphyseal, calf, mg/cm^3). Models are adjusted for age, race, clinical centre, alcohol, smoking, comorbidities, limb length, weight, % fat, physical activity, cognition, fall history, grip strength, chair stands and gait speed.

J Bone Miner Res. Author manuscript; available in PMC 2024 September 01.

Table 1.

Population characteristics by quartiles (Q) of Tt.BMD (distal tibia, mg/cm^3) and D_3Cr muscle mass (whole body; kg).

	Q1 Tt.BMD (120.20–249.40 mg/cm^3) + Q1 Muscle Mass (11.7–21.18kg)	**Q1 Tt.BMD (120.20–249.40 mg/cm^3) + Q2–4 Muscle Mass (21.19–37.71kg)**	**Q2–4 Tt.BMD (245.10–479.4mg/cm^3) + Q1 Muscle Mass (11.7–21.18kg)**	**Q2–4 Tt.BMD (245.10–479.4mg/cm^3) + Q2–4 Muscle Mass (21.19–37.71kg)**	***P value***
Sample size, *n*=	(N= 108)	(N= 230)	(N= 229)	(N= 786)	
Age (years), mean ± SD	87.90 ± 4.46	86.26 ± 4.28	83.75 ± 3.69	83.13 ± 3.40	<0.001
White, n (%)	100 (92.59)	211 (91.74)	211 (92.14)	718 (91.35)	0.961
Education level, n (%)					
<high school	4 (3.70)	13 (5.65)	7 (3.06)	23 (2.93)	0.429
high school	16 (14.81)	40 (17.39)	33 (14.41)	112 (14.25)	
college/grad school	88 (81.48)	177 (76.96)	189 (82.53)	651 (82.82)	
Smoking status, n(%)					
Never	60 (55.56)	114 (49.57)	113 (49.34)	394 (50.13)	0.678
Past	46 (42.59)	114 (49.57)	112 (48.91)	386 (49.11)	
Current	2 (1.85)	2 (0.87)	4 (1.75)	6 (0.76)	
Drinks per week, n(%)					
<1 drinks/week	56 (51.85)	133 (58.59)	101 (44.10)	363 (46.30)	0.004
1–13 drinks/week	43 (39.81)	82 (36.12)	119 (51.97)	385 (49.11)	
14+ drinks/week	9 (8.33)	12 (5.29)	9 (3.93)	36 (4.59)	
Number of medical conditions, n (%)					
0	65 (60.19)	137 (59.57)	153 (66.81)	525 (66.79)	0.033
1	25 (23.15)	61 (26.52)	59 (25.76)	193 (24.55)	
2+	18 (16.67)	32 (13.91)	17 (7.42)	68 (8.65)	
Body mass index (kg/m^2), mean ± SD	24.89 ± 3.31	25.30 ± 3.05	26.65 ± 3.51	27.42 ± 3.62	<0.001
Percentage fat mass, DXA, mean ± SD	27.44 ± 6.73	27.70 ± 5.91	27.18 ± 6.16	27.89 ± 5.63	0.422
D_3Cr muscle mass, kg, mean ± SD	18.79 ± 1.90	19.35 ± 1.38	25.36 ± 3.01	25.91 ± 3.27	<0.001
D_3Cr muscle mass/weight, kg, mean ± SD	0.27 ± 0.04	0.27 ± 0.04	0.31 ± 0.04	0.32 ± 0.05	<0.001
Muscle volume (diaphyseal, calf), mm^3, mean ± SD	26833.10 +/− 6774.74	27560.41 +/− 5442.77	29503.61 +/− 5413.74	31430.17 +/− 6434.00	<0.001

