Osteoporosis International (2025) 36:2031–2039
https://doi.org/10.1007/s00198-025-07653-4

ORIGINAL ARTICLE

Associations between muscle mass and strength and bone microarchitecture in Caucasian postmenopausal women

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Received: 24 March 2025 / Accepted: 30 July 2025 / Published online: 19 August 2025

Abstract

Summary This study examines associations between muscle mass, strength, and bone microarchitecture in 160 postmenopausal women from the OsteoPreP Study. Findings reveal that greater appendicular lean mass index (ALMI) and hand grip strength correlate with increased cortical area and trabecular vBMD, although ALMI was associated with lower cortical bone density, explained by physical activity.

Purpose To investigate associations between muscle mass, strength, and bone microarchitecture in postmenopausal women.

Methods Postmenopausal women ($n = 160$) (mean ± standard deviation: 55.9 ± 2.6 years) were included as part of the baseline examination from the OsteoPreP Study. Appendicular lean mass (ALM) was calculated as the sum of lean mass in the upper and lower limbs obtained using dual-energy X-ray absorptiometry. Participants completed hand grip strength testing using a dynamometer. Bone microarchitecture parameters including cortical and trabecular volumetric bone mineral density (vBMD), trabecular thickness, cortical area, and porosity were analyzed by using high-resolution peripheral quantitative computed tomography (HR-pQCT) at the distal tibia and radius. Metabolic equivalents (METs) were objectively determined by accelerometer. Linear regression (unstandardised β-coefficients; *p*-values) analyses were performed with adjustments for confounders.

Results Higher appendicular lean mass index (ALMI; ALM/height^2 in kg/m^2) was significantly associated with greater cortical area (2.55 mm^2 per 1 kg/m^2 increase in ALMI, $p < 0.001$) and greater trabecular vBMD (9.44 mg/cm^3 per 1 kg/m^2, $p = 0.013$), but with lower cortical vBMD (− 11.37 mg/cm^3 per 1 kg/m^2, $p = 0.039$) at the radius, after adjustment. Higher hand grip strength (kg) was also significantly associated with greater cortical area at the radius (0.67 mm^2 per 1 kg, $p = 0.001$), with similar associations at the tibia. Additionally, physical activity levels (MET-hours/week) partially mediated the association between ALMI and cortical vBMD (− 2.01 mg/cm^3, 95% CI: − 5.25 to − 0.03).

Conclusion In summary, greater ALMI and hand grip strength are associated with increased cortical area and trabecular vBMD, but lower cortical vBMD, which is partially explained by physical activity levels. Although greater muscle mass is correlated with larger bones, it comes at the expense of cortical vBMD in postmenopausal women.

Keywords Bone microarchitecture · HRpQCT · Lean mass · Muscle strength · Osteoporosis · Postmenopausal women

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Introduction

Human aging has become closely associated with two physical conditions affecting the musculoskeletal system, osteoporosis, and sarcopenia. Osteoporosis is a common condition characterized by low bone mass and microarchitectural deterioration of bone tissue and is defined as a T-score of ≤ -2.5, according to the World Health Organisation guidelines, while sarcopenia is defined by low levels of muscle strength, muscle quantity/quality, and physical performance [1, 3]. Together, osteoporosis and sarcopenia are significant musculoskeletal conditions leading to increased risk of fractures, functional impairment, and loss of independence which lead to increased morbidity in older adults [4, 8]. Postmenopausal women are particularly vulnerable to musculoskeletal decline due to hormonal changes that start during perimenopause and result in accelerated bone loss and muscle degeneration [9, 10]. The interplay between muscle health and osteoporosis in this population is complex and multifaceted, involving intricate physiological mechanisms and several interrelated pathways [11, 12].

Traditionally, bone health has been assessed using dual-energy X-ray absorptiometry (DXA), which provides measurements of areal bone mineral density (aBMD) [13, 14]. However, DXA lacks the resolution to distinguish between trabecular and cortical bone compartments [15]. This is a major limitation since bone microarchitecture plays a crucial role in bone strength and fracture risk and may provide further insights into the interplay between bone and muscle [16, 18]. The second-generation high-resolution peripheral quantitative computed tomography (HR-pQCT) offers superior resolution and enables detailed assessment of bone microarchitecture at peripheral skeletal sites, such as the radius and tibia [19, 21]. Assessments at the 30% site, which predominantly comprises of cortical bone, are particularly valuable as this compartment plays a critical role in mechanical strength and resistance to bending and torsion [21]. This compartment- and site-specific approach provides a more comprehensive understanding of skeletal integrity and fracture risk [18]. Therefore, HR-pQCT may offer a more comprehensive understanding of musculoskeletal health and fracture risk by characterizing site-specific and compartment-specific interactions [18]. Although age-related fracture risk and deterioration in bone microarchitecture have been previously investigated, the influence of muscle mass and strength on bone microarchitecture and their predictive value remain insufficiently investigated especially in Caucasian postmenopausal women. Given that physical activity plays a critical role in maintaining musculoskeletal integrity and mitigating conditions such as sarcopenia, understanding its relationship with bone health is essential. However, accurately assessing physical activity levels remains challenging, particularly among older adults [22]. Although self-reported questionnaires are commonly used, they are prone to recall bias and may lack precision in capturing activity intensity and frequency [23]. In contrast, accelerometer-determined physical activity data provides objective, continuous, and detailed measurements of movement patterns, offering a more reliable assessment of physical activity [23, 24]. Given the potential mechanistic associations between physical activity and bone microarchitecture, further research is warranted to address this gap.

This study therefore aims to help fill this gap by comprehensively examining the associations between muscle mass and strength and bone microarchitecture assessed by HR-pQCT in a cohort of Caucasian postmenopausal women. By elucidating these relationships, this study aims to enhance the understanding of the complex interplay between muscle and bone and to identify potential lifestyle interventions aimed at preserving musculoskeletal health and reducing fracture risk in this population.

Methods

Study design and participants

This cross-sectional analysis utilised baseline data from a sample of postmenopausal women participating in a double blinded, placebo-controlled, randomized clinical trial conducted at the Australian Catholic University (ACU), Melbourne, Australia designed to evaluate the impact of synbiotic (probiotic + prebiotic) ingestion on bone health [25]. One hundred and sixty postmenopausal women aged between 40 and 65 years, residing in Melbourne, Australia, were recruited via flyers, online advertisements and Services Australia mailouts. Participants were included in this study if they were Caucasian, postmenopausal (defined as being more than 1 year since their final menstrual period), able to walk without the use of an aid, had up to date Covid-19 vaccination status, and stated availability throughout the duration of the 12 months study period. Participants were however excluded if they had a T-score of -2.5 or less at the femoral neck or lumbar spine (L1–L4) assessed by the DXA, HbA1c $\geq 6.5\%$, and blood pressure of systolic > 180 mmHg and/or diastolic > 120 mm. In addition, participants were excluded if they were diagnosed with osteoporosis, untreated hyperthyroidism, rheumatoid arthritis, disease-causing secondary osteoporosis (chronic obstructive pulmonary disease, inflammatory bowel disease, celiac disease, type 1/type 2 diabetes, or chronic liver disease), had undergone bariatric surgery or recently diagnosed with malignancy (within the last 5 years). Participants were also excluded if they had current or recent (< 1 year) oral corticosteroid (any dose within the last 3 months, or 5 mg of Prednisolone

(or equivalent) or a higher daily dose for 14 days or more) (current or during the last 3 years), any antiresorptive therapy (including systemic hormone replacement therapy, bisphosphonates, RANK ligand inhibitor, selective estrogen receptor modulators, strontium ranelate, or use of teriparatide (current or during the last 3 years)), or had antibiotic treatment 2 months prior. In addition, participants were also excluded if they were unwilling to cease taking probiotic or prebiotic supplements (current use).

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ACU Ethics Committee (Protocol ID: 2021-122HC*)* and all participants provided written informed consent.

Questionnaires

At baseline, participants completed self-administered questionnaires including questions on demographics and smoking status.

Physical activity

Each participant was provided with an Actigraph wGT3X-BT accelerometer (Actigraph, Pensacola, CA, USA) and instructed to wear the accelerometer at the side of the hip for ten consecutive days except during showering, water activities, and sleeping. A diary was also provided, to record the time of the day that the device was worn and removed, physical activity performed and sleep times. After 10 days, the participants returned the accelerometer to the study team. The accelerometer data was recorded at a rate of 30 Hz and transferred into ActiLife v6.13.4 software for analysis. The ActiLife software analyzed data in epoch length of 60 s. Physical activity was transformed into counts per minute (CPMs) with an activity threshold of 100 CPMs. Physical activity was categorized based on the following Freedson adult cut points of 1 to 99 CPMs (sedentary), 100 to 1951 CPMs (light) and > 1952 CPMs (moderate-to-vigorous physical activity, MVPA). The percentage of time spent in each category was calculated by dividing the time spent in each activity level by the total valid wear time and multiplying by 100. Due to the low amount of recorded vigorous physical activity in this population of older women, moderate and vigorous physical activity were combined into a single variable. Additionally, physical activity intensity was assessed in terms of metabolic equivalent of task (METs) [26].