	Q1 Tt.BMD (120.20–249.40 mg/cm^3) + Q1 Muscle Mass (11.7–21.18kg)	**Q1 Tt.BMD (120.20–249.40 mg/cm^3) + Q2–4 Muscle Mass (21.19–37.71kg)**	**Q2–4 Tt.BMD (245.10–479.4mg/cm^3) + Q1 Muscle Mass (11.7–21.18kg)**	**Q2–4 Tt.BMD (245.10–479.4mg/cm^3) + Q2–4 Muscle Mass (21.19–37.71kg)**	***P value***
Muscle density (diaphyseal, calf), mg/cm^3, mean ± SD	9.15 +/− 4.68	11.00 +/− 4.73	11.53 +/− 4.20	12.79 +/− 4.25	<0.001
Tt.BMD, distal radius, mg/cm^3, mean ± SD	216.40 ± 43.17	286.60 ± 49.88	223.25 ± 38.95	295.78 ± 53.35	<0.001
Tb.BMD, distal radius, mg/cm^3, mean ± SD	135.30 +/− 32.24	181.41 +/− 33.92	138.47 +/− 26.64	181.30 +/− 35.52	<0.001
Ct.BMD, distal radius, mg/cm^3, mean ± SD	744.98 +/− 69.75	794.70 +/− 66.16	763.12 +/− 63.90	816.13 +/− 59.55	<0.001
Ct.Ar, distal radius, mm^2, mean ± SD	53.83 +/− 10.16	63.50 +/− 12.04	59.28 +/− 10.32	70.46 +/− 13.37	<0.001
Tt.BMD, distal tibia, mg/cm^3, mean ± SD	211.62 ± 27.35	299.40 ± 39.58	217.34 ± 24.86	304.12 ± 42.01	<0.001
Tb.BMD, distal tibia, mg/cm^3, mean ± SD	135.30 +/− 32.24	181.41 +/− 33.92	138.47 +/− 26.64	181.30 +/− 35.52	<0.001
Ct.BMD, distal tibia, mg/cm^3, mean ± SD	744.98 +/− 69.75	794.70 +/− 66.16	763.12 +/− 63.90	816.13 +/− 59.55	<0.001
Ct.Ar, distal tibia, mm^2, mean ± SD	102.86 +/− 23.14	139.47 +/− 26.14	114.75 +/− 20.52	151.79 +/− 26.22	<0.001
Grip strength, kg, mean ± SD	28.67 ± 9.14	30.31 ± 8.85	36.69 ± 8.80	36.29 ± 9.62	<0.001
Leg force (newtons/kg body weight)	15.72 +/− 1.66	16.26 +/− 1.84	16.51 +/− 1.90	16.93 +/− 1.83	<0.001
Chair stands per 10 seconds, mean ± SD	2.75 ± 2.18	3.32 ± 1.85	3.58 ± 1.69	4.06 ± 1.62	<0.001
Gait speed, m/s, mean ± SD	0.93 ± 0.26	1.01 ± 0.24	1.08 ± 0.23	1.12 ± 0.23	<0.001
Physical activity score (PASE), mean ± SD	92.68 ± 63.05	107.25 ± 70.17	123.73 ± 66.65	124.61 ± 60.96	<0.001
Mini Mental score, mean ± SD	91.05 ± 7.29	91.39 ± 6.86	92.36 ± 7.19	92.84 ± 6.61	0.006
Previous falls, n(%)	45 (41.67)	98 (42.61)	78 (34.06)	263 (33.46)	0.038
Incident nonvertebral fractures, n (%)	27 (25.00)	33 (14.35)	56 (24.45)	93 (11.83)	<0.001
Incident vertebral fractures, n (%)	6 (5.56)	6 (2.61)	9 (3.93)	14 (1.78)	0.059
Incident all fractures, n (%)	32 (29.63)	39 (16.96)	67 (29.26)	106 (13.49)	<0.001
Follow up time (years), mean ± SD	4.85 +/− 2.38	5.20 +/− 2.22	5.99 +/− 2.14	6.44 +/− 1.90	<0.001

Table 2.

Continuous interactions terms (*p* values) between Tt.BMD (at distal radius and tibia) and muscle variables in predicting fractures.

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tt.BMDdistal radius (mg/cm^3)	1340	199	0.339	987	149	0.736	987	149	0.291	1669	246	0.627	1172	171	0.309
Tt.BMDdistal tibia (mg/cm^3)	1353	209	0.790	1018	157	0.288	1018	157	0.600	1683	254	0.977	1178	173	0.912
Vertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tt.BMDdistal radius (mg/cm^3)	1340	33	0.678	987	30	0.995	987	30	0.262	1669	42	0.686	1172	27	0.078
Tt.BMDdistal tibia (mg/cm^3)	1353	35	0.634	1018	31	0.419	1018	31	0.471	1683	45	0.401	1178	27	0.871
All fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tt.BMDdistal radius (mg/cm^3)	1340	234	0.564	987	182	0.857	987	182	0.381	1669	293	0.746	1172	203	0.687
Tt.BMD distal tibia (mg/cm^3)	1353	244	0.931	1018	190	0.275	1018	190	0.572	1683	302	0.708	1178	204	0.951

Note, to tests whether there was a synergistic effect of bone and muscle variables on fracture risk, we ran Cox proportional hazards models including only main effect estimates and the interaction term. Data are unadjusted for covariates. No significant interactions were observed ($p>0.05$).

Table 3.