Anthropometry

Weight (kg) was measured to the nearest 0.1 kg using an electronic scale (Seca 877, Seca Ltd, Birmingham, UK; precision 100 g; range 2–200 kg) and height (m) was measured to the nearest 0.1 m using a stadiometer (Livingstone International, Australia; precision 0.1 cm; range 0–200 cm) with footwear and heavy items of clothing removed. Body mass index (BMI; kg/m^2) was calculated as weight(kg)/height(m^2). Waist and hip circumference were measured to the nearest 0.1 cm using a measuring tape (Livingstone International, Australia; precision 0.1 cm; range 0–150 cm) and utilised to calculate waist/hip ratio. Waist circumference was measured between the lowest rib and top of the hip bone directly over the skin yet not compressing the skin of the participant after breathing out normally. Hip circumference was measured at the largest circumference around the hips/buttocks.

Muscle strength

Hand grip strength (HGS) was measured using a dynamometer (JAMAR, HMG Direct, Australia). Participants gripped the dynamometer with maximal force in a seated position with their elbow at a 90° angle. Participants repeated this measurement three times in both hands with a 30-s rest between trials, and for the purpose of this study, the mean force of the three trials in the dominant hand was used to calculate average HGS.

Dual-energy X-ray absorptiometry

Whole-body DXA scans assessed body composition parameters, including body fat percentage and lean mass (GE Lunar iDXA Pro, enCORE software Version 16, GE Healthcare, Boston, MA, USA). All scans were performed by the same operator to minimize inter-operator variability. Appendicular lean mass (ALM) was calculated as the sum of lean mass in the upper and lower limbs. DXA scans were also utilised to assess aBMD at the lumbar spine and the femoral neck (non-dominant total hip). Osteopenia was defined as a T-score between − 1 and − 2.5 and osteoporosis as a T-score of ≤ − 2.5 at the total hip [27]. The DXA scanner was calibrated daily using the manufacturer's spine phantom. The coefficients of variation (CV) for bone densitometry scans repeated on 30 individuals in our laboratory was 0.69% for aBMD at the whole-body and 0.91% for whole-body total fat. The CV for total lean mass was 0.55%.

High-resolution peripheral quantitative computed tomography

HR-pQCT scans were performed on the non-dominant distal tibia and radius at the standard (4%) and 30% sites to estimate volumetric BMD (vBMD), bone microarchitecture and strength (XtremeCT II, ScanCo, Swtizerland) [28, 29].

A two-dimensional scout view scan was used to identify the region of interest (22.5 mm proximal to the reference line placement at the end plate of the tibia and 9.5 mm proximal

to the reference line placement at the end plate of the radius). The participant's leg/hand was positioned into the scanner using the manufacturer-provided cast to prevent movement artifact. One hundred and sixty-eight parallel computed tomography slices were obtained over a 10.2-mm region of the distal tibia using an isotropic resolution of 61 µm. HR-pQCT images were analyzed according to the manufacturer evaluation protocol to measure cortical and trabecular bone variables using software version 6.1 [28]. Scans were graded according to a 5-point scale to account for any motion artifacts (1 = perfect, 5 = severe motion artifact) [30]. A semi-automated slice-by-slice contouring was also performed on all scans to extract the bone region from the surrounding soft tissue and manual corrections were applied where necessary [21].

Bone variables included total vBMD (mg HA/cm^3), cortical area (mm^2), cortical vBMD (mg/cm^3), cortical porosity (%), trabecular area (mm^2), trabecular vBMD (mgA/cm^3), trabecular thickness (mm), trabecular separation (mm), and trabecular number (1/mm) (21). The CV, estimated by repeated scans performed on 30 individuals in our laboratory, was 1.24% for cortical area, 0.84% for cortical vBMD, 1.53% for cortical thickness, 0.29% for trabecular area, 0.95% for trabecular vBMD, 1.55% for trabecular thickness, 2.85% for trabecular separation, and 3.61% for trabecular number.

Statistical analysis

All data analyses were performed using SPSS Statistics 25 (IBM, NY, USA). Participant characteristics were reported as mean ± standard deviations for continuous variables, or as percentages for categorical variables. Linear regression (β-coefficients; *p*-value) analyses were performed to determine the associations between muscle mass (ALMI: ALM/height^2, kg/m^2), muscle strength (HGS, kg per kg) and bone microarchitecture with adjustments for age, smoking status, time since menopause, height, and self-reported moderate-to-vigorous physical activity. Table 1 presents the fully adjusted model, while Supplementary Table 1 provides results from models with individuals adjustment sets. Furthermore, to determine the associations between ALMI and bone microarchitecture, an additional analysis was performed with HGS in the same model.

Associations between muscle mass and strength and accelerometer-determined physical activity were assessed using linear regression, with physical activity expressed as percentage of time spent sedentary, in LPA, in MVPA, and as average daily METs. Models were adjusted for age, smoking status, BMI, and time since menopause, and results are presented as unstandardised beta coefficients with p-values (significance at $p < 0.05$) (Supplementary Table 2). Mediation analysis was performed to evaluate whether METs and MVPA mediated the association between ALMI and cortical vBMD. Path X represents the effect of ALMI on METs and MVPA, while path Y represents the effect of METs and MVPA on cortical vBMD. The total effect was represented by the direct (Z) and indirect (Z′) effects, with METs and MVPA as mediators. The percentage mediation (PM) was calculated using the formula: $PM = XY/(XY + Z')$ [31]. For all analyses, $p < 0.05$ was considered statistically significant.

Results

A total of 160 Caucasian postmenopausal women with a mean age of 55.9 ± 2.6 years were included (Table 1). No individuals were classified as having sarcopenia when graded against the revised European Working Group on Sarcopenia in Older People 2 definitions (a combination of low ALMI) (< 5.5 kg/m^2) and low HGS (< 16 kg) (32). However, 4 (2.5%) individuals had low HGS, and 7 individuals had low ALMI (4.4%) based on the abovementioned cut points.

Both ALMI (kg/m^2) and HGS (kg) were significantly and positively associated with cortical area (mm^2) at both the radius and tibia, measured at the standard (4%) and distal (30%) sites (all $p < 0.05$) (Table 2). Similar associations were observed in analyses with covariate adjustments, with ALMI demonstrating consistent positive associations

Table 1 Descriptive characteristics

	Mean ± SD or *N* (%)
Age (years)	55.9 ± 2.6
Weight (kg)	71.2 ± 13.0
Height (m)	165.6 ± 6.0
BMI (kg/m^2)	26.0 ± 4.6
Waist circumference (cm)	88.11 ± 12.19
Waist/hip ratio	0.84 ± 0.07
HGS (kg)	27.7 ± 4.8
Current smokers (%)	2 (1.3%)
Self-reported MVPA (hours)	1.9 ± 1.8
Body composition	
ALMI (kg/m^2)	6.8 ± 0.8
Total body fat (%)	38.7 ± 8.0
BMD (g/cm^2)	
Femoral neck	0.91 ± 0.12
Lumbar spine	1.10 ± 0.14
Sarcopenia	
Defined by HGS (kg)	4 (2.5%)
Defined by ALMI (kg/m^2)	7 (4.4%)

Data presented as mean ± standard deviation or number (percentage). *BMI*, body mass index; *BF%*, body fat percentage; *BMD*, bone mineral density; *HGS*, hand grip strength; *ALMI*, appendicular lean mass index; *MVPA*, moderate-to-vigorous physical activity