Continuous interactions terms (*p* values) between Tb.BMD (at distal radius and tibia) and muscle variables in predicting fractures.

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tb.BMDdistal radius (mg/cm^3)	1340	199	0.626	987	149	0.855	987	149	0.726	1669	246	0.327	1172	171	0.421
Tb.BMDdistal tibia (mg/cm^3)	1353	209	0.435	1018	157	0.309	1018	157	0.680	1683	254	0.806	1178	173	0.559
Vertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tb.BMDdistal radius (mg/cm^3)	1340	33	0.731	987	30	0.942	987	30	0.936	1669	42	0.815	1172	27	0.373
Tb.BMDdistal tibia (mg/cm^3)	1353	35	0.725	1018	31	0.647	1018	31	0.735	1683	45	0.639	1178	27	0.382
All fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Tb.BMDdistal radius (mg/cm^3)	1340	234	0.876	987	182	0.985	987	182	0.658	1669	293	0.363	1172	203	0.801
Tb.BMDdistal tibia (mg/cm^3)	1353	244	0.684	1018	190	0.189	1018	190	0.911	1683	302	0.692	1178	204	0.367

Note, to tests whether there was a synergistic effect of bone and muscle variables on fracture risk, we ran Cox proportional hazards models including only main effect estimates and the interaction term. Data are unadjusted for covariates. No significant interactions were observed ($p>0.05$).

J Bone Miner Res. Author manuscript; available in PMC 2024 September 01.

Table 4.

Continuous interactions terms (*p* values) between Ct.BMD (at distal radius and tibia) and muscle variables in predicting fractures.

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.BMD distal radius (mg/cm^3)	1340	199	0.932	987	149	0.318	987	149	0.138	1669	246	0.720	1172	171	0.328
Ct.BMD distal tibia (mg/cm^3)	1353	209	0.544	1018	157	0.744	1018	157	0.787	1683	254	0.610	1178	173	0.431
Vertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.BMD distal radius (mg/cm^3)	1340	33	0.509	987	30	0.702	987	30	0.077	1669	42	0.967	1172	27	0.036
Ct.BMD distal tibia (mg/cm^3)	1353	35	0.773	1018	31	0.808	1018	31	0.337	1683	45	0.288	1178	27	0.244
All fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.BMD distal radius (mg/cm^3)	1340	234	0.923	987	182	0.198	987	182	0.239	1669	293	0.817	1172	203	0.510

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.BMD distal tibia (mg/cm^3)	1353	244	0.658	1018	190	0.649	1018	190	0.972	1683	302	0.856	1178	204	0.410

Note, to tests whether there was a synergistic effect of bone and muscle variables on fracture risk, we ran Cox proportional hazards models including only main effect estimates and the interaction term. Data are unadjusted for covariates.

Table 5.

Continuous interactions terms (*p* values) between Ct.Ar (at distal radius and tibia) and muscle variables in predicting fractures.

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.Ar distal radius (mm^2)	1340	199	0.367	987	149	0.946	987	149	0.271	1669	246	0.609	1172	171	0.881
Ct.Ar distal tibia (mm^2)	1353	209	0.911	972	148	0.754	1018	157	0.693	1683	254	0.373	1178	173	0.135
Vertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.Ar distal radius (mm^2)	1340	33	0.597	987	30	0.800	987	30	0.141	1669	42	0.535	1172	27	0.338
Ct.Ar distal tibia (mm^2)	1353	35	0.649	1018	31	0.738	1018	31	0.187	1683	45	0.232	1178	27	0.569
All fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**	**Sample size (*n*=)**	**Number of events (*n*=)**	***P* value**
Ct.Ar distal radius (mm^2)	1340	234	0.526	987	182	0.853	987	182	0.412	1669	293	0.919	1172	203	0.993

Nonvertebral fractures															
	D_3Cr muscle mass (kg)			**Muscle volume (diaphyseal, calf) (mm^3)**			**Muscle density (diaphyseal, calf) (mg/cm^3)**			**Grip strength (kg)**			**Leg force (newtons/kg body weight)**		
	Sample size (*n*=)	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***	**Sample size (*n*=)**	**Number of events (*n*=)**	***P value***
Ct.Ar distal tibia (mm^2)	1353	244	0.914	1018	190	0.920	1018	190	0.611	1683	302	0.849	1178	204	0.274

Note, to tests whether there was a synergistic effect of bone and muscle variables on fracture risk, we ran Cox proportional hazards models including only main effect estimates and the interaction term. Data are unadjusted for covariates. No significant interactions were observed (p>0.05).