Table 2 Associations between muscle mass and strength and bone microarchitecture

	ALMI (kg/m^2)	HGS kg (kg)
HR-pQCT – radius (standard)		
Total area (mm^2)	**15.48 (< 0.001)**	**2.01 (0.017)**
Total vBMD (mg/cm^3)	− 3.70 (0.740)	1.98 (0.316)
Cortical area (mm^2)	**2.55 (< 0.001)**	**0.67 (0.000)**
Cortical vBMD (mg/cm^3)	**− 11.37 (0.039)**	− 0.78 (0.443)
Cortical porosity (%)	0.00 (0.478)	0.00 (0.058)
Trabecular area (mm^2)	**13.16 (0.007)**	1.46 (0.096)
Trabecular vBMD (mg/cm^3)	**9.44 (0.013)**	**1.72 (0.011)**
Trabecular thickness (mm)	**0.00 (0.046)**	**0.00 (< 0.001)**
Trabecular separation (mm)	− 0.07 (0.099)	− 0.01 (0.617)
Trabecular number (1/mm)	**0.09 (0.003)**	0.01 (0.119)
HR-pQCT – radius (30%)		
Total area (mm^2)	2.14 (0.283)	0.49 (0.159)
Total vBMD (mg/cm^3)	− 0.44 (0.963)	− 0.17 (0.916)
Cortical area (mm^2)	**1.89 (0.045)**	**0.34 (0.039)**
Cortical vBMD (mg/cm^3)	− 2.24 (0.520)	− 0.35 (0.575)
Cortical porosity (%)	− 0.01 (0.176)	0.00 (0.055)
HR-pQCT – tibia (standard)		
Total area (mm^2)	**34.21 (0.002)**	2.25 (0.250)
Total vBMD (mg/cm^3)	6.13 (0.508)	2.37 (0.148)
Cortical area (mm^2)	**24.84 (0.038)**	**1.15 (0.000)**
Cortical vBMD (mg/cm^3)	6.71 (0.385)	− 0.38 (0.734)
Cortical porosity (%)	− 0.00 (0.218)	0.00 (0.346)
Trabecular area (mm^2)	**24.84 (0.038)**	1.00 (0.641)
Trabecular vBMD (mg/cm^3)	**10.16 (0.008)**	0.93 (0.178)
Trabecular thickness (mm)	0.00 (0.057)	0.00 (0.003)
Trabecular separation (mm)	**− 0.07 (0.014)**	0.00 (0.794)
Trabecular number (1/mm)	**0.08 (0.001)**	− 0.01 (0.879)
HR-pQCT – tibia (30%)		
Total area (mm^2)	**19.62 (< 0.001)**	**2.71 (< 0.001)**
Total vBMD (mg/cm^3)	2.37 (0.683)	0.97 (0.341)
Cortical area (mm^2)	**15.00 (< 0.001)**	**1.90 (< 0.001)**
Cortical vBMD (mg/cm^3)	**− 12.82 (< 0.001)**	− 0.31 (0.598)
Cortical porosity (%)	0.000 (0.905)	0.000 (0.831)

Data presented as unstandardised beta coefficient (*p*-value). Bold indicates significance at $p < 0.05$. Adjusted for age, smoking status, time since menopause, height, and self-reported MVPA. *vBMD*, volumetric bone mineral density; *ALMI*, appendicular lean mass index; *HGS*, hand grip strength; *MVPA*, moderate-to-vigorous physical activity; *HR-pQCT*, high-resolution peripheral quantitative computed tomography

Table 3 Associations between muscle mass and bone microarchitecture, independent of hand grip strength

	ALMI (kg/m^2)
HR-pQCT – radius (standard)	
Total area (mm^2)	**13.757 (0.005)**
Total vBMD (mg/cm^3)	− 8.627 (0.466)
Cortical area (mm^2)	**1.865 (0.013)**
Cortical vBMD (mg/cm^3)	**− 12.605 (0.032)**
Cortical porosity (%)	0.000 (0.876)
Trabecular area (mm^2)	**12.176 (0.018)**
Trabecular vBMD (mg/cm^3)	6.735 (0.092)
Trabecular thickness (mm)	0.002 (0.345)
Trabecular separation (mm)	− 0.070 (0.121)
Trabecular number (1/mm)	**0.078 (0.013)**
HR-pQCT – radius (30%)	
Total area (mm^2)	1.662 (0.429)
Total vBMD (mg/cm^3)	− 0.676 (0.946)
Cortical area (mm^2)	1.621 (0.094)
Cortical vBMD (mg/cm^3)	− 2.014 (0.587)
Cortical porosity (%)	**− 0.001 (0.027)**
HR-pQCT – tibia (standard)	
Total area (mm^2)	**34.810 (0.002)**
Total vBMD (mg/cm^3)	1.337 (0.892)
Cortical area (mm^2)	**7.391 (< 0.001)**
Cortical vBMD (mg/cm^3)	6.252 (0.330)
Cortical porosity (%)	− 0.002 (0.215)
Trabecular area (mm^2)	**27.028 (0.033)**
Trabecular vBMD (mg/cm^3)	**9.107 (0.025)**
Trabecular thickness (mm)	0.002 (0.363)
Trabecular separation (mm)	**− 0.082 (0.007)**
Trabecular number (1/mm)	**0.093 (< 0.001)**
HR-pQCT – tibia (30%)	
Total area (mm^2)	**16.816 (< 0.001)**
Total vBMD (mg/cm^3)	0.442 (0.943)
Cortical area (mm^2)	**13.041 (< 0.001)**
Cortical vBMD (mg/cm^3)	**− 13.666 (< 0.001)**
Cortical porosity (%)	0.000 (0.809)

Data presented as unstandardised beta coefficient (*p*-value). Bold indicates significance at $p < 0.05$. Adjusted for age, smoking status, time since menopause, height, and self-reported MVPA. ALMI and HGS in the same model with beta coefficient presented for ALMI. *vBMD*, volumetric bone mineral density; *ALMI*, appendicular lean mass index; *HGS*, hand grip strength; *MVPA*, moderate-to-vigorous physical activity; *HR-pQCT*, high-resolution peripheral quantitative computed tomography

and HGS showing limited relationships (Supplementary Table 1). In addition, ALMI was positively associated with trabecular vBMD at the standard sites of both the radius ($\beta = 9.44$ mg/cm^3 per 1 kg/m^2 increase in ALMI, $p = 0.013$) and the tibia ($\beta = 10.16$ mg/cm^3, $p = 0.008$). However, negative associations were observed between ALMI and cortical vBMD at the standard site of the radius ($\beta = -11.3$ mg/cm^3 per 1 kg/m^2 increase in ALMI, $p = 0.039$) and the 30% site of the tibia ($\beta = -12.82$ mg/cm^3, $p < 0.001$), indicating an inverse relationship between muscle mass and cortical vBMD after adjusting for potential confounders (Table 2). Further analyses revealed that ALMI was positively associated with vBMD and several bone microarchitecture

Table 4 Associations between muscle mass, METs, and cortical vBMD

Path	Effect	*p*-value	95% CI
MVPA (%)			
ALMI → MVPA (*X*)	0.140	0.641	(−0.452, 0.732)
MVPA → cortical vBMD (*Y*)	−3.280	0.064	(−6.755, 0.194)
ALMI → cortical vBMD (*Z*)	−14.027	0.027	(−26.429, −1.624)
ALMI → cortical vBMD (*Z*′)	−17.307	0.016	(−30.132, −4.483)
Percentage mediation	**3.2%**		
METs	---		
ALMI → METs (*X*)	0.040	0.015	(0.008, 0.073)
METs → cortical vBMD (*Y*)	−49.947	0.125	(−113.873, 13.978)
ALMI → cortical vBMD (*Z*)	−12.472	0.054	(−25.177, 0.233)
ALMI → cortical vBMD (*Z*′)	−62.419	0.061	(−126.432, 1.594)
Percentage mediation	**13.9%**		

Mediation analysis to assess whether METs and MVPA mediated the relationship between ALMI and cortical vBMD. Path (*X*) represents the effect of ALMI on METs and MVPA, while path (*Y*) corresponds to the effect of METs and MVPA on cortical vBMD. The total effect is represented by the direct (*Z*) and indirect (*Z*′) effects with METs and MVPA as mediators. The percentage mediation (PM) was calculated as $PM = XY/(XY + Z')$, providing the effect size of the mediation. *ALMI*, appendicular lean mass index; *METs*, metabolic equivalents of task; *MVPA*, moderate-to-vigorous physical activity; *vBMD*, volumetric bone mineral density

parameters independently of HGS (all $p < 0.05$) after adjustment for confounders (Table 3).

In adjusted analyses, ALMI was positively associated with MVPA (β = 0.781, p = 0.034) and METs (β = 0.045, p = 0.031), while no significant associations were observed for sedentary time or LPA. Hand grip strength was not significantly associated with sedentary time, LPA, MVPA, or METs after adjustment for confounders (Supplementary Table 2). Mediation analysis showed that total weekly physical activity, measured in MET-hours/week, partially mediated the association between ALMI and cortical vBMD (Table 4). ALMI was positively associated with METs ($\beta = 0.043$ MET-hours/week per 1 kg/m^2 increase in ALMI, $p = 0.015$). The indirect effect of ALMI on cortical vBMD through METs was small but statistically significant ($\beta = -2.01$ mg/cm^3, 95% CI: –5.25 to –0.03). The direct effect of ALMI on cortical vBMD was not statistically significant ($\beta = 12.47$ mg/cm^3, $p = 0.054$), and the proportion mediated (PM) was 13.95%, suggesting that approximately 14% of the association between ALMI and cortical vBMD is explained by METs. In contrast, there was no significant mediating effect of MVPA on this relationship.

Discussion

In this population of Caucasian postmenopausal women, several statistically significant associations were observed between muscle specific endpoints (ALMI and HGS) and various bone microarchitecture parameters assessed by HR-pQCT. Our findings imply that greater muscle mass and strength may contribute to improvements in bone structure and size, particularly evident for cortical area and trabecular vBMD. These findings suggest that maintenance of muscle health in terms of strength and mass is necessary for improved bone health. Furthermore, this study reports that while muscle mass is associated with larger bones, it comes at the potential expense of cortical vBMD, highlighting the complicated interplay between muscle and bone microarchitecture in this population, which warrants further investigation in order to identify the mechanisms at play. Moreover, the findings suggest that higher levels of physical activity may play a role in the relationship between muscle mass and bone health, further emphasizing the importance of physical activity in preserving bone density.

The positive associations observed in this study between muscle mass and cortical area and trabecular bone parameters demonstrate that ALMI is associated with more favorable bone geometry and microarchitecture in this population of Caucasian women. In line with our findings, in a study including 175 men and 167 women aged between 72 and 81 years, it was evident that ALMI was positively associated with cortical area and trabecular number at the radius and tibia sites [33]. Higher muscle mass imposes greater mechanical stress on bones, potentially stimulating bone formation and augmenting bone size, as evidenced by the positive associations with cortical area in the current study across both the standard and 30% radius and tibia sites [34]. Moreover, the observed enhancements in trabecular structure and density associated with higher ALMI may signify improvements in bone quality and strength, given the pivotal role of trabecular bone in impact absorption and bone integrity [33]. Strategies focusing on preserving or augmenting muscle mass, such as resistance training and ensuring adequate energy and protein intake, may not only help maintain muscle mass and attenuate muscle loss but may also, through secondary effects, help contribute to the maintenance of optimal bone health and mitigate fracture risks, particularly in older adults [35, 36].

The negative associations between ALMI and cortical vBMD at the standard radius and 30% tibia sites in this population of older women raise questions about the effects of muscle mass on cortical bone density, warranting further investigation. One potential explanation for the findings in the current study is that muscle forces exerted during physical activity can stimulate bone formation and

enhance bone strength by increasing bone size. However, in a study investigating exercise-induced bone gains in ex-national level male tennis players, the authors reported that mechanical loading may adversely affect bone density, particularly in cortical bone [37]. Individuals with higher ALMI may engage in activities or possess biomechanical characteristics that lead to increased mechanical loading on bones, potentially resulting in bone remodeling processes prioritizing bone size over density at the cortical compartment [37]. This could result in a dilution effect, where bone mass increases due to mechanical loading, but bone density decreases relative to bone size. It is also plausible that other factors, such as cortical thickness or tissue mineralisation, may contribute to the observed changes in cortical vBMD independent of porosity. Additionally, mediation analysis revealed that METs partially mediated the relationship between ALMI and cortical vBMD, suggesting that physical activity levels play a key role in modulating the relationship between muscle mass and bone density. Therefore, the use of accelerometer data, compared to self-reported questionnaires, offers a more objective, precise, and continuous measure of physical activity, mitigating recall bias and providing more reliable insights into the effects of mechanical loading on bone health [23, 38]. These findings underscore the complex relationship between muscle mass, physical activity, and bone health and emphasize the importance of targeted interventions to prevent musculoskeletal decline in postmenopausal women.

The positive associations observed between HGS and total bone area as well as cortical area indicate that higher HGS is associated with enhanced bone microarchitecture. This was particularly evident in cortical regions at both the radius and tibia, across standard and 30% sites. These findings demonstrate the potential impact of muscle strength on bone morphology and size, particularly at the cortical compartments [39]. Consistently, in an 8-year prospective follow-up study including 821 older men, low HGS was associated with rapid deterioration of cortical bone microarchitecture determined by HR-pQCT [40]. Similarly, in another study including 810 men aged 60 years and older, low HGS was associated with poor cortical and trabecular microarchitecture at the nondominant distal radius after adjustment for confounder [41]. Higher HGS implies greater muscle forces exerted on bones; this mechanical loading stimulates bone formation and remodeling, explaining the increased bone size and cortical area [40, 42, 43]. In a study including 508 men and 651 women aged between 50 and 95 years, the positive associations between hand grip strength and distal radius bone strength were shown to be driven primarily by bone size, further supporting the findings of the current study that HGS is associated with increased total and cortical bone area [42]. Additionally, these findings highlight the importance of preserving muscle strength through physical activity/strength training interventions to support optimal bone health and to ultimately reduce the risk of age-related bone loss and fractures.

Although ALMI and HGS were both associated with more favorable cortical area and trabecular vBMD, this study suggested that ALMI is overall a better predictor of bone microarchitecture, particularly at the tibia as many of the significant associations were independent of HGS. This study implies that muscle mass, as reflected by ALMI, may have a more direct influence on bone density and bone quality compared to muscle strength alone. These findings are consistent with previous studies including 129 postmenopausal women and 189 older adults aged 65 years and older, both of which found that muscle mass and strength are important determinants of bone quality [44, 45]. Although mechanical loading is primarily influenced by muscle strength, the stronger associations observed with ALMI in our study may reflect long-term cumulative effects of muscle mass in skeletal loading, or the possibility that ALMI captures both structural and metabolic aspects of muscle that are relevant to bone health. In addition to mechanical loading, shared systemic factors such as nutritional status, and circulating anabolic hormones (IGF-1 and growth hormone) may also contribute to both muscle and bone health. Moreover, emerging evidence supports a biochemical interaction between bone and muscle via secreted factors such as myokines and osteokines, which may modulate tissue-specific adaptations beyond mechanical loading [46, 47]. These pathways could partially explain why associations between muscle mass and bone microarchitecture appear stronger than those observed with muscle strength in our study. Future studies should therefore focus on how muscle mass-focused interventions could be optimized to enhance bone health, particularly in weight-bearing bones such as the tibia.

This study provides important insights into the associations between muscle mass and strength and bone microarchitecture in Caucasian postmenopausal women. There are however some limitations. Firstly, this was a cross-sectional analysis which limits inferences of causation in the association between muscle mass and strength and bone microarchitecture. Therefore, longitudinal studies involving larger sample sizes are required to confirm the findings across other ethnicities, age groups, and in men. Additionally, it should also be noted that individuals included in the study were healthy postmenopausal women, which may limit the generalizability of the findings to other populations, such as those with existing health conditions or younger women. Finally, while HR-pQCT provides valuable insights into bone microarchitecture, this study did

not incorporate micro finite element analysis, which would offer a more detailed assessment of bone strength.

In conclusion, these findings indicate that muscle mass and strength are important in maintaining bone size and overall bone health although at the expense of cortical vBMD in this population of Caucasian postmenopausal women. In addition, it is evident that ALMI is overall a better predictor of bone microarchitecture, particularly at the tibia. The mediation analysis also indicates that METs partially mediate the relationship between muscle mass and cortical bone density, suggesting that physical activity levels may influence bone health. These findings suggest the potential implications for lifestyle interventions aimed at preserving the integrity of muscle to potentially reduce fracture risk in postmenopausal women. Further research is needed to elucidate the underlying mechanisms driving these associations and to develop targeted lifestyle strategies for optimizing muscle mass and bone quality in this population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07653-4.

Acknowledgements The authors would like to express their sincere gratitude to all the participants who generously dedicated their time and effort to contribute to this study. The authors also acknowledge Pendulum Therapeutics for their in-kind donation of the investigational products and for providing partial funding for the trial.

Funding Open access funding provided by University of Gothenburg. The trial and research staff are supported by internal funding from Australian Catholic University, awarded to Professor Mattias Lorentzon (funding number 904165). Additionally, the trial received partial sponsorship from Pendulum Therapeutics Inc., San Francisco, CA, USA.

Declarations

Conflicts of interest LGK is on the scientific advisory boards of Vital Proteins and NUUN, has participated on advisory boards for Liquid I.V., has received personal fees from RNWY and Nestlé Health Science, and is a board member of Siftlink. All other authors declare no conflicts of interest in regard to the contents of this manuscript. Pendulum Therapeutics Inc., was not involved in the study design, data collection or in the analyses of study results.

